HEART RATE VARIABILITY AND EXERTIONAL TASK ANALYSIS IN THE RECOVERY OF MILD TRAUMATIC BRAIN INJURY IN SERVICEMEMBERS (HEARTS)

Julianna H. Prim

A dissertation submitted to the faculty of the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree Doctor of Philosophy in the School of Medicine (Curriculum in Human Movement Science).

Chapel Hill
2019

Approved by:

Karen McCulloch

Amy Cecchini

Maria Davila-Hernandez

Flavio Fröhlich

Johna Register Mihalik

Shabbar Ranapurwala

ABSTRACT

Julianna H. Prim: Heart Rate Variability and Exertional Task Analysis in the Recovery of Mild Traumatic Brain Injury in Servicemembers (HEARTS)
(under the direction of Karen McCulloch)

Context: The Defense and Veterans Brain Injury Center (DVBIC) guideline for Healthcare Providers treating mild traumatic brain injury (mTBI) recommends an exertional test before return to duty (RTD), yet no standardized test currently exists. Autonomic nervous system (ANS) impairments after concussion may be measured by heart rate variability (HRV). **Objective:** To develop clinically feasible exertional tasks to assess ANS balance with HRV measurements that can identify deficits and aid clinicians in RTD decisions for service members (SMs) with acute mTBI. **Methods**: 44 participants (40 Heathy Controls-HC, 4 mTBI) completed our exertional testing protocol while wearing heart rate (HR) monitors. After baseline rest, participants completed two short exertional tasks: a stepping and push-up task with a recovery period after each. The stepping task was 6 minutes with speed increases every 2 minutes utilizing a metronome for pacing and a 12' step. The push-up task was a maximum of two minutes, self-paced, with total number recorded. **Main Outcomes**: (1) HR and HRV measures for two sensors, observational measures of time, space, equipment, physiological response in HC; (2) mTBI and HC HRV measures during resting, exertion, and recovery. Case series of task performance for mTBI participants, (3) successful task completion, exertion level, symptoms, HR. **Results**: (1) High reliability between the PolarH10 monitor and Faros180 ECG in HR and HRV component analyses during resting and exertional conditions was found. Both tasks met standards of clinical feasibility and physiological response. (2) mTBI SMs had lower baseline and recovery values of cardiac vagal control compared to HC. mTBI SMs also had lower rate of cardiac vagal recovery and heart period recovery compared to HC. Both tasks provoked symptoms in a majority of mTBI SMs, even with reported readiness to RTD. (3) Both tasks had similar completion, symptom and exertion levels. **Conclusions**: Completion of exertional tasks provided insight on recovery. An objective physiological measure could be used alongside symptom report and clinical opinion in prescribing activity and managing recovery after acute mTBI. Future research should prioritize clinical implementation of exertional tasks and how the physiological measure of HRV can be used clinically.

DEDICATION

This dissertation is dedicated in honor of my two greatest role models: my parents Clinton "Oz" and Valerie Prim.

For the passion they bring daily in teaching and coaching. For the way they encourage and care for everyone they mentor. For the sacrifices they made to help me succeed. For the positivity in challenging times and the unconditional love they give. For being my biggest supporters and instilling in me values that I will always take with me.

"Have I ever told you, you're my hero...you are the wind beneath my wings"

ACKNOWLEDGEMENTS

To my advisor, Dr Karen McCulloch. Thank you for all your time and energy over these last four years. Thank you for supporting me as I transitioned from basic science, teaching me how to have a clinical mindset, being an example of keeping work-life balance, connecting me with folks within the DoD research community, and empowering me to lead. I appreciate your encouragement to explore multiple research areas and the freedom to be involved in so many things to discover new passions. Thank you for being willing to take a Wolfpacker and making me a part of the Carolina family.

To Dr. Johna Registar Mihalik. Thank you for all your support during my time at UNC. Your genuine positivity is inspiring and the energy you put into teaching and research has been a great example of how to lead. Thank you for always making feel me a part of the sports concussion and Active Rehab group and enabling me to be a part of such a dynamic multi-site study.

To Dr. Shabbar Ranapurwala. Thank you for the time and expertise that you have brought to this project. I appreciate all the meetings and advice on design and analysis on multiple studies. You have the unique ability to understand the clinical and numbers side of research and have taught me more than you know.

To Dr. Amy Cecchini. Thank you for playing such a vital role in this project and sharing your insight about military research. Thank you for being an active clinician that cares so much about good science. I appreciate all your input and ideas for this project and the time you continue to put in. Your passion for clinical research and improving military healthcare is inspiring.

To Dr. Maria Davila-Hernandez. Thank you for investing in me and my research these last two years. Thank you for your open-door policy and all the help you’ve given to assist with this study. I am grateful for your caring heart and the time you spent in helping me become proficient in HRV theory and analysis. I appreciate all of your encouragement and support.

To Dr. Flavio Fröhlich. Your mentorship has been one of the best things I’ve encountered during my doctoral work. Thank you for including me from the beginning as part of the Carolina Neurostimulation Center and empowering me to own a study from start to finish. Thank you for challenging me as an academic and as a person to grow and making me believe that research could change the world.

To Dr. Miles Engell. Thank you for your mentorship for my undergrad studies and beyond. You are a role model of a strong woman in science, an enthusiastic professor, and a caring, invested advisor. Your guidance during my time at NC State was invaluable.

To Ms. Rebecca Bryant. Thank you for inspiring me in my early days to pursue a career in science and encouraging your students to dream big.

To Dr. Wesley Cole. Thank you for your support as site PI on this study and the assistance with space and logistics. You are essential to the continued success of this study.

To past and present members of the Carolina Neurostimulation Center and Frohlich Lab. Thank you for all you have taught me and letting me join the family. I am blessed to have been a part of such a diverse and dynamic group.

To the HMSC program and faculty. Thank you for the opportunity to study at such a fantastic University and renowned program. Thank you for teaching and training us to be well-rounded scientists.

To my HMSC peeps. Thank you for your friendship and your encouragement. I appreciate all the advice and direction along the way.

To my UNC community. Thank you for accepting me and loving me so well these past four years. Thank you for reminding me where to get value from and making life fun in the process. I will cherish the memories with such great friends.

To my family and friends. Thank you for all the encouragement, the wisdom, and the love you have shared with me. From North Carolina to Florida, you all have played a part in helping me succeed. It has been a long journey and I certainly would not be here without you all. I love you all so much!

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ACFT	Army Combat Fitness Test
ADHD	attention deficit hyperactivity disorder
ADSM	Active duty service member(s)
AMMP	Assessment of Military Multitasking Performance
ANAM	Automated Neuropsychological Assessment Metrics
ANS	Autonomic Nervous System
APFT	Army Physical Fitness Test
B–A plots	Bland-Altman Plots
BCTT	Buffalo Concussion Treadmill Test
BDNF	brain derived neurotrophic factor
bpm	beats per minute
CAN	cardiac autonomic network
CBF	cerebral brain fluid
CISG	Concussion in Sport Group
CNS	central nervous system
CPVD	Cardio Peak-Valley Detector
CST	Chester Step Test
CVC	cardiac vagal control
DOD	Department of Defense
DVBIC	Defense and Veterans Brain Injury Center
DVPRS	Defense and Veterans Pain Rating Scale
ECG	electrocardiogram
HC	Healthy Controls
HEARTS	Heart Rate Variability and Exertional Task Analysis in the Recovery of Mild Traumatic Brain Injury in Servicemembers
HF	high frequency
HP	heart period
HR	heart rate
HRV	heart rate variability
IBI	inter-beat intervals
IRB	Institutional Review Board
ISC	Intrepid Spirit Center
LF	low frequency
MACE	Military Acute Concussion Evaluation
MHS	Military Health Service
MPF	moving polynomial filter
mTBI	mild traumatic brain injury
NSI	Neurobehavioral Symptom Inventory
PCD	post-concussion disorder
PCL-5	Posttraumatic Stress Disorder Checklist-5

PCM	primary care managers
PCS	post concussive syndrome
PHQ-2	Patient Health Questionnaire-2
PNS	Parasympathetic nervous system
PRA	Progressive Return to Activity
PTS	Post-traumatic stress
RHC-A	US Army Regional Health Command- Atlantic
RPE	rate of perceived exertion
RSA	respiratory sinus arrhythmia
RTA	return to activity
RTD	return to duty
RTP	return to play
SAC	Standardized Assessment of Concussion
SCAT5	Sport Concussion Assessment Tool 5th Edition
SMs	servicemembers
SNS	sympathetic nervous system
TBI	traumatic brain injury
USMC PFT	US Marine Corps Physical Fitness Test
VOMS	Vestibular Ocular Motor Screening
WAMC	Womack Army Medical Center

CHAPTER 1: INTRODUCTION

BACKGROUND

Concussion or mild traumatic brain injury (mTBI) is a prevalent injury in civilians, athletic and military populations alike. Over 380,000 service-members (SMs) have sustained a mTBI since 2000.[1] The rate of concussion continues to be significant in the garrison environment as a result of training exercises and non-duty activities of a young active population. According to the Department of Defense (DOD), mTBI is defined as "an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and/or difficulty concentrating". [2] Along with common cognitive, vestibular, and visual symptoms, concussions are also associated with exertional and physiological changes in other organ systems, including the autonomic nervous system (ANS). [3,4]

The ANS, made up of two branches the excitatory sympathetic nervous system (SNS) and inhibitory parasympathetic nervous systems (PNS), controls a range of vital involuntary physiological functions, including regulating blood pressure, temperature, respiratory systems, gastrointestinal systems, and heart rate during rest and in response to stressors.[5] Individuals after concussion demonstrate reduced parasympathetic activity and less efficient response to autonomic challenges,[6,7] as compared to healthy controls. This ANS impairment has been demonstrated acutely (from 48 hrs. to report of asymptomatic at rest),[8] but may also persist years post injury.[9,10]

Regulatory ANS function can be assessed by the analysis of heart rate variability (HRV), which is the variation in time between successive heartbeats and reflects the balance of PNS and SNS activation.[11,12] HRV serves as a proxy for ‘top–down’ integration of the brain mechanisms that guide flexible control of behavior with peripheral physiology and can provide insight on stress level and overall health.[11] Generally, greater HRV suggests that the parasympathetic nervous system (PNC, specifically vagal nerve) is appropriately responding to the requirements of the environment, while lower HRV suggests that PNS is not modulating the heart rate as efficiently.[13] This interactive communication between the cardiac and the regulatory neural systems (i.e., the body and the brain) may be disrupted after mTBI.[14] In more severe TBI, an “uncoupling” of pacemakers in heart tissue and ANS input to heart has been observed.[15] Evidence suggests that concussion temporarily disrupts autonomic control of cardiovascular function[16] with abnormalities in HRV present in mTBI.[6,17–19] Some HRV responses after mTBI have been variable, especially at rest,[8] suggesting it may be necessary to induce physical stress to observe subtle ANS and cardiovascular dysfunction.[20]

The use of exertional testing to identify possible ANS dysfunction is a reasonable approach in clinical practice.[21] Currently the only validated exertional task investigating the ANS in acute and prolonged recovery after mild traumatic brain injury is the Buffalo Concussion Treadmill Task (BCTT).[22] While this approach offers an advantage with standardized test procedures, it is not always clinically feasible. In the military context, individuals with concussion are typically seen by primary care providers, who are encouraged to use exertional testing to guide return to activity.[23] These practitioners are limited by time, space, and equipment,[24,25] preventing use of the BCTT. A more field expedient test of exertion would be beneficial to aid primary care manager examination and inform the progressive return to activity process.

STATEMENT OF THE PROBLEM

MTBI results in a variety of symptoms that limit activity. Returning to normal activity too soon, as well as prolonged rest, have been shown to increase symptom duration.[26–28] Currently patient self-report of symptoms is a primary measure that clinicians use in return-to-activity decisions,[29] but evidence shows that physiological deficits may persist beyond self-report symptom resolution.[30, 31] A physiological biomarker, such as HRV, could provide insight into the recovery process and provide an objective measure to guide clinical decision-making. When to begin activity may be aided by examining such objective physiologic measures. Current Defense and Veterans Brain Injury Center (DVBIC) guidelines recommend use of an exertional test before return to duty decisions, yet implementation of a physical test varies and there is currently no standardized exertional assessment that is clinically feasible and validated.

PURPOSE

Our **long-term research goal** is to improve the assessment and management of acute concussion within the military health system (MHS). The **purpose** for this project was to develop clinically feasible exertional tasks to assess ANS balance with HRV measurements. These tasks identify deficits and may be used to aid clinicians in return to activity (RTA) and return to duty (RTD) decisions that can be implemented in a primary care environment. We proposed the use of a modified 6 minute Chester Step Test, a graded step test developed for use in quantifying occupational aerobic capacity that has been tested in emergency service populations.[32,33] This step task progressively increases speed every two minutes, similar to the BCTT.[34] A second exertional task was performance of push-ups for two minutes. The pushup task is a component of the current Army Physical Fitness Test (APFT), with clear military and functional health relevance,[35,36] but has not been researched after concussion. The **rationale** was to investigate proposed ANS dysfunction in patients with mTBI and its relationship to exertion.[21] Our **central hypothesis** was that the exertional conditions of both tasks will provoke ANS and exertional impairments within the concussed population that may not been seen in a resting state. This research is **innovative** in that we investigated the ability of time-efficient clinically feasible tasks, requiring minimal equipment, ecologically valid tasks to capture meaningful physiological responses in a military population.

SPECIFIC AIMS AND HYPOTHESES

We tested our central hypothesis with the following aims:

Specific Aim 1: To test the feasibility of two exertional task protocols for use in military population

1 A: Determine whether a stepping task, (modified from the Chester Step Test-CST) and Push-up task (from the Army Physical Fitness Test-APFT) are clinically feasible.

Hypothesis: We hypothesized that both the stepping test and push-up test would be clinically feasible. Rationale for this hypothesis is based on standards[25,37,38] that the duration, equipment, and space requirements are consistent with the resources available for a routine concussion appointment with a military primary care manager.

1 B: Determine whether physiologic responses to a stepping task, (modified from CST) and Push-up test (from APFT) are consistent with expected physiological responses to exertional conditions.

Hypothesis: We hypothesized that both the stepping test and push-up test would demonstrate expected physiological responses that were measurable using clinically available equipment. Based on the CST and APFT, a similar stepping and push-up task have been utilized to assess aerobic and strength capacity.[33,35] HRV has been successfully collected during a stepping task.[39]

1.C: Determine the accuracy and reliability of beat-to-beat heart rate data for the exertional protocol collected by the Polar H10 HR monitor through Bluetooth capabilities compared to the gold standard ECG recordings.

Hypothesis: We hypothesized that the Polar H10 would be accurate and reliable compared to ECG from Faros180 based on previous studies comparing the suitability of the selected sensor and system for collecting HRV data.[40]

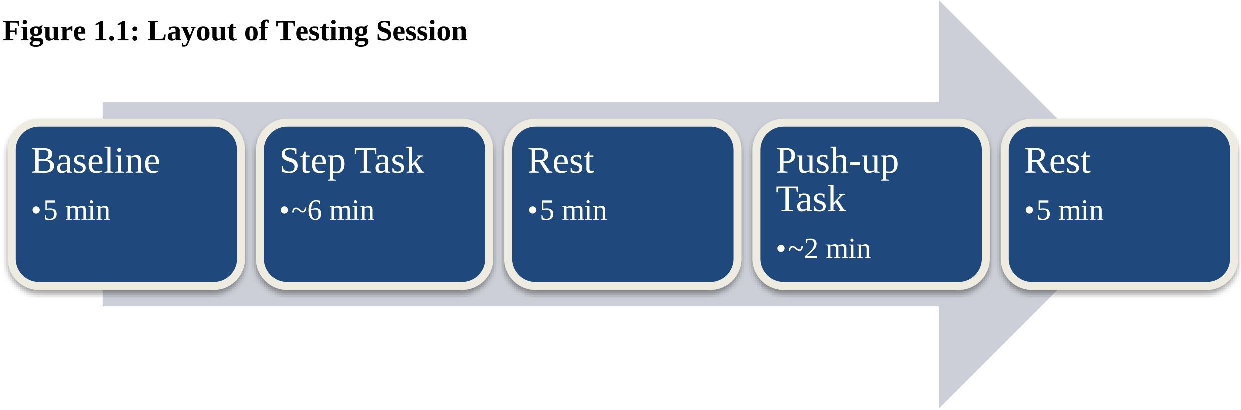
Table 1.1: Summary of Specific Aim 1

Research Question	Independent Variable	Dependent Variable	Analysis
1.A Clinical Feasibility	Stepping Task	Equipment, space, time, costs, difficulty in assessing standards	Observational measures Discussions with PCM at Ft. Bragg and individuals associated with DVBIC
	Push-Up Task	Equipment, space, time, costs, difficulty in assessing standards	
1.B Physiological Response	Stepping Task	RPE, HR, HRV measures	Observational measures to confirm exertional state reached
	Push-Up Task	RPE, HR, HRV measures	
1.C Reliability of the POLAR10 for exertional protocol	Polar H10 HR monitor vs. Faros 180	HRV measures RSA, LF, HP	Bland Altman plots

Specific Aim 2: To examine ANS balance at baseline, during exertional tasks, and throughout heart rate recovery (Figure 1.1) in both mTBI and healthy service-members.

2.A Characterize the extent of HRV difference between service-members with acute mTBI to age-matched healthy controls at rest, in reaction to exertion, and recovery after exertion.[41]

Figure 1.1: Layout of Testing Session



Hypothesis: We hypothesized that participants with mTBI would have impaired vagal tone during initiation of exertional tasks[42] and heart rate recovery based on evidence of PNS hypoactivation.[3,16,43] We expected Total HRV (also described as Heart Period), a proxy for ANS flexibility, to be lower in participants with mTBI during initiation and recovery of exertional conditions.[42] One HRV component, Respiratory Sinus Arrhythmia (RSA), a validated measure of vagal tone, [44] was our primary candidate for investigating ANS issues after concussion. We expected that RSA would be impaired in exertional conditions. We also hypothesized that the low frequency (LF) component of HRV, which captures baroreceptor activity,[45] may be impaired with position change[9], such as the push-up task.

Table 1.2: Summary of Specific Aim 2

Research Question	Independent Variable/ Predictor Variable	Dependent Variable/ Outcome Variable	Analysis
2.A: HRV measures	mTBI or Healthy Control	HRV measure (e.g. RSA, LF, Total HRV)	-Group differences for all outcome variables -Linear Regression- at resting, initiation of exertion, and heart rate recovery

Exploratory Aim 3: To compare two short clinically feasible exertional tasks that are relevant for military populations in terms of tolerability and self-reported symptoms during exertion.

Hypothesis: Based on the previous literature,[46] a stepping exertional task will likely be tolerable for acutely concussed individuals. A push-up task, incorporating baroreceptor activity through position change, may be more symptom provoking.

Table 1.3: Summary of Exploratory Aim 3

Research Question	Independent Variables	Dependent Variable	Analysis
Comparison of exertional task conditions	Stepping task vs. push-up task	Step: Completion of Exertional Task (0,1) Push-up: score of 60 on APFT (0,1)	Logistic Regression
	Stepping task vs. push-up task	HRV, RPE, and symptom scores	Linear Regression

SIGNIFICANCE

This project was translational in nature as it filled known gaps in current acute concussion care in the military context. First, a standardized exertional assessment that is ecologically valid for military populations can be utilized by primary care managers to guide return to activity or return to duty decisions. Performance on such an exertional task can also help clinicians prescribe appropriate levels of activities, during progressive return to activity, and may have utility as a predictor of duration of symptoms. Second, physiological measures may be used alongside symptom report and clinician opinion in return to activity or duty decisions. As a simple, noninvasive measure of ANS balance, HRV could act as a marker of recovery and would be a valuable addition in clinical care. Currently patient symptom report is the primary way clinicians gauge recovery, but self-report of symptoms is known to be somewhat unreliable due to under- or over-reporting. In the military population reporting is further influenced by operational needs, command pressure, or other demands and aspects of warrior culture.[47] The identification of possible ANS impairment also serves to inform rehabilitation interventions to improve the ability to tolerate and recover from exertion, which is inherent in training and combat activities in the military.

OPERATIONAL DEFINITIONS

1. Mild traumatic brain injury: an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and/or difficulty concentrating
2. Recovery from mTBI: was defined as symptom resolution to normal, confirmed by a normal physical examination (i.e., a normal neurological examination including normal vestibular and oculomotor systems)
3. Heart rate recovery is the period when physical capacity is regained and defined as the change from peak heart rate to the HR at a specific time point post exertion[48]

4. Exertional conditions are defined by physical tasks where HR reaches 65-85% of HRmax and rate of perceived exertion (RPE) is between 11-16 on the Borg RPE Scale.
5. Return to activity refers to the timepoint when an individual who had sustained a mTBI can begin the five-stage graded exertion progression, usually guided by PCM.
6. Return to play is defined by the timepoint when an athlete who had sustained a mTBI has been released by a clinician to participate in unrestricted activity like a competition (stage 6 of progression)
7. Return to Duty is defined by the timepoint when a servicemember who had sustained a mTBI, has been released by a clinician to participate in all duty-related activities with no limitations.
8. Cardiac Vagal Control: efficiency of the parasympathetic nervous system, specifically related to vagal nerve function and its contribution to cardiac function, captured by RSA measures.
9. Rate of Cardiac Vagal Reactivity: the slope of the line of best fit of all the RSA measures with a given time (one minute and two minutes) after the start of the exertional task
10. Rate of Cardiac Vagal Recovery: the slope of the line of best fit of all the RSA measures with a given time (one minute and two minutes) after the beginning of a rest period

CHAPTER 2: REVIEW OF LITERATURE

MILITARY CONCUSSION

In the past 20 years, over 383,000 Department of Defense (DoD) service members (SM) have sustained traumatic brain injury (TBI) with 82.4% of these cases classified as mild (mTBI) or concussion.[1] The DOD defines MTBI or concussion[49] as "an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and/or difficulty concentrating".[2] MTBI remains a prevalent injury during military deployment, with increased reporting beginning in 2000 coinciding with heightened awareness of the risks of mTBI during the military conflicts in Iraq and Afghanistan.[50] While combat operations in Afghanistan and Iraq are significantly reduced, concussions remain prevalent within military populations with predictions of 20,000 or more cases per year. The majority of mTBI injuries occur in the non-deployed environment as a result of motor vehicle crashes, falls, sports, and recreational activities, and military training.[1] The Army, as the largest service branch, has the highest incidence for TBI out of all the military branches accounting for 64% of injuries between 2010-2014.[51]

The Defense and Veterans Brain Injury Center (DVBIC), created by the DoD in 1992 as a research organization and enlarged in the early 2000's to include clinical and educational programs, enhances and coordinates TBI care provided in the military health system (MHS).[50] DVBIC has developed clinical recommendations for military primary care managers and rehabilitation providers for treatment and management of mTBI that have incorporated current evidence, but on times rely on expert consensus for specific recommendations for practice.[52–55] The DoD has made great progress through prioritizing TBI clinical care, education, and research, but there remains gaps in research based evidence for the management of servicemembers post-concussion.[50]

This review will focus on three primary areas related to the topic of military concussion to support the current study hypotheses: (1) pathophysiology and recovery of mTBI, (2) influence of the Autonomic Nervous System and Heart Rate Variability, and (3) exertional tasks and Return to Duty Assessments. In summary, return to duty decisions after an mTBI are an important military health concern, yet there has been a paucity of research investigating assessments to gauge recovery with objective measures after an acute concussion. Therefore, the **aims of this study** seek to increase our understanding of physiological deficits that are associated with mTBI and their relationship with exertion. Use of a simple physiological measures and feasible exertional tasks during a primary care appointment, along with patient self-report of symptoms, will improve a clinician's ability to make the best decisions on return-to–activity, ultimately contributing to return to duty.

Pathophysiology of Concussion

TBI has been called "the most complicated disease of the most complex organ of the body" [56,57] and is an increasingly high-profile public health issue. Indeed, the pathophysiology of mTBI is complex, although great progress has been made in the last ten years.[30] A mTBI is caused by an injury event, "resulting from an external force and/or acceleration/ deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and/or difficulty concentrating".[2] After mTBI, the lack of macroscopic neural damage after biomechanical injury that results in neurological signs and symptoms[54] has led to general hypothesis that dysfunction is the result of predominantly functional or microstructural injury to neural tissue.[58] The neurometabolic cascade that occurs post-injury, is a well-supported hypothesis for the pathophysiology in acute concussion and involves bioenergetic challenges, cytoskeletal and axonal alterations, impairments in neurotransmission, vulnerability to delayed cell death and in some cases leads to chronic dysfunction.[58,59]

After mTBI, the initial ionic flux and glutamate release result in significant energy demands and a period of metabolic crisis for the injured brain.[30,59] This energy crisis leads to changes to cell membrane permeability, ion transport regulation, neurotransmitter release, cellular metabolism, and changes to cerebral blood flow.[60] Biomechanical forces imparted onto neurons and glia can damage delicate and complex dendritic arbors, axons, and astrocytic processes.[61,62] Axons prove to be particularly vulnerable to biomechanical stretch.[63] Ligand-gated excitatory and inhibitory neurotransmission changes, as well increased inflammatory response and the activation of microglia, have been reported after TBI.[64,65] While the pathophysiology and mTBI-related perturbations likely disturb many components within the nervous system and contribute to various symptom, identification of dysfunction and neurological signs can help characterize impairments and targets for intervention.[60]

Symptom Presentation and Diagnosis

The acute symptoms of mTBI are often unique to each individual, as no impairment is common across all cases. Instead, concussion can cause patients to have a multitude of complaints including headache, disorientation, language impairments, loss of consciousness, dizziness, mood disruptions, cognitive deficits, sleep disorders, sensitivity to light and sound, and problems with balance or gait.[66] MTBI is diagnosed based on clinical assessment after an injury event with temporal links to acute physical signs and symptoms[67] often incorporating cognitive impairment, neurobehavioral features and sleep/wake disturbance.[54]

Most concussion symptoms resolve in weeks to months,[54] but as many as 20-48% of those with military mTBI have persistent or prolonged symptoms including oculomotor, vestibular, cognitive, emotional, sleep, or exertional complaints.[68–70] This prolonged symptomatology once referred to as a “blanket” post-concussion syndrome (PCS) [71] is sometimes classified as one of three kinds of physical post-concussion disorders (PCD): physiologic PCD, vestibulo-ocular PCD, and cervicogenic PCD. [60] Physiological PCD may represent impairments to global brain metabolism, the energy crisis of the neurometabolic cascade,[30] and is often exacerbated by cognitive and physical activity.[72] One manifestation of acute and chronic physiological dysfunction after mTBI may be exertional intolerance, the worsening of symptoms after physical effort. While targeting specific impairments is important for focused rehabilitation,[4,73,74] there are often overlap of symptoms and other biopsychosocial factors associated with mTBI recovery.[75] Within the military, there is also a high prevalence of comorbid post-traumatic stress, depression, and sleep problems accompanying PCD at 3-12 months post-injury.[76,77]

The "poly-trauma clinical triad" illustrates overlap in symptoms across three conditions: mTBI, posttraumatic stress (PTS), and chronic pain, and is prevalent in the military population.[78,79] Common self-report measures used in the MHS to assess symptoms of each are listed in Table 2.1. Cifu [79] reported that most veterans with mTBI report comorbid pain or PTS complaints with more than half of the veterans having all three. Within the MHS, health care costs for a SM with mTBI were three times the amount of a healthy SM.[80] When a SM has the "poly-trauma clinical triad", health care costs are almost seven times the amount of a healthy SM. [80] PTS, chronic pain, and sleep disruption include concussion-like symptoms[81–84] making it hard to tease apart whether these symptoms are a result of mTBI, a comorbidity stemming from the injury, or a problem that preceded the injury because of military service.[85]

Table 2.1 Common Military Self-Report Measures

Variable	Measure of	Description
Neurobehavioral Symptom Inventory (NSI)[185,186]	Post-concussion symptoms	symptom severity, extent of disturbance by mTBI symptoms over last month
Defense and Veterans Pain Rating Scale (DVPRS) [187]	Pain severity and limitations	graphic tool to facilitate self-reported pain and how it affects mood, sleep, and stress in the last 24 hours
Posttraumatic Stress Disorder Checklist (PCL-5)[218,219]	Post-Traumatic Stress symptoms	Presence and severity of symptoms related to PTSD over last month

An individual's recovery trajectory is influenced by dynamic interactions between preinjury function (e.g., cognitive, behavioral, and psychosocial function, genotype), injury specifics and context (e.g., severity, frequency, mechanism), immediate post injury events (e.g., acute characteristics, diagnosis, treatment), and intervening life events (e.g., life stressors).[86] While predictors of clinical recovery vary between studies, in general, hypotheses exist that age and prior concussion history influence recovery, with younger age and greater lifetime concussions correlating with longer recovery.[87] While evidence supports pre-injury mental health factors such as depression or post-traumatic stress are associated with persistent symptoms,[69,85,88] more research is needed on migraines, headache history, and neurodevelopmental disorders like ADHD to understand how these factors influence outcome.[87,89] The acute symptom burden of mTBI may contribute substantially to prolonged symptom recovery,[90–93] moreso than traditional measures of injury severity like loss of consciousness or amnesia.[86,94] A greater acute symptom burden likely reflects the combined effect of neurobiology, adverse acute psychological reactions and greater preinjury propensity towards experiencing symptoms.[87] For military servicemembers, the prevalence of the "poly-trauma clinical triad", repeat exposures to mTBI, and various mechanisms of injury may contribute to increased risk of prolonged symptoms.[69,78,79,95,96] Although complete recovery is expected in most mTBI cases, this timeframe may take weeks to months, and the long-term consequences are still unknown.[97–99]

Since symptoms often affect multiple domains encompassing cognitive, balance, vestibular, visual, mood, and sleep/wake disturbances,[100] the currently recommended and widely utilized clinical assessment of concussion involves a multifaceted test battery, including balance, cognition, and self-reported symptoms after a potential injury event using baseline test scores and reference values.[16,32,54] While underreporting of concussions remains highly problematic, this multifaceted assessment approach is highly sensitive to the diagnosis of concussion (0.89–0.96) once a concussion is suspected, with neurocognitive tests having the lowest sensitivity.[101] The Sports Concussion Assessment Tool version 5 (SCAT5) is a sideline evaluation tool for sports concussion and is often the first assessment a clinician completes after an athlete sustains a suspected concussion.[54,102] The SCAT5 includes the Standardized Assessment of Concussion (SAC), a valid and reliable cognitive battery in assessing acute effects,[103] symptom ratings, and orientation questions.[54]

Baseline (premorbid) measures are typically not available for deployed servicemembers in contrast to athletes. The Automated Neuropsychological Assessment Metrics (ANAM) is completed pre and post deployment, but reliability is inconsistent and use of ANAM data for clinical management is not widespread.[104,105] DVBIC released the Military Acute Concussion Evaluation (MACE) in 2006 specifically for assessing the mechanism of injury, acute characteristics, and cognitive deficits in military personnel.[106,107] Building on the SCAT5, but targeted for a military population, the MACE provides a quick, initial assessment of acute injury. The MACE includes a historical portion that documents injury, loss of consciousness, and acute symptoms and an objective testing that replicates the SAC. In 2018, DVBIC released the MACE2,[108] which added the Vestibular/Ocular-Motor Screening (VOMS).[109] Like many neurocognitive assessments, the MACE lacks sensitivity and specificity and is not used beyond 12 hours after injury, but may provide one component of a multidimensional approach to mTBI assessment.[106] While much research has focused on a diagnostic biomarker including advanced neuroimaging, fluid (blood, saliva, cerebralspinal fluid) biomarkers, and genetic testing,[54] currently there is no single measure used to diagnose mTBI.

Acute Recovery Progression after Concussion

Current recommendations for sports concussion rehabilitation include a brief 24-48 hour period of physical and cognitive rest followed by an exertional "return to activity" progression once stable and administered by monitoring symptom response.[54] Clinicians may instruct a patient to wait until they are “asymptomatic at rest” before beginning activity, based on the increased risk of re-injury during the acute period of metabolic dysfunction that may result in exacerbated symptoms and prolonged recovery.[110,111] Animal models of TBI also exhibit worsened pathologies following unrestricted physical activity.[112] However, studies found that after mTBI, animals who were allowed to exercise voluntarily had better recovery outcomes especially if the rats were active preinjury.[113–115] Recent evidence in humans suggests that prolonged rest may not be beneficial in recovery and strict rest in some cases was associated with adverse sequelae. Rather, physical deconditioning, reactive depression and anxiety are suggested as a result of prolonged physical and cognitive rest.[28,116] Therefore, research into active rehabilitation is shifting the concussion management paradigm as studies show earlier cognitive and physical activity may be beneficial and may decrease recovery time.[4,117] Most recommendations include the use of 24-48 hours of rest since "asymptomatic at rest" is difficult to define.[118] Low level monitored activity may be beneficial in symptomatic individuals. It remains a challenge to know how much rest is necessary for an individual, the timing of initiation of physical activity or whether to prescribe exercise after a concussion.[4,31,72,119]

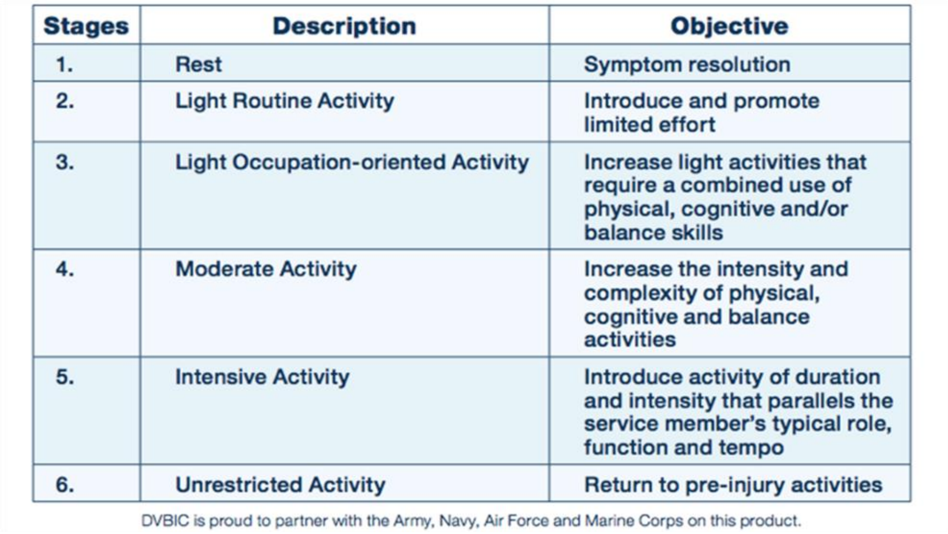
Current return to play (RTP) protocols for sports concussion follow a step wise progression beginning with rest or no activity as the first step, followed by light aerobic exercise, sport-specific exercises, non-contact training drills, full-contact practice, and concluding with full return to play in a game situation.[54] Each stage of the progression assesses symptom exacerbation as a checkpoint to move to the next level and only one stage can be completed within a 24-hour period. The level and extent of exercise in each stage often relies on clinical judgment, therefore the use of a standardized exercise test could help guide decisions around activity progression.[120] While this gradual increase in activity (return to play progression) was not developed for rehabilitation, treatment reviews mounting evidence suggests that interventions including cervical and vestibular rehabilitation, cognitive behavioral therapy, multifaceted collaborative care, and closely monitored sub-symptom threshold exercise may be of benefit.[121–123]

Return to Duty after Military Concussions

Military medical treatment clinicians, especially in deployed settings, are currently challenged to objectively assess spectrum of vulnerabilities associated with mTBI. Currently clinicians facilitate recovery and decrease risk of cumulative injury by focusing on early rest and graded return to activity based on sports concussion guidance. Clinicians commonly determine duty readiness based on the absence of symptoms and return to “normal” performance on clinical assessments that may have ceiling effects in the military.[37] The tendency of military personal to downplay or underreport symptoms increases the risk of premature RTD. This “military culture” of pushing through discomfort following concussion can lead to an elevated risk of PCS, increase likelihood of repeat exposure, and creates greater risk to self and unit due to diminished situational awareness.[47] It is especially critical to have adequate diagnostic tools to accurately determine the recovery of mTBI.[116]

DVBIC worked with a group of clinicians and researchers to develop clinical recommendations for military primary care managers (PCM)[23] and rehabilitation providers in mTBI treatment focusing on a progressive return to activity.[52] Based on RTP guidelines

Figure 2.1 Stages of Progressive Activity Following Acute Concussion/mTBI[23]



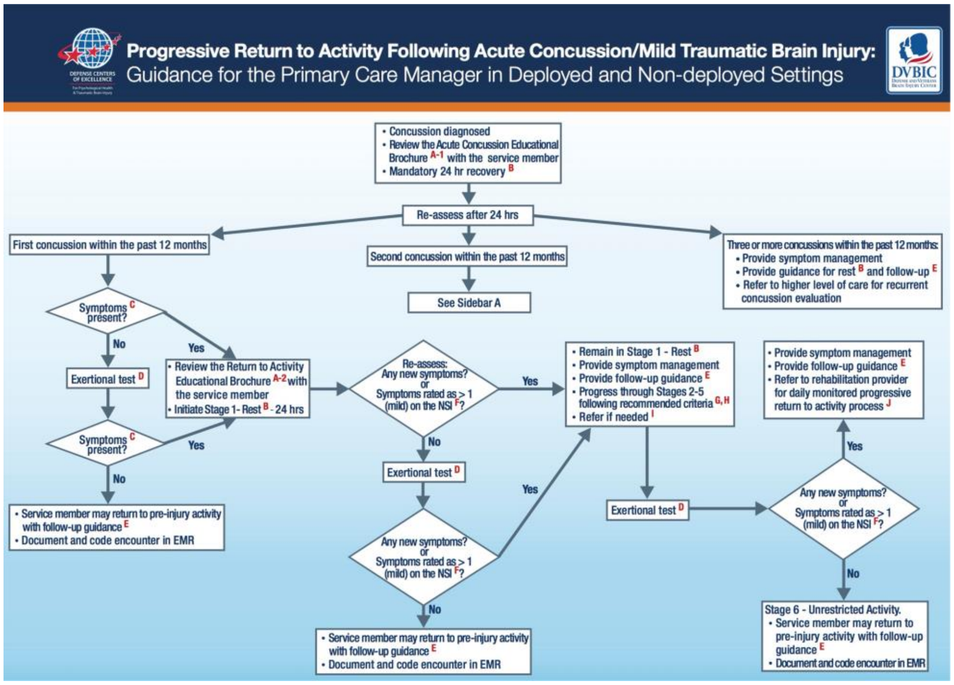
Stages	Description	Objective
1.	Rest	Symptom resolution
2.	Light Routine Activity	Introduce and promote limited effort
3.	Light Occupation-oriented Activity	Increase light activities that require a combined use of physical, cognitive and/or balance skills
4.	Moderate Activity	Increase the intensity and complexity of physical, cognitive and balance activities
5.	Intensive Activity	Introduce activity of duration and intensity that parallels the service member’s typical role, function and tempo
6.	Unrestricted Activity	Return to pre-injury activities

DVBIC is proud to partner with the Army, Navy, Air Force and Marine Corps on this product.

developed in sports concussion research, the six-stage progression (Figure 2.1) is outlined in the recommendations with a focus on patient education. Primary care managers treat the majority of acute concussions, with only a subset being referred to specialist or rehabilitation clinicians.[124]

Patients education remains a priority as it can increase adherence to rest acutely, improve understanding of recovery process and risk of re-injury, support gradual return to activity, and enhance compliance for follow-up.[125] While the PCM recommendations were released in 2014, recent efforts are focused on educating providers on the clinical implementation of the recommendations.[126] Clinicians who learn more about DVBIC recommendations demonstrate better recovery outcomes for patients with concussion.[127] The use of an exertional task is recommended as a tool to inform readiness to begin gradual return to activity (Figure 2.2), yet most clinicians do not report performing an exertional task during their exam. Possible obstacles for clinicians include the lack of a standardized exertional task, short appointment duration, limited space during appointments, and lack of follow-up appointments.[24,25,126]

Figure 2.2 Defense and Veterans Brain Injury Center Clinical Support Tool for Concussion/mTBI[23]



The nature of individual concussive injury and recovery remains complex. The neurometabolic cascade to describe the basic neurobiology of mTBI has been well studied in animal models and increasingly corroborated in human studies of mTBI.[30] The prevalence of exertional intolerance as a symptom shows that after concussion physiological impairments influence the ability of an individual to respond to physical stress.[3] Not all individuals report exertional intolerance after mTBI, since each injury is accompanied by its own diverse physical, cognitive and emotional symptoms acutely and sub-acutely. However, evidence supports that autonomic nervous system dysfunction may be contributing to a proportion of patients' symptoms.[13] Continuing to further understand the links between the pathophysiology of concussion and the early clinical signs and symptoms may lead to prevention of repeated injury and appropriate use of domain focused therapies.[30,119]

AUTONOMIC NERVOUS SYSTEM CHANGES POST CONCUSSION

The Autonomic Nervous System is a vital contributor of vascular and cardiac regulation and functions without conscious voluntary control.[13] The sympathetic branch of the ANS is responsible for the "fight or flight" response which involves the whole body and includes a release of epinephrine and norepinephrine from the adrenal medulla, as well as a widespread vasoconstriction in the body.[128] The parasympathetic branch helps to conserve energy under resting conditions ("rest and digest") by decreasing the heart rate (HR), and is more active at night.[3] The ANS also innervates cardiac muscle, smooth muscle, and various endocrine and exocrine glands throughout the body, helping to regulate organ systems to respond optimally to changes in the internal or external environment. If ANS fibers to an organ are cut, the organ may continue to function, but capacity to respond to changing conditions are compromised.[129] The ANS plays a critical role in regulating blood pressure, HR, gastrointestinal responses, thermoregulation and metabolism involving multiple feedback loops in the body, including the hypothalamic–pituitary–adrenal axis and immune systems.[130]

The ANS contributes to the regulation of blood vessel diameter throughout the body. After mTBI, the role the ANS has in cerebral perfusion, the flow of blood in the brain, has been a research focus.[3] The two main ways the ANS affects cerebral perfusion regulation are 1) to regulate baroreceptors, a system to maintain tolerances of overall blood pressure entering the brain based on ANS modulation of cardiac functioning, and 2) to provide extrinsic innervation of surface cerebral blood vessels by the ANS.[3] Baroreceptors at the carotid sinus have a sensitivity and tolerance to respond to changes in arterial blood pressure,[131] part of a reflexive ANS feedback loop to maintain stable blood flow to brain tissue.[131] Upon standing the baroreflex increases blood pressure and pulse to avoid fainting. Cerebral arteries and arterioles respond to sympathetic nerve stimulation with constriction, while parasympathetic activation causes dilation. Alterations in cerebral blood flow (CBF) are one of the most lingering metabolic changes associated with concussion in animal models[30] and observations in patients with concussion show anomalies in cerebral perfusion may persist for months, and correlate with post-concussive symptoms.[132–135]

It is hypothesized that mTBI leads to subtle impairments of the central autonomic network that may induce cardiovascular autonomic changes.[136,137] The central autonomic network is a complex network in the central nervous system involving the cerebral cortex amygdala, hypothalamus, and brainstem centers that assure autonomic regulation.[13] A lack of connection between the ANS and cardiovascular system may impair the normal response to change.[129] For instance, observations after concussion suggest an overactive SNS, reduced PNS activity, and less efficient responses to autonomic challenges.[6,7]

Although the cause of concussive symptoms is likely multifactorial, one possible contributor to impairments is ANS dysfunction.[3,4] Various methods of ANS measurements have been studied after mTBI including heart rate variability (HRV), exertional conditions, pupillary dynamics, eye pressure, transcranial doppler, and arterial pulse wave in those with mild TBI.[3,138,139] Most studies have shown ANS dysfunction in concussion post-injury that is characterized as reduced parasympathetic involvement and suboptimal response to autonomic challenge of position change or isometric hand grip.[9,137,140] Autonomic dysregulation, specifically cerebral perfusion anomalies and baroreflex inefficiency, has also been found in disorders with similar symptom profiles to concussion including depression, chronic pain, and insomnia.[82,141–144]

Heart Rate Variability

Heart Rate Variability (HRV) is an ideal non-invasive physiological measure to monitor concussion recovery, but few well-controlled studies have specifically examined the contribution of ANS branches to HRV during concussion recovery.[97] HRV quantifies how the period of time between two successive heart beats (inter-beat intervals) is not exactly the same,[3] largely driven by PNS and SNS regulation. The variability of these inter-beat intervals (IBIs) is considered a marker of ANS balance, as both branches work together to optimize heart output to situational demands.[3,12] Higher HRV is associated with better emotion regulation and stress adaptability to physical demands of the day.[11,145] HRV also influences circadian rhythm so that it fluctuates, typically being higher at night during sleep, and lower during the day.[146]

HRV is also influenced by baroreceptor reflex activity, breathing rate, hormones and many external factors[97] and is often used to describe the control of autonomic cardiovascular function.[13] The current “gold standard” for HRV analysis includes electrocardiogram (ECG) data collected for at least five minutes.[147] ECG modalities such as the Faros180 are optimal, since the sequence of times between R-peaks can provide a non-invasive (but not non-contact) measure of the neural regulation of the heart,[148] but this type of measurement is not always feasible. Multiple studies utilize other recording methods that are less expensive,[149] including the use of high quality of HR monitors like the Polar H10. Polar HR IBIs are reliable compared to ECG in a resting state and under exertional conditions.[40,150,151] Hernado et al. found HR monitor and ECG methods to be interchangeable when analyzing HRV at rest.[40] During high intensity exercise, the two methods still had high correlation ($p>0.8$) and excellent reliability and agreement indices (above 0.9).[40] Since some studies found lower reliability under higher exertion conditions,[152] we will test our study sequence with both the Polar H10 HR monitor and Faros180 ECG.

HRV Analysis

The two standard metrics for measuring HRV include a time domain analysis (changes over time) and a frequency domain analysis (measurement of a spectrum of oscillatory components of the heart).[13] HRV analysis helps with identification of neurophysiological mechanisms of behavioral, psychological, and health parameters by determining sensitivity of specific HRV components.[149]

HRV analysis uses principal components analysis to determine rhythmic frequency elements that are theorized to reflect specific pathways of ANS neural regulation.[153–155] Heart

Table 2.2 Heart Rate Variability Components Description

HRV component	Characteristics	Translation to ANS
RSA or HF[44,45]	high-frequency band (0.15–0.4 Hz)	Parasympathetic input
LF[157]	low-frequency band (0.04–0.15 Hz)	PNS, SNS, baroreceptor & peripheral vasomotor activity that regulates blood pressure
Total HRV or HP[149]	average IBI over a period of time	Flexibility/balance of ANS

Period (HP) represents the average IBI over a period of time. One salient variable associated with respiratory oscillation, is Respiratory Sinus Arrhythmia (RSA) also described as high frequency (HF) HRV.[44] RSA has been validated as a representative measure of parasympathetic input.[45] A slower frequency rhythm (low frequency LF) is theorized to capture baroreceptor and peripheral vasomotor activity that regulates blood pressure.[156,157] Some authors describe the LF component as representing sympathetic input, but evidence points to more heterogeneous contributions from parasympathetic, sympathetic, and baroreceptor input all contributing to LF HRV.[157,158] Likewise, some researchers have used LF:HF ratio as a marker of sympathovagal balance[159] based on autonomic reciprocity (increased activation of either parasympathetic or sympathetic system is accompanied by inhibition of the other). However, this simplistic model is not supported by current research. The interaction between parasympathetic and sympathetic input is likely more dynamic and complicated.[157,160] Many variables are described in the HRV literature, with a lack of consensus on those that are most important to track during exercise and following concussion. This study focused on the HRV variables described in Table 2.2.

ANS and HRV during Exercise

At the initiation of exercise, it is expected that HRV decreases due to withdrawal of PNS input to allow the heart rate to rise while CO_2 increases, leading to increased blood pressure.[161] As the intensity and/or duration of physiological work continues, SNS outflow increases, causing greater stroke volume. Then arterial chemoreceptors signal to the brainstem to increase respiratory and heart rate to enhance CO_2 off-loading and buffer blood.[137] The metabolic reflex then drives the system and the transition between ANS control and metabolic drive can vary between individuals and over time due to training adaptations or a transient neurological impairment such as mTBI.[21]

Healthy athletes demonstrate vagal tone that is characterized by the predominance of parasympathetic activity at rest with higher RSA levels during exertion and followed by a faster recovery than untrained individuals.[162,163] In moderate exercise (rest to 70% VO_2max), Perini found the decrease in HRV was largely due to LF decrease as the HF power may slightly increase above resting.[164] RSA is detectable during both exercise and recovery. Early studies found RSA decreased during absolute exercise and progressively increased during recovery.[163]

HRV After Concussion

Although previous studies have found abnormalities in HRV in concussed individuals under different conditions (e.g. rest, isometric handgrip exercise, aerobic exercise), others have failed to find these changes.[16] Hiltz et al[9] found differences in HRV components (decreased HP, LF, HF) at rest, whereas Abaji et al[43] found that only during an exertional isometric handgrip task were HRV impairments exposed including lower RSA and total HP. Both of these studies included subjects with wide ranges of time since injury, therefore some of the participants in these studies may have recovered. (Table 2.3) HRV disturbances post-concussion can persist past symptom resolution and return to play protocols in athletes.[8]

A recent systematic review suggests cardiac autonomic function (HRV) is altered during physical activity after a concussion.[21] Table 2.3 summarizes HRV-mTBI study designs and results. Studies with large ranges of time since injury may limit interpretations to acute mTBI The majority of HRV-mTBI studies have methodological limitations including lack of reporting of confounding variables, small sample size, varied duration of recordings, lack of within-subject and between-subject comparisons, and unexplained analysis strategies.[41,97,147] Variables that could affect HRV include demographics such as age, sleep, physical fitness, alcohol and caffeine intake.[11,97] These limitations make comparisons between studies difficult and the implications of the findings unclear.[97]

Few studies have investigated military populations specifically but Mirow et al. [10] reported long-term evidence of hyperactivation of the sympathetic nervous system (measured by LF/HF), while Tan et al.[165] reported impaired HRV in veterans with concomitant diagnoses of mTBI, PTS, and chronic pain. Very few studies have examined HRV acutely or subacutely in a military population.[165] A study of acute mTBI (72 hrs. post-injury) in an active duty cohort found that HRV measures during postural changes (sit to stand, supine to stand, etc.) had a high sensitivity in classifying individuals with mTBI. (Gotshall et al, unpublished)

Table 2.3 Summary of HRV-mTBI Studies

Author	N (mTBI)	Time Post Injury	Measurement Time	HRV Measures	Results/Conclusions
Mirow 2016[10]	61 (only mTBI)	3 mo. – 5 yrs.	24 hr.	LF/HF as sympathetic activation	SNS Hyperactivation
Tan 2009[6]	28 (only mTBI)	Not stated	15 min resting	Total HRV (SDNN)	Lower HRV compared to pop norms
Abaji 2016[17]	24 (12)	95 days (65)	At rest Isometric hand grip	Freq. domain	<u>Exertion</u> Reduced HF Higher LF/HF
Gail 2004[6,17,43,165]	28 (14)	~5 days	At rest During 10 min cycle	HP, HF, LF, HF/LF	<u>Exertion</u> Reduced HP. HF
Hutchinson 2017[7]	42 (21)	First week, and week after RTP	2 -5 min seated, standing	Freq./time domain	<u>Seated</u> Increased LF Decreased HF <u>Transition to Standing</u> decreased reactions to change
Senthinathan 2017[8]	22 (11)	1 week, asymptomatic, 1 wk. RTP	2 - 5min seated 1 5min standing	Freq./time domain	<u>Seated</u> Reduced HF <u>Transition to Standing</u> decreased reactions to change
Hilz 2011[9]	40 (20)	20 mo. (5-43)	Supine then 1 min standing	Freq/time domain	Reduced HP both conditions Reduced HF
Lino 2016[136]	247 (165)	2 weeks, 6 weeks, 12 weeks	5 min resting HRV	Freq domain	Reduced HP at all timepoints
Sung 2016[159]	164 (181)	First week, f/u 3,6 mo.	5 min resting	Freq domain	Reduced HP Reduced HF Reduced LF
Su 2005[194,]	35 (18)	Admission to ED	5 min	Freq domain	No dif in LF, HF, or LF/HF
Bishop 2017[8,9,138,161,220,221]	32 (12)	First week	Resting then squat-stands	Freq/Time domain	Reduced HP
Gilchrist 2018	32(31)	72 hours	3 posture changes with3 min standing	Only total HRV	Mean RR lower during transition

Most HRV studies with mTBI that have included exertion have used very short tasks, such as isometric hand grip or 10 second squat-stands.[43,161] During the initiation of longer aerobic exercise, mTBI participants have a slower increase in HR and may have lower HR at corresponding RPE conditions than HC reflecting a lack of ANS flexibility.[42] No mTBI study to date has analyzed HRV during the heart rate recovery time period after exertion. Heart rate recovery describes the period after exercise when physical capacity is regained and sustained.[48] During heart rate recovery, the parasympathetic (vagal) activation begins to dominate the ANS over sympathetic activity and is predicted to take longer due to ANS impairments after mTBI.[42]

HRV may be useful to assess and monitor the recovery status of concussed SMs. The diverse and sometimes conflicting HRV results in the current literature are likely influenced by both the complex nature of concussive injury and control of cardiovascular function along with individual physiological differences.[16] Continued HRV-concussion research that addresses and minimizes limitations is warranted.[41] As a simple, non-invasive and cost-effective approach, HRV can be applied in a number of easily administrable clinical protocols that challenge both the cardiovascular and autonomic nervous systems.[97] Implementing HRV measurement during exercise for the military population is important because of the physical demands and high stress of military culture, and the evidence that neurobiological recovery might extend beyond clinical recovery.[31,166]

EXERTIONAL TASKS

Current standard of care recommends physical and cognitive rest following an mTBI, followed by gradual return-to-activity.[54] Clinicians must judge when a patient is physiologically ready to return to higher levels of exertion. The use of a clinical exertional assessment could provide a way to evaluate exertional tolerance in a controlled and safe environment.[167] Currently, there is no criterion standard protocol for activity assessment after mTBI and outcome measures vary between studies. Heart rate, symptom checklist, rate of perceived exertion (RPE), and blood pressure are the most commonly assessed measures.[167] Individuals with mTBI report a higher RPE during aerobic exercise at the same heart rate.[42]

Exertional tasks have high utility of provoking ANS anomalies after concussion. The degree of autonomic dysregulation can be elucidated by examining HR control upon initiating and engaging in an exercise task.[42] A lack of control over parasympathetic withdrawal on cardiac rhythm, resulting in a dampened sympathetic response with initiation of exercise has been observed after concussion.[114] After exercise during heart rate recovery, this response shifts to one of sympathetic hyperactivity as the appropriate parasympathetic-sympathetic balance is restored.[42] The first 30 seconds of heart rate recovery after exertion is mediated primarily by vagal reactivation, independent of sympathetic withdrawal (exercise intensity) while at two minutes post exertion, heart rate recovery is affected by sympathetic nerve activity and exercise work load.[168] A heart rate recovery of less than 12 beats per minute (bpm) in the first minute is considered a low value and associated with health concerns.[169]

Exertional tasks also play an important role in the management of concussion. Graded exercise testing has been studied as a method to safely and reliably diagnose physiologic/ autonomic dysfunction in concussion from other subtypes as well as promising results as a component of rehabilitation.[60,72,170] Moderate physical activity does not hinder recovery after concussion.[171] Asymptomatic individuals may benefit from exercise as prolonged rest can lead to physical deconditioning which may further impair autonomic control of CBF. [172] Exercise training improves CBF regulation, ANS balance, and CO_2 sensitivity, and can have other positive benefits.[72,173,174] Exercise also upregulates BDNF genes, enhancing neuroplasticity, and may improve mood and sleep quality.[170,175]

Buffalo Concussion Treadmill Test

The Buffalo Concussion Treadmill Test (BCTT) is a safe[34] and reliable[120] standardized assessment designed to aid in diagnosis of physiological dysfunction in mTBI.[22] The BCTT was developed by Leddy and Willer and is based upon the Balke cardiac treadmill test, a safe and standardized test used for cardiac and orthopedic patients.[34] It can last up to twenty minutes with an incremental ramp protocol, where first the incline and then the speed increases progressively. Blood pressure, HR, RPE, and symptom scores are assessed throughout the protocol and monitored for safety considerations. The outcome is the submaximal symptom-limited threshold, which is determined by the HR when symptom exacerbation occurs. This HR threshold from the exercise test to prescribe subthreshold aerobic activity to begin graded return to exercise.[22,42] The BCTT can be a valid measure of readiness to begin the return to activity process.[22]

While the BCTT was originally tested in a chronic PCS population, studies have found that an acute mTBI population can safely complete the BCTT.[46] Individuals completing the BCTT within the first 48 hours had no difference in time to recovery from concussion.[46] Lower HR threshold on the BCTT also predicted longer recovery times,[46] which demonstrates possible ANS dysfunction. The BCTT was designed for a rehabilitation environment, and therefore is not always feasible in primary care due to time, equipment, and personnel. Return to activity readiness is established after successful performance of provocative exercise without symptom exacerbation.[176] An alternative exertional task is needed for the primary care environment.

Return to Duty Assessments

Previous military research has focused on the development of RTD assessments for service-members experiencing long-term effects of mTBI.[37,177–179] These tasks were created for a rehabilitation setting with dual and multi-task paradigms to detect subtle deficits that may persist in servicemembers with chronic symptoms.[37] The Assessment of Military Multitasking Performance (AMMP), which consisted of six ecologically valid tasks, included a Patrol task with a physical component of a stepping task at a constant level of exertion (70% HR max).[180] Continued research on developing similar RTD test batteries that can be implemented in the clinic is a priority for the field, yet little research has been done in RTD assessments with an acute mTBI population.

Exertional tasks are safe and feasible in an acute population. The BCTT has also been tested in an acute mTBI population within 48 hours post injury and had no effect in symptom severity or duration of recovery.[174] Squat-to-stand sequences and step protocols have been tested in an mTBI population to collect HRV data.[161] While DVBIC recommends the use of an exertional task to determine readiness for progressive return to activity, there is currently no validated or standardized task recommended for this test, which is likely contributes to a lack of exertion test implementation. DVBIC suggests at least two minutes at 65-85% of target heart rate (THR=220-age) using push-ups, sit-ups, running in place, step aerobics, stationary bike, treadmill and/or hand crank.[181] We developed two short exertional tasks from the DVBIC example list (step testing, push-ups) where heart rate is monitored throughout. Standards for a clinically feasible task include brief duration, easy administration, minimum space and equipment requirements so it could be implemented during PCM appointments.[24,25,37]

Exertional Task Development

Clinical exercise testing protocols typically utilize either an incremental approach (workload progressively increased over test protocol) or continuous approach (workload consistent throughout).[182] Reflecting the gradual progression of the BCTT and other mTBI-tested

Table 2.4 Overview of Step Tasks

Test	Step height/ cm	Steps/ min	Duration/min	Pacing
Master 2-step Test[222]	23 .0	30.0	3.0	Self-paced
Harvard Step Test[223,224]	50.8	30.0	5.0	Externally-paced (verbal cues, "up-2-3-4")
Harvard Pack Test[225]	40.0	30.0	5.0	Externally-paced
Astrand-Ryhming step test [226]	40.0 men 33.0 women	22.5	5.0	Externally-paced
4 box step test[227]				
Original	10, 20, 30, 40	30.0	3.0	Externally-paced (metronome)
Modified	2.0-50.0	30.0	20.0	
Kurucz Test[228]	38, 38, 50.8	24, 30, 30;	5 in each phase	Externally-paced (metronome)
Queen's College Step Test[229]	41.3	24.0 men 22.0 women	3.0	Externally-paced (metronome)
YMCA Step Test[230]	30	24	3.0	Externally-paced (metronome)
Chester Step Test[33]	15, 20, 25, OR 30	15, 20, 25, 30, and 35	2 min each phase	Externally-paced (metronome)

protocols, [120] an incremental approach was optimal for our step task. The majority of the step tasks tested in both healthy and clinical populations follow a continuous approach (Table 2.4), but the Chester Step Test [32,33,183] follows an incremental Bruce protocol (increased workload increments in relatively large adjustments every few minutes).[182] Unlike the ramping method of the BCTT, a Bruce protocol may be desirable for our military population since it is better suited for screening individuals who are young and physically active to allow for optimally challenging exercise capacity within a brief total testing time.[182] Therefore, a modified CST was designed including a maximum six minute protocol on a 10 in step. The key components of the CST of metronome paced stepping, increasing speed every two minutes, and monitoring heart rate all remained.[33]

As part of the Army Physical Fitness Test, a two-minute push-up task has clear external validity to servicemembers.[35] Whereas stationary cycle or handgrip assessments may not be transferable to everyday skills for individuals engaging in high levels of fitness, push-ups are both familiar and functional.[182] Push-up capacity has been previously used as an objective measure of functional status in healthy individuals where increased maximum push-ups correlated with better longitudinal health outcomes.[36]

A significant gap remains in our understanding of measures of readiness for duty after mTBI in an acute population. In the acute population, an exertional task is recommended before RTA and the establishment of an objective, clinically feasible exertional task could aid clinicians in RTA decisions. The use of physiological measures like HRV could clarify the extent of ANS impairments post injury that are currently missed in a clinical setting. The early prediction of those at risk for prolonged symptoms can allow for quicker referral and may influence the need for rehabilitation to optimize return to activity. Investigating the acute time period post mTBI is critical because that is when servicemembers are at increased risk of re-injury. Identifying any exertional or parasympathetic dysfunction is important for recovery and can decrease premature RTD.

CHAPTER 3: EXPERIMENTAL DESIGN AND METHODS

PARTICIPANTS

Aim 1

Participants were healthy individuals between the ages of 18-45 that exercise regularly (three or more times a week). Participants consisted of active duty servicemembers and healthy college students. Exclusion criteria were (1) any medical condition or injury that limits ability to perform a Physical Training (PT) session or moderate exertion for ten minutes, stepping, or push-ups, (2) history of moderate to severe TBI. Participants were recruited from the University of North Carolina and North Carolina State University as well as the Raleigh-Durham area. Recruitment is limited by level of participation in physical activity and an age range because it is more representative of the active-duty military population.

Aim 2, 3

Participants in this study were active duty service-members (men or women) from Fort Bragg Army Base. There were two groups (1) SMs who had sustained an acute mTBI and (2) age and gender matched Healthy Controls (HC). MTBI participants were ADSM that satisfied the following criteria: (1) diagnosed with acute mTBI in the previous 72 hours, (2) 18-45 years of age, (3) first mTBI in last 12 months, (4) no clinical evidence indicating greater than mild TBI. HC participants were ADSM that satisfied the following criteria: (1) eligible for deployment, (2) gender and age (+/- 2 years) matched to mTBI participants, (3) any prior concussions greater than one-year post-injury with no ongoing symptoms. In both groups, individuals with symptoms of mild or moderate behavioral health conditions or chronic pain could be included, but they could not be on activity restrictions or physical profile that would limit their ability to perform protocol physical exertion tasks. Full inclusion and exclusion are listed in Table 3.1 and 3.2.

Table 3.1 Aim 2,3 Inclusion Criteria for Study Participants

Individuals with mTBI:	**Healthy Controls:**
-Service men or women (active duty) diagnosed with acute mTBI in the previous 72 hours -18 to 45 years of age. - Individuals with symptoms of mild or moderate behavioral health conditions will be included, as will those who have complaints of chronic pain. -Functional vision and hearing	-Service men or women (active duty who remain with their unit and are eligible for deployment) -18 to 45 years of age. - Prior history of concussion is allowable if > 1 year prior and without ongoing symptoms as a result of that injury - Individuals with symptoms of mild or moderate behavioral health conditions will be included, as will those who have complaints of chronic pain. -Functional vision and hearing

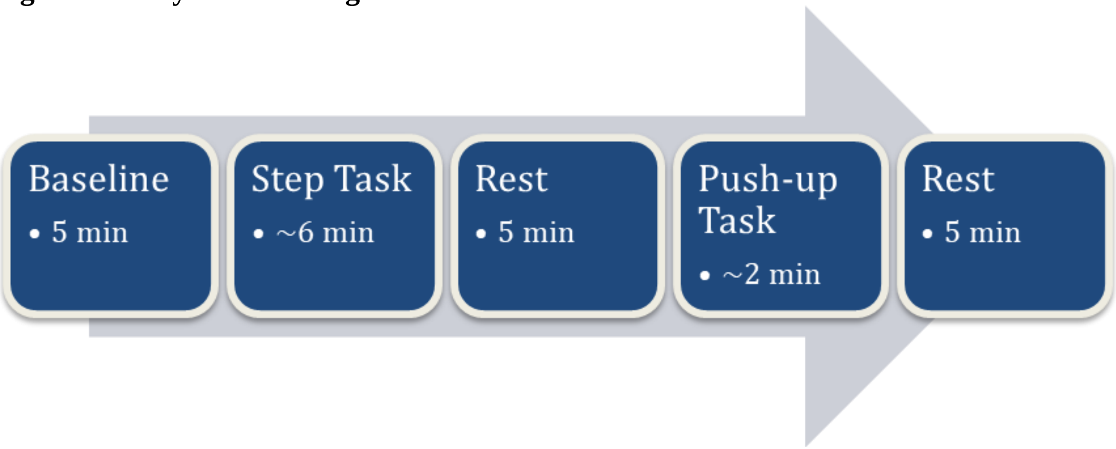
Table 3.2 Aim 2,3 Exclusion Criteria for Study Participants

mTBI only
-Any initial medical assessment of current injury indicating greater than mTBI/ concussion (e.g.: loss of consciousness of more than 30 min., post-traumatic amnesia of more than 24 hours, Glasgow Coma Scale score less than 13, alteration of consciousness (AOC) for longer than 24 hours) -Abnormal results on structural imaging studies (CT or MRI) related to current injury -Prior concussion within the past 12 months (greater than 12 months is allowable)
Both groups:
- SM diagnosed with severe brain injury or who have sustained a penetrating head injury. - SM has documented activity restrictions incompatible with safe performance of test protocol. - SM is at any stage of confirmed or suspected pregnancy. - Any type of heart pacemaker or other implanted electronic medical device -Cardiac conditions associated with blood pressure dysregulation including valvular heart disease, chronic bericarditis, vascular reconstruction - SM presents with any medical or behavioral health condition that render him/her unable to perform moderate exertion for up to 10 minutes and quick change of positions including getting up from the floor, rolling, running, jumping, and performing activity for up to 30 minutes. - SM has hearing deficits that render him/her unable to communicate effectively in a clinical or community setting, as the metronome-paced stepping-task requires functional hearing.
Relative Exclusion Criteria
- Following informed consent, as part of screening, the RA will describe the test protocol and then ask the SM if he/she would like to continue. Given the activities of the test battery, we anticipate an individual with significant pain complaints might choose not to continue study participation. If the SM agrees to participate and has difficulty, the task can be discontinued. We will honor SM concerns about their abilities, as they are most in tune to what they can and can't do physically.

RESEARCH DESIGN

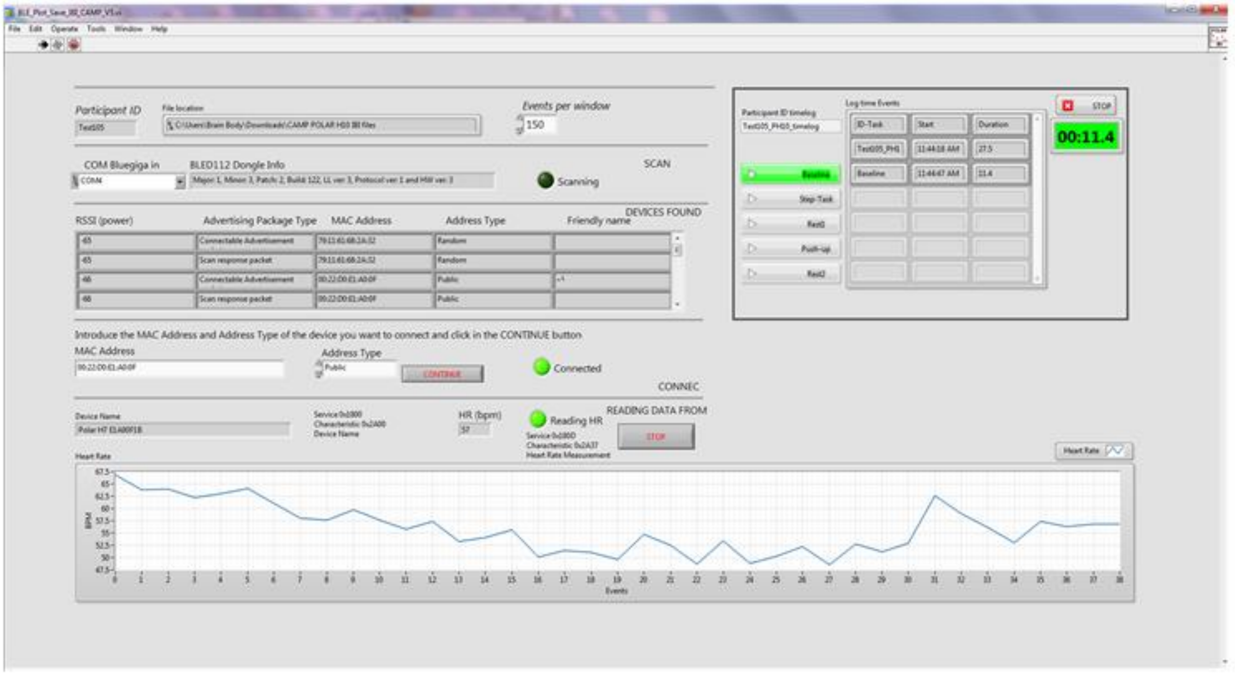
This quasi-experimental, known-group, single site study included one testing session. While Aim 1, used a different group of study participants to test feasibility and reliability, it provided support for the testing of Aim 2 and 3. All aims included the same testing sequence (Figure 3.1). We aimed to minimize study limitations associated with HRV by (Aim 1) testing reliability of data recordings of our full protocol with the "gold standard" ECG, and (Aim 2) age-and-gender matching, recruiting from a semi-homogenous population (e.g. activity levels, lifestyle), collecting data on specific factors known to affect HRV (caffeine, alcohol, sleep, depression), and following Task Force guidelines on other parameters (e.g. duration, editing, analysis).[147] We also planned to target a specific duration since mTBI, which is lacking in many mTBI-HRV studies.[97] A LabVIEW™ platform was designed for Polar H10 data collection to ensure correct time point for our task sequence (Figure 3.2).

Figure 3.1: Layout of Testing Session



Note: exertional tasks were counterbalanced, Aim 1 had 3 min Baseline and Rest Periods.

Figure 3.2 LabVIEW™ Platform designed for study protocol



Participant ID: Test05

Events per window: 150

BLED112 Dongle Info: Major 1, Minor 3, Patch 2, Build 122, LL ver 3, Protocol ver 1 and HW ver 3

RSSI (power)	Advertising Package Type	MAC Address	Address Type	Friendly name
-65	Connectable Advertisement	79:11:61:68:2A:52	Random	
-65	Scan response packet	79:11:61:68:2A:52	Random	
-66	Connectable Advertisement	00:22:D0:E1:A0:0F	Public	
-66	Scan response packet	00:22:D0:E1:A0:0F	Public	

Introduce the MAC Address and Address Type of the device you want to connect and click in the CONTINUE button

MAC Address: 00:22:D0:E1:A0:0F

Address Type: Public

Device Name: Polar H7 E1A00F1B

Service 0x1800
Characteristic 0x2A00
Device Name

HR (bpm): 57

Service 0x180D
Characteristic 0x2A37
Heart Rate Measurement

Participant ID timelog: Test005_PH05_timelog

ID-Task	Start	Duration
Test005_PH1	11:44:18 AM	27.5
Baseline	11:44:47 AM	11.4

Aim 1

The experimental design included 1 testing session lasting approximately 45-60 minutes with the order of exertional tasks counterbalanced. Consent was obtained before any data was collected. All testing took place at the University of North Carolina at Chapel Hill in a laboratory space or office space in Raleigh. We recorded heart rate (HR) and inter-beat intervals (IBIs) continuously with two HR monitors: Polar H10 HR monitor (Polar Electro Oy, Kempele, Finland) and Faros180 device (Mega Electronics Ltd., Pioneerinkatu, Finland) for the entire session, starting with a 3 minute baseline in a seated position. After baseline, one exertional task was completed followed by a 3 minute recovery in a seated position, then the other exertional task, followed by another 3 minute seated recovery period. Participants wore the Polar H10 around their chest and the Faros180 was connected by three lead electrodes to the right and left collarbone and left ribcage. All testing procedures were approved by University of North Carolina at Chapel Hill Institutional Review Board (IRB), #17-0429.

Aim 2, 3

The experimental design included 1 testing session lasting approximately 45-60 minutes. Consent was obtained at the beginning if it was not obtained at the initial appointment. All testing took place at the Intrepid Spirit Center at Fort Bragg. Demographics and self-report surveys were collected prior to the testing sequence shown in Figure 3.1. We recorded heart rate (HR) and inter-beat intervals (IBIs) continuously via the Polar H10 HR monitor (Polar Electro Oy, Kempele, Finland) throughout the session, starting with a 5 minute baseline in a seated position. Participants wore the Polar H10 monitor around their chest. After baseline, one exertional task was completed followed by a 5 minute recovery in a seated position, then the other exertional task, followed by another seated 5 minute recovery period. The exertional tasks were counterbalanced and mTBI participants completed the same sequence as the matched HC. HC of variable ages were tested and mTBI participants were matched as they were recruited to avoid further limiting enrollment. All testing procedures were approved by Womack Army Medical Center (WAMC) and The US Army Regional Health Command- Atlantic (RHC-A) IRB, #2019-001.

PROCEDURES

Recruitment and Consent

Aim 1

Healthy volunteers were recruited from flyers, email, and recruitment briefings. Individuals interested in participating provided contact information to the study coordinator, who followed-up for scheduling. Screening occurred via a “self-screening” procedure with inclusion/exclusion explained in person or research team conducted follow-up. Volunteers were free to opt out based on age, physical limitations, activity tolerance, or medical history at any time during any phase of the testing procedures.

Aim 2, 3

Healthy control participants were recruited from those who had expressed interest in participating in the study and had filled out a contact index card at briefings arranged by the DVBIC Regional Education Coordinator (REC). The REC conducts several monthly large group informational briefings at different locations on Ft. Bragg covering topics including concussion education and awareness, services available at the Intrepid Spirit Clinic, and research initiatives conducted through DVBIC and/or the Intrepid Spirit Clinic. Potential volunteers could also contact study staff and express interest using study contact information obtained from these materials. Control participants recruited for this study were of variable ages which could allow for age (+/-2 years) and gender matching to mTBI participants as they were enrolled. Pre-screening procedures for healthy control participants occurred via a 'self-screening' method whereby potential volunteers were given basic inclusion criteria of age and being concussion free for at least one year then were asked to consider volunteering only if they meet those basic criteria.

Recruitment of mTBI participants was done in collaboration with primary care providers at the Department of Brain Injury Medicine at Intrepid Spirit Clinic or at Robinson Health Clinic and at the new “PEACE” program, an acute mTBI education program, at the ISC. Providers identified individuals who had sustained a mTBI within 24-72 hours and a member of the study provided information about the study. Consent procedures, screening and enrollment could occur at this initial appointment, however testing did not occur until the individual reported absent or mild symptoms (scores of < 2 on our global symptom scale question; Appendix 1) at rest and the participant was within 2 weeks of the injury. Testing could occur at a follow up appointment when the service member was being considered for release from medical care and return to activity. Pre-screening procedures for mTBI participants included referral from the individual's primary care provider at their initial post injury visit indicating they had a qualifying injury for inclusion consideration.

Consenting procedures occurred in a private office space within the Intrepid Spirit Center, in the same office where other test procedures will be conducted. The consent process was followed by the formal screening that described all inclusion and exclusion criteria and testing procedures. SMs were free to opt out based on age, physical limitations or medical history at any time during any phase of the testing procedures. Consent and screening will take approximately 15 minutes.

Self-Report Measures

Aim 1

Participants completed a demographic questionnaire including questions on concussion and military history. Specific questions on sleep, pain, and caffeine drinks were also included, to address factors that influence HRV.

Aim 2, 3

Participants completed a series of clinical assessments at baseline to characterize personal and health history, concussive symptoms, and pain limitations including:

1. Demographic questionnaire includes specific self-report questions addressing current military occupational specialty (MOS), duty status, concussive history, PTS, sleep, readiness for combat, deployment history. The PHQ-2 surveys depressive symptoms with two questions that are valid and reliable to detect depression..[184]

2. Neurobehavioral Symptom Inventory (NSI) is a valid and reliable measure of post-concussive symptoms. The NST consists of 22-item self-report symptom questions where individuals rate the severity of each symptom within the past 2-weeks on a 5-point Likert scale ranging from 0 (none) to 4 (very severe).[185,186]

3. Defense and Veterans Pain Rating Scale (DVPRS) is a valid and reliable pain measure that was developed specifically for the military population. The DVPRS consists of an 11 point numeric pain rating scale (0-10) that includes word and facial descriptions, and domain specific questions about pain interference in activity, mood, sleep, and stress in the last 24 hours. [187]

All baseline self-report measures are outlined in Table 3.3.

Table 3.3 Aim 2,3 Baseline Self-report Measures

Variable	**Data Source**	**Description**
Demographics	Survey	Current MOS, duty status, concussive history (#), PTS (Y/N), sleep
Neurobehavioral Symptom Inventory (NSI)[185,186]	Survey	symptom severity, patient self-report to indicate the extent to which each mTBI symptom has disturbed them
Defense and Veterans Pain Rating Scale (DVPRS) [187]	Survey	graphic tool to facilitate self-reported pain

Exertional Tasks

Both of the exertional tasks require minimum equipment, space, and time. The exertional range for heart rate (65-85% of predicted HRmax) was monitored using HRmax estimations from the Fox and Haskell's[188] (HRmax = 220 − age) equation. This equation was chosen because it is simple, commonly used, part of the BCTT protocol[34], and one of two HRmax equations recommended for use in military populations for graded exercise tests.[189] Clinicians commonly monitor symptoms (headache, vertigo, photophobia, balance, dizziness, nausea, visual changes, etc.) and HR before, during, and after an exertional task to assess physiological recovery and prescribe activity.[167] Similar safety measures from the BCTT were applied.[120] During both exertional tasks, heart-rate was monitored real time via Bluetooth, and rate of perceived exertion-RPE (Borg scale) and symptoms on a 0-10 Likert scale were assessed every minute (Table 3.4). Rate of perceived exertion (RPE), a subjective measure of workload, allowed us to investigate its relationship to actual HR during exercise.[167] Evidence supports that concussed patients may report a higher RPE at a lower heart rate during the BCTT.[42]

Table 3.4 Data collected during testing protocol

Variable	Data Source	Description
Heart rate (HR)	Polar H10 monitor Faros180*	Target range for exertion, measure recovery
Inter-beat Intervals (IBIs)	Polar H10 monitor Faros180*	Used in HRV analysis
Symptom scores	Self-report during exertional tasks each minute	0-10 Likert scale with faces and description, modified from BCTT symptom scale Safety measures to assess symptoms
Borg RPE	Self-report during exertional tasks each minute	6-20 numerical rating scale with colors and descriptions to measure exertion, used in BCTT Safety measures to assess rate of perceived exertion
Exertional task completion	Performance assessment	Yes/no if participant could complete full task at expected standards

*only collected during Aim 1 part of the study

The examiner stopped testing if participant HR is greater than 85% of predicted HR max, the RPE on the Borg scale is >16, the participant reports an increase >2 on the symptom scale, or the examiner perceived that testing was unsafe. The participant was also instructed that they could discontinue testing at any time if needed. If a participant could not complete the first task due to concussive symptom exacerbation that does not resolve in the 5 minutes of rest between tasks, the second task was completed.

Step Task

The stepping exertional task was adapted from the Chester Step Test protocol.[33] The Chester Step Test was shown to be a valid test for the estimation of aerobic capacity in a healthy population. The error of measurement is sufficiently small and suggests that this method is well suited to monitoring changes in aerobic capacity in rehab settings.[190] Our step task was a maximum of six minutes in duration, as a participant will step on and off a 12-inch step at the pace of a metronome- starting at 80 beats per minute (bpm) (equaling 20 steps per minute) and increasing by 20 bpm at each of 3 levels that last 2 minutes. The test was discontinued for the safety reasons mentioned above and also if the participant cannot keep up with the pace.

Table 3.5 Instructions for Step Task

Condition	Instructions
Step Task	"You will begin to step at the rate of the metronome and the pace will increase every two minutes, at my instruction. This task will have three different speed levels and will last for a maximum of six minutes. You can switch your lead leg if you wish. At the beginning of each minute I will ask your rate of perceived exertion (Borg RPE) and symptom level (Likert scale). At my prompting, state the number on both scales that best represents how you are feeling. If at any time you feel overtired, breathless or dizzy then please stop and recover. Do you have any questions? Listen to tone of metronome prior to stepping and begin when ready"

Push-up Task

The push-up task was two-minutes in length where participants were instructed to complete as many push-ups as they can for a maximum of two minutes. This is especially relevant for military populations since it is part of the Army Physical Fitness Test. The test was discontinued for safety reasons mentioned above or if the participant relaxed from plank position to rest at any point.

Table 3.6 Instruction for Push-Up Task

Condition	Instructions
Push Up Task	"During this push-up task you will complete the maximum push-ups that you can at one time or complete push-ups for two-minutes, whichever comes first. Push-ups can be self-paced. If you release from plank position or rest on ground during the testing, we will stop the test. At one-minute, I will ask your rate of perceived exertion (Borg RPE) and symptom score (Likert scale). At my prompting, provide the number on both scales that best represents how you are feeling. If at any time you feel you cannot continue for whatever reason, then you may stop. Do you have any questions? Begin when you are ready."

Data Processing and Reduction

HRV Measures

Aim 1

Data collected from the Polar H10 were reduced from the heart rate electrical signal to an IBI value by the devices. The Faros180 recorded a complete ECG waveform at 1 kHz. Inter-beat intervals (IBI), the time between consecutive heartbeats expressed in milliseconds, were derived from detected R peaks in ECG using the Cardio Peak-Valley Detector (CPVD) [191] to derive the IBI event series. The CPVD is a LabVIEW™ based algorithm that extracts peaks or valleys of different physiological waves, such as the ECG, photoplethysmography (PPG), and respiration.

Prior to analysis, each sequence of IBIs was first synchronized automatically to timelog, then manually inspected to ensure proper alignment of the IBI series (e.g., the IBIs from the Polar H10 and the ECG derived IBIs). Each aligned sequence was then transformed into a 2 Hz equally sampled time-series by linear interpolation. This step is involved in the extraction of HRV parameters, and also prevents the two series from becoming de-coupled.

The unedited IBI file was visually inspected and edited offline with CardioEdit software (developed in the Porges laboratory and implemented by researchers trained in the Porges laboratory). Editing consisted of integer arithmetic including dividing intervals between heart beats when detections of R-wave from the ECG were missed or adding intervals when spuriously invalid detections occurred. The resulting normal RR intervals were used in analysis when abnormal beats, like ectopic beats (heartbeats that originate outside the right atrium's sinoatrial node) were removed[12]

HRV frequency components were calculated with CardioBatch software (Brain-Body Center, University of Illinois at Chicago), which implements the Porges-Bohrer metric.[154] This metric is neither moderated by respiration, nor influenced by nonstationarity, and reliably generates stronger effect sizes than other commonly used metrics of RSA. Analysis steps are described in depth by Porges et al.[192] and validated in Lewis et al.[154] To determine RSA, a third-order, 21 point moving polynomial filter (MPF) was applied to the 2 Hz IBI time series to remove low frequency oscillations and slow trend. The residual detrended output of the MPF was filtered with a Kaiser FIR (finite impulse response) windowed filter with cut-off frequencies that removes variance not related to spontaneous breathing in adults (0.12 to 0.40 Hz). The filtered detrended output was divided into sequential 30-second epochs and the variance within each epoch was transformed by a natural logarithm (ln(ms2)). The mean of these epoch values was used as the estimate of RSA for the specific segment. To determine LF values, a third-order, 51 point moving polynomial filter (MPF) was applied to the 2 Hz IBI trend to remove extremely low frequency oscillations and slow trend. The residual detrended output of the MPF was filtered with a Kaiser FIR windowed filter with cut-off frequencies (0.04 to 0.10 Hz). The filtered detrended output was divided in 30 second epochs and the variance within each epoch is transformed with a natural logarithm (ln(ms2)). The mean of the epoch values was used as an estimate of LF for the segment.[193] Heart Period was derived from the mean IBI for each epoch used in frequency component analysis. Data variables include: 1) Average Heart Rate 2) Respiratory Sinus Arrhythmia (i.e., RSA or high frequency HRV defined by the frequencies of spontaneous breathing (.12-.4 Hz), 3) Low Frequency HRV (i.e., i.e., occurring within the frequencies of spontaneous vasomotor and blood pressure oscillations; .06-.10 Hz), and 4) Heart Period.

Aim 2

Bluetooth allowed for direct transfer of the Polar H10 data to the laptop with time logs. HRV components were extracted from Polar IBI data [45,154] to evaluate changes in neural regulation of the ANS before, during, and after exertional tasks. HRV analysis used principal components analysis to determine rhythmic frequency elements that are theorized to reflect specific pathways of ANS neural regulation.[153,154] The same processing procedures used for Aim 1 were applied in Aim 2.

DATA ANALYSIS

Means, standard deviations, medians, interquartile ranges, and 95% confidence intervals were calculated for all demographic and questionnaire data where appropriate. Alpha was set *a priori* at $a < 0.05$ for all statistical analyses. Only participants with complete data were analyzed for each specific aim. Normality was assessed for all dependent variables using the Shapiro-Wilk test. For any outliers information on caffeine or sleep questions were used for exploratory analysis.

Data Analysis for Aim 1

To test the feasibility of two exertional task protocols for use in military population

1.A, 1.B. To test clinical feasibility and physiological response observational measures will be the primary means of analysis.

1.C. To compare the Polar H10 generated IBI values with the IBI values generated by the Faros180 ECG signals.

Independent measurements were examined by visualizing the distribution between the mean measurement and the difference.[194] Bland–Altman (B-A) plots enabled the determination of agreement between two sensors, by plotting the mean between pair of measurements against its difference. Visual inspection of the B–A plots was used to identify systematic biases and possible outliers. Paired *t*-tests evaluated whether the differences between the signals were biased (i.e., one signal source generating longer or shorter values). B–A plots and the *t*-test were performed on IBIs collected from all participants during all tasks. Scatter plot and linear regression analyses were used to visualize and calculate the level of convergence between the Polar H10 and Faros180. A strong correlation of threshold of $R^2=0.9$ or higher of IBI time series represented strong agreement. Value of the partial eta-squared for the TIME effect, obtained by repeated measures ANOVA of the HP, RSA, and LF for each sensor across the five tasks was used to evaluate if the effect size of the experimental manipulations observed by the two sensors were in the same magnitude and of the same level of significance.

Data Analysis for Aim 2

To examine HRV measures at baseline, during exertional tasks, and throughout recovery in both mTBI and healthy service-members.

For Aim 2, the variables of primary interest were the heart rate variability (HRV) measures including RSA, LF, HR, and HP. For Aim 2, task completion, ratings of perceived exertion (RPE), and symptom scores were additionally of interest. Following best practices, all statistical estimates were reported along with their 95% confidence intervals (C.I.s). For each HRV measure we used linear regression models with generalized estimating equations (GEE) to estimate differences (and 95% CIs) for tasks throughout the session (e.g., baseline, step, rest 1, push-up, rest 2). GEE takes into account within-person and between-person variance in the differences. To compare group differences, we used independent t-tests at specific timepoints: baseline, exertional (push-up and step task), and recovery (rest 1 and rest 2).

Data Analysis for Exploratory Aim 3

To compare two short clinically feasible exertional tasks that are relevant for military populations in terms of tolerability and self-report exertion.

For Aim 3, to compare task completion we will use logistic regression models with generalized estimating equations (GEE) to compare the odds of task success (completion of step task, 60 pts on APFT for push-ups) among the two exertional tasks; we will present odds ratios and 95% CIs of task completion. In addition, we will use linear regression models with GEE to estimate mean differences (and 95% CIs) on RPE and symptom scales between tasks.

Table 3.7 Aims 2,3 Statistical Tests

	Independent/ Predictor Variable	Dependent/ Outcome Variable
Descriptive Statistics (Aim 2,3)	mTBI or Healthy Control	Baseline demographic data (e.g. years in service, physical readiness to deploy in 72 hours;) clinical measures (e.g. NSI)
Independent T-tests (Aim 2) – during each task	mTBI or Healthy Control	HRV measure (e.g. RSA, LF, Total HRV)
Logistic Regression (Aim 3)	Stepping task or Push-up task	Step: Ability to complete full task without stopping (Yes/No) Push-up: Passing APFT score (Yes/No)
Linear Regression (Aim 3)	Stepping task or Push-up task	HRV, RPE, and symptom scores

CHAPTER 4: SUMMARY OF RESULTS

Aim 1

To test the feasibility of two exertional task protocols for use in military population and reliability of a commercially available HR monitor

Results

Participants

A total of fifteen healthy adults completed our testing protocol. Thirteen of the participants were active reservists for the United States Marine Corps. Four of the Marine participants had a history of concussion and nine have been deployed serving an average of 2.8 deployments (SD=0.8). Full demographics are presented in Table 4.1 and 4.2.

Table 4.1. Demographic characteristics of Aim 1 Participants. Values are n (%) or M (SD),

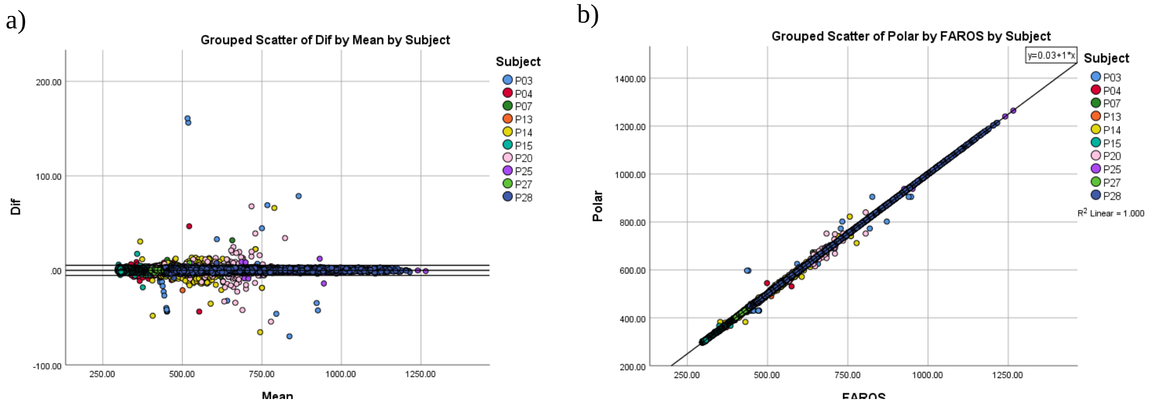
Characteristic	N=15
Age in years	29.33 (6.36)
Sex	
Women	2 (13.3%)
Men	13 (86.7%)
Race/Ethnicity	
Caucasian	7 (46.7%)
Hispanic/Latino	4 (26.7%)
African American	2(13.3%)
Native American	2(13.3%)
Education	
High School	1 (6.7%)
Trade School	1 (6.7%)
Some college/ Associate's Degree	8 (53.3%)
Bachelor's Degree	4 (26.7%)
Advanced Degree	1 (6.7%)
Military Affiliation	
USMC	13 (86.7%)
None	2 (13.3%)

Table 4.2. Military and Health History of Aim 1 Servicemembers. Values are n (%) or M(SD).

Characteristic	N=13
Time Serving	10.0(5.5)
Military Rank/ Pay Grade	
E1-E5	4 (30.8%)
E6-E9	6 (46.1%)
O1-O3	3 (23.1%)
Deployment History	
Yes	9 (69.2%)
No	4 (30.8%)
Concussion History	
Yes	4 (30.8%)
No	9 (69.2%)
Behavioral Health History	
Combat Stress	1(7.7%)
Post-Traumatic Stress	2 (15.3%)
Anxiety	2 (15.3%)
Depression	1(7.7%)
Caffeine (drinks/ supplements in last 24 hrs.)	1.9 (2.0)
Sleep (hrs. in last 24 hrs.)	5.7 (1.2)

Ten participants had complete data for both the PolarH10 and the Faros 180 devices after a Bluetooth issue was identified and resolved. The Faros180 did not consistently detect HR peaks during push-ups and required more than 5% editing of total IBIs (beyond the recommended editing standard from HRV Task Force guidelines),[147] therefore the reliability analysis focused on the stepping task alone. Visual inspection of the B–A plot located in the A panel of Figure 2 demonstrate excellent agreement and minimal bias between the sequential IBIs measured with PolarH10 and Faros180 (color coded by participant). The B–A plots suggest that error magnitude was driven by a few participants and the IBI differences were closer to zero on the left side with shorter IBIs (higher exertion). A scatterplot with regression analyses contrasting the sensor pair is illustrated in the B panel of Figure 4.1. The linear regression of RSA between PolarH10 and Faros180 (ECG) provide excellent fit to the IBI data with R^2 of 0.984 for the model of y= 0.99x+5.23.

Figure 4.1: Bland–Altman and scatter plot for inter-beat interval (IBI) from the Faros180 (ECG) and PolarH10, a) Plot of the IBI differences vs the means for the Faros180 and PolarH10. Outer black lines indicate the 95% confidence interval. b) Scatter plot of the Faros vs PolarH10 IBIs

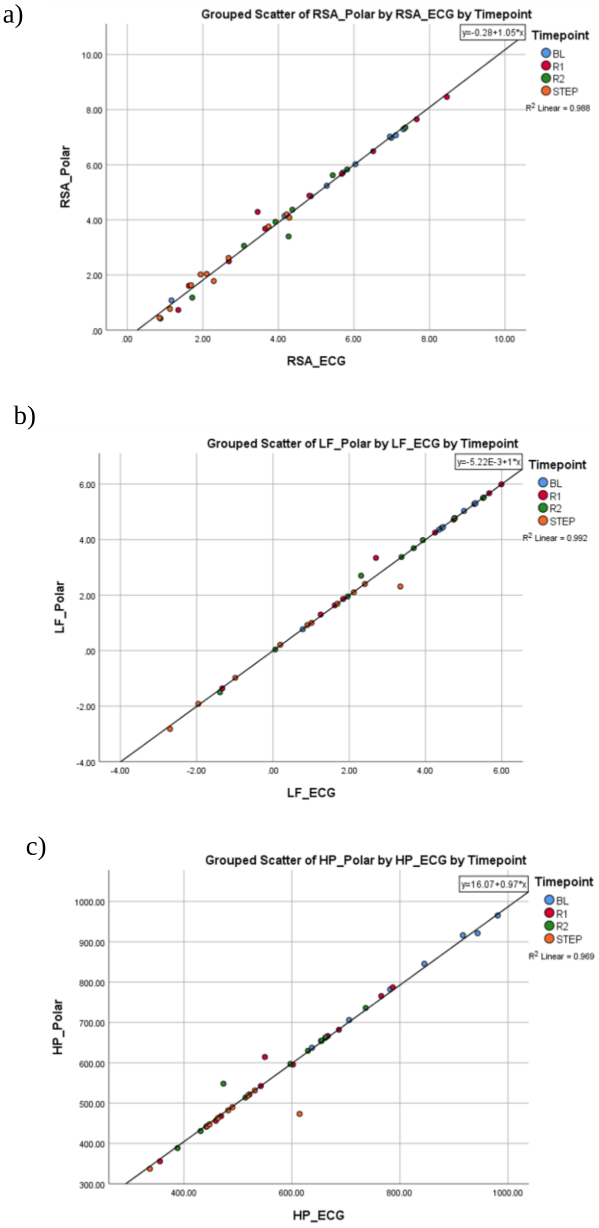


After HRV analyses were completed for the IBIs from both sensors, a scatterplot with regression analysis (Figure 4.2) contrasted the derived HRV components from the sensor pair and confirmed excellent fit with R^2 above 0.90. GEE was used to demonstrate the sensitivity of both sensors regarding the change across timepoints in each HRV parameter. For RSA, sensor type was not a significant predictor (Z = 1.81, p-value = 0.07) showing that for our protocol both methods of HR recordings yielded RSA component results that were not significantly different from each other. The exertion Step task compared to resting time points (BL, R1, R2) was a significant predictor of lower RSA (BL: Z = 1.99, p-value = 0.046 R1: Z = 4.78, p-value = <0.001, R2: Z = 3.07, p-value = 0.002) with estimates of 0.98, 2.05, and 1.23 greater than the Step value respectively. Similarly, for LF, sensor type was not a significant predictor (Z = 0.03, p-value = 0.29) of LF value supporting the reliability of the Polar10. Yet, the Step task was a significant predictor of lower LF compared resting points (BL, R1, R2) (BL: Z = 7.61, p-value = <0.001 R1: Z = 6.59, p-value = <0.001, R2: Z = 5.18, <0.001) with estimates of 2.36, 2.35, and 1.76 respectively. For HP, sensor type was not a significant predictor (Z = 1.91, p-value = 0.06) but Step task was a significant predictor compared to resting time points (BL, R1, R2) (BL: Z =

7.77, p-value = <0.001 R1: Z = 4.33, p-value = <0.001, R2: Z = 3.67, p-value= 0.002) with estimate of 284.07, 123.92, and 103.12 respectively with the Step task causing a decrease in HP.

Figure 4.3 shows how BL, Step, and "Rest directly after step" compare between the sensors in RSA, LF, and HP.

Figure 4.2: Scatterplots between Sensors for HRV components, color coded by timepoint a) respiratory sinus arrhythmia (RSA), b) Low-frequency (LF), c) Heart-Period (HP)

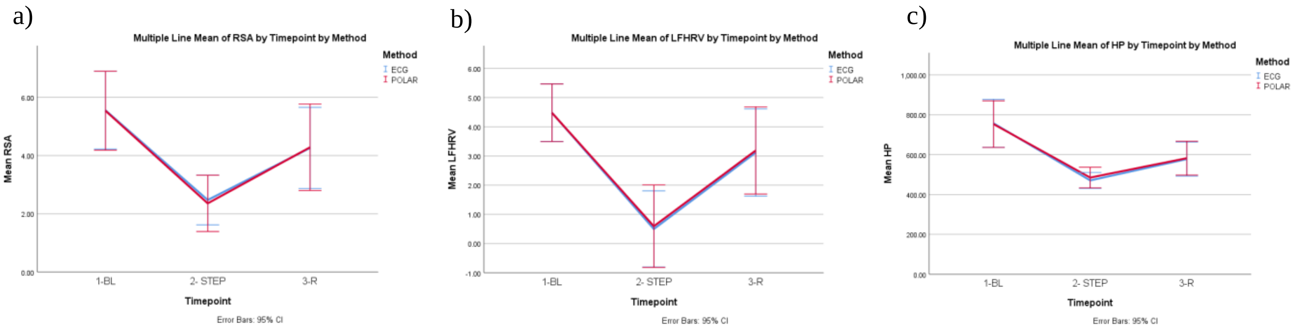


Clinical and Physiological Feasibility

All fifteen participants were able to complete both tasks as instructed without the examiner having to stop based on safety criteria. None of the participants reported symptom exacerbation during either task. HRV analysis was feasible for all of the phases (BL, ST, R1, PU, R2) based on IBI recordings from the commonly available PolarH10.

Both the stepping and push-up task evoked appropriate exertional physiological responses. All participants reached 60-85% of age predicted HRmax during the six-minute step test and the two minute push-ups. During the stepping task participants reported RPEs between 12 and 16 at least once during the task. Fourteen of fifteen participants reported RPE ratings in the exertional range (12 to 16) for the push-up task.

Figure 4.3: Mean of HRV measures at Baseline, Exertion, and Rest after Exertion for Faros180 (ECG) and PolarH10. a) Respiratory sinus arrhythmia (RSA), b) Low Frequency (LF). c) Heart Period (HP). Exertional task is stepping task and rest is recovery period right after step task.



Summary

We found the PolarH10 recordings of beat-to-beat heart rate data for the exertional protocol collected through Bluetooth capabilities to be accurate and reliable compared to the gold standard ECG recordings. We also found excellent reliability and agreement indices of the HRV components between sensors based on analysis of the step task and rest periods.

The step task and push-up task were clinically feasible requiring minimal time, space, and equipment for administration. Both exertional tasks evoked an appropriate physiological response in terms of heartrate (60-85% of Age-predicted VO2 max) and perceived exertion (≥12 on Borg RPE) in healthy controls. Both tasks are of greater difficulty than current commonly used concussion balance assessments with the goal of minimizing ceiling effects. [37] Testing our exertional task protocols in healthy participants allowed us to ensure feasibility, assess adequate physiological response, characterize HR recovery, make protocol improvements, and confirm reliability of a more affordable and clinically available HR monitor.

Aim 2

To examine ANS balance at baseline, during exertional tasks, and throughout heart rate recovery in both mTBI and healthy service-members.

Results

A total of 29 participants completed the testing protocol including 4 SMs with acute concussion and 25 healthy controls. Six of the HC participants reported a concussion history and one was excluded from healthy control analysis due to exhibiting increased symptoms during both exertion tasks. Full demographics are presented in Table 4.3.

Table 4.3. Demographic Characteristics of Servicemembers that Performed Testing Protocol

Characteristic	Healthy Controls N=25	mTBI N=4	p-value
Age in years	25.7 (5.9)	31.5 (8.7)	0.10[1]
Sex (Male)	25 (100%)	4 (100%)	1.00[2]
Race/Ethnicity			
Caucasian	14 (56%)	2 (50%)	0.381[2]
African American	5 (20%)	0 (0%)	
Hispanic	3 (12.0%)	2 (50%)	
Asian/Pacific Islander	2 (8.0%)	0 (0%)	
Other	1 (2.0%)	0 (0%)	
Education			
High School	9 (36%)	1 (25%)	0.008[2]
Associate's Degree/ Some college	11 (44%)	2 (50%)	
Bachelor's Degree	1 (4%)	1 (25%)	
Advanced Degree	4 (16%)	0 (0%)	
Years in military	5.1 (5.5)	9.0 (5.4)	0.20[1]
Been Deployed (Y)	8 (32%)	3 (75%)	0.10[2]
Neurobehavioral Symptom Inventory (NSI) Total	5.5 (8.6)	24.3 (13.3)	<0.001[1]
Defense and Veterans Pain Rating Scale (DVPRS) Total Functional Score	2.4 (4.1)	8.5 (7.0)	0.02[1]
0-10 Numeric Pain Rating Scale (#1 on DVPRS)	0.56 (1.0)	1.5 (1.3)	0.11[1]

Table 4.3. NOTE. Values are n (%), mean (SD). [1]t-Test, [2]Chi-Square, * p-value=<.05

Heart Rate Variability

For each HRV measure, we used linear regression models with generalized estimating equations (GEE) to estimate task and group differences (and 95% CIs) throughout the session (e.g., baseline, step, rest 1, push-up, rest 2). Due to the small n of the mTBI group, we could not complete our planned analysis but do report preliminary analyses. For RSA, group (HC or mTBI) was a significant predictor (Z=-1.98, p-value=0.048) showing that throughout our protocol mTBI participants had a lower mean RSA of 0.90 compared to healthy controls. Also, the exertional task conditions (Step and Push-up) were both significant predictors of lower RSA with estimates of -4.14 and -3.15 lower than baseline respectively (Z=-19.74, p-value=<0.001, Z=-11.54, p-value=<0.001). In addition, there was no significant difference in HCs between baseline RSA and RSA during the last minute of Rest 1 or Rest 2 confirming that RSA recovered to near baseline levels during the five minute rest after each task (mTBI excluded). For the HRV components there was no significant difference between groups when including all timepoints, but we examined HRV measures at specific timepoints (baseline, exertional conditions, rest).

Tonic Measures

At baseline, there was a significant difference in mean RSA between our mTBI (M=5.62, SD=0.79) and HC (M=6.67, SD= 1.19) group; t(26) =2.311, p-value=0.02. There were no significant differences in HP between mTBI and HC groups at baseline (Table 2). Under exertional conditions, there were no significant differences on any of our HRV measures between groups. During the recovery periods, there was a significant difference in RSA between

Table 4.4: Group Differences in Tonic Heart Rate Variability Measures at Different Timepoints
$^{\#}$=Independent T-tests, * p-value=<0.05

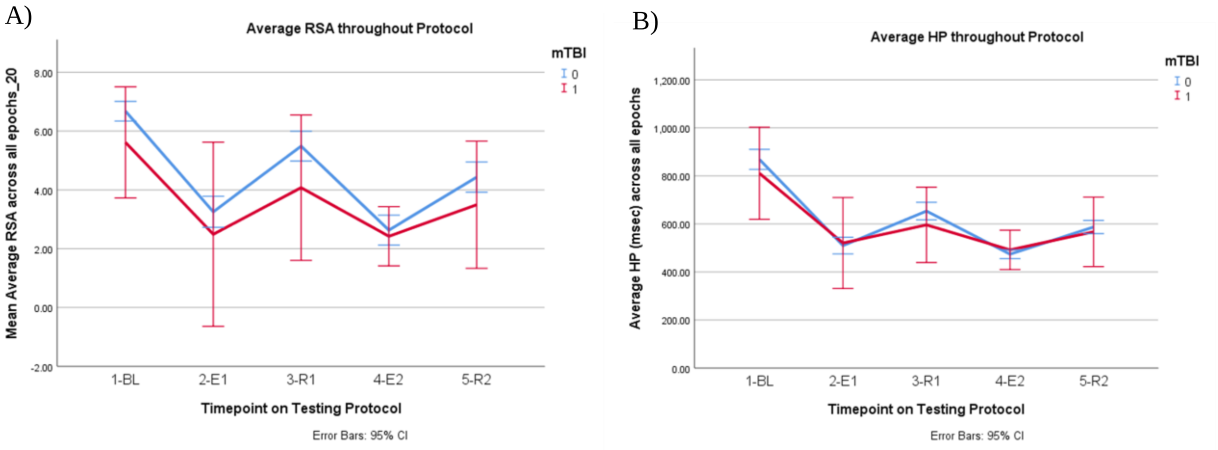
Variable	Time point	Group	M(SD)	Mean difference (95% CI)$^{\#}$
Respiratory Sinus Arrhythmia (RSA) or High Frequency (HF) HRV	Baseline	HC	6.64 (0.79)	1.03 (.078-1.97)*
		mTBI	5.61 (1.19)	
	Exertional Tasks	HC	2.95 (1.27)	0.49(-.51-1.50)
		mTBI	2.45 (0.86)	
	Rest Periods	HC	4.89(1.29)	1.11(0.10-2.11)*
		mTBI	3.79(1.39)	
Heart Period (HP)	Baseline	HC	861.09 (93.5)	50.2(-58.13-158.53)
		mTBI	810.88 (93.64)	
	Exertional Tasks	HC	500.69 (53.22)	-14.58(-69.04-39.89)
		mTBI	552.01 (51.28)	
	Rest Periods	HC	612.79(75.55)	31.31(-28.28-90.90)
		mTBI	581.49(89.14) *	

mTBI (M=3.78, SD= 1.39) and HC (M=5.03, SD=1.28) groups; t(54) =2.521, p-value=0.015. There were no differences on mean HP measures between groups during the recovery periods.

Reactivity

There were no significant differences on the rate of cardiac vagal reactivity to exertional task measured by the slope of RSA nor rate of heart period reactivity measured by slope of HP during first minute of exertion between groups (Table 3). When looking at only second task reactivity (slope of RSA first minute during exertion), the mTBI group (M=-0.017, SD=0.049) and HC group (M=-0.058, SD=0.036) exhibited trend-level differences (t(25)=-1.98, p-value=0.058). Two HC did not complete the push-up task for a duration long enough to calculate a slope (1:00 allowed for 3 epochs).

Figure 4.4: Mean HRV Measures at Testing Timepoints for mTBI and Healthy Controls. A) Respiratory Sinus Arrhythmia (RSA), B) Heart Period (HP). 1-BL: Baseline, 2-E1: first exertional task, 3-R1: first rest period, 4-E2: second exertional task, 5-R2: second rest period



Recovery

There were significant differences in rate of heart period recovery after exertional tasks measured by the slope of HP during first minute after exertional task between groups (HP t(52)=3.41, p-value=0.001; RSA t(52)=1.95, p-value=0.056) with HC SMs having a steeper HP slope indicating faster recovery than mTBI SMs (Table 3). This difference was found in cardiac vagal recovery (slope of RSA) when examining a longer recovery duration of two minutes and still present in rate of HP recovery. (RSA t(52)=2.18, p-value=0.03; HP t(52)=3.32, p-value=0.002).

Exertional Symptoms

Fisher's exact test was used to compare task success and symptom exacerbation between groups. For task success (step task completion, 60 on push-up AFPT score), the Fisher's Exact test was significant (p=<0.001) between mTBI and HC with an odds ratio of 18.43 (3.08-110.23). For symptom exacerbation, Fisher's Exact test was significant (p=<.001) and all mTBI participants reported onset or worsening of symptoms during exertional tasks, despite reporting a level of symptoms that suggested readiness to return to activity. In addition, there was no difference in maximum RPE between mTBI (M=13.76, SD=2.4) and HC (M=14.1, SD=2.5) groups, t(54) =-0.39, p-value=0.69.

Table 4.5: Group Differences in Phasic Heart Rate Variability Measures during Reactivity and Recovery ($^{\#}$=Independent T-tests, * p-value=<0.05)

Variable	Time point	Group	M(SD)	Mean dif(95% CI)
Respiratory Sinus Arrhythmia (RSA) or High Frequency (HF)	Rate of Reactivity (slope of 1 min)	HC	-0.054(0.04)	-.024 (-0.06—0.01)
		mTBI	-0.030(0.05)	
	Rate of Recovery (slope of 1 min)	HC	0.037(0.04)	0.031(-0.001-0.062)
		mTBI	0.006(0.03)	
	Rate of Recovery (slope of 2 min)	HC	0.027(0.02)	0.016(0.002-0.03)*
		mTBI	0.011(0.02)	
Heart Period (HP)	Rate of Reactivity (slope of 1 min)	HC	-3.336(1.53)	-.592(-1.82-0.619)
		mTBI	-2.744(1.28)	
	Rate of Recovery (slope of 1 min)	HC	2.18(1.15)	2.10(0.86-3.32)*
		mTBI	0.084(3.25)	
	Rate of Recovery (slope of 2 min)	HC	1.98(0.78)	1.79(0.71-2.87)*
		mTBI	0.73(3.3)	

Case Description

A total of 4 participants with mTBI completed the testing protocol. Since the number of subjects was limited, we have included observational descriptions of each case. The order of exertional tasks was age and gender matched to a HC. In addition, a healthy control who had concussion related exertional issues is also described as a case. All 5 participants sustained their mTBI while completing airborne operations training duties. Descriptions of the cases are presented in Table 4.

In addition to the observational measures the tests provided, one SM reported his surprise on how “symptomatic” he still was and inquired if we could share this information with his command. The second case had previously reported being asymptomatic for three consecutive days prior to testing, but described a headache upon arrival to testing session since he had just stopped taking his headache medication. The third case, reported a “pounding” headache after stopping during the push-up task but when asked to re-score symptom on the symptom scale he scored it at 2/10 because it was tolerable.

Overall the healthy SM population was able to successfully complete both tasks consistent with our performance standards (88% push-ups, 84% step). Three SMs did not complete enough push-ups to get an age-adjusted score of 60 on the AFPT, but continued performing push-ups for the entire 2 minutes. Four SMs did not complete the Step task, one SM was stopped during testing because of a reported RPE of 17 at 5:00, 2 had a HR greater than 85% of the age-predicted HR max (one SM at 4:00 and another SM at 5:00), and one SM was unable to maintain with the required step cadence (age 41, with significant knee pain). At the end of the rest periods 76% of the HC reported a RPE of 6 and the remaining SMs reported either 7 or 8. In addition, the push-up task provoked symptoms in three SMs (N,H,F- all scores of 1), while the stepping task provoked symptoms in two (H, D-scores of 1-2).

Table 4.6: Case Descriptions of mTBI Participants. The symptom scale included headache (H), dizziness (D), Light/sound Sensitivity (S), Nausea (N), and Fogginess (F).

Subjects	Days Post Injury	NSI	DVPRS Total (#1)	Self-report RTD	Days of reporting min. sym.	Resting Baseline Values	First Task	Step Task Observations	Rest 1 Values	Push-Up Task Observations	Rest 2
Male, 32	5	6	6(1)	Y	4	H=1 RPE=6 HR=90	Step	Examiner stopped at 5:30 b/c HR exceeded 85% age-pred. Max. (H=1, RPE=11, HR=165)	H=1 RPE=10 HR=108	SM performed push-ups for 1:20 before stopping with the total# met standard for successful completion (total PU=38, H=2, RPE=12, HR=150)	H=1, RPE=8 HR=110
Male, 22	9	30	16(3)	N	2	H=1, N=2, S= 1 RPE=7 HR=82	Push-up	Examiner stopped at 4:00 b/c N increased from 2 to 5, RPE=17, and SM could not keep up with cadence (H=3, S=3, HR= 155)	H=2, N=2, S=3 RPE=9 HR=102	Examiner stopped at 1:00 after SM reported RPE=17 (total PU=44, H=3, HR=145)	H=4, N=4, S=2 RPE=11 HR=102
Male, 29	11	37	0 (0)	Y	4	F= 2 RPE=6 HR=72	Push-up	Examiner stopped at 5:00 b/c D increased from 1 to 4 (N increased to 1, RPE=15, HR=156)	D=1, F=3 RPE=6 HR=86	Examiner stopped at 1:00 b/c D increased from 0 to 3, (RPE=15, HR=117, total PUs=30)	D=1, N=0, F=3 RPE=6-7 HR = 99
Male, 43	13	24	12(2)	N	5	H=4 RPE=6 HR=63	Step	SM completed the full 6:00 (H=3, RPE=15, HR=128), reported N=5 after the end of task	N=4, H=4 RPE=8 HR=73	SM performed push-ups very slowly and stopped at 1:32 (N=4, H=4, D=1, RPE=11, HR=117 total PU=32)	N=4, H=4, D=2 RPE= 7 HR= 76
Male, 28	(2 yrs.)	34	2(0)	Y	(2 yrs.)	sym. =0 RPE=6 HR=64	Push-up	SM completed the full 6:00 (H=4, RPE=14, HR=150)	H=2 RPE=6 HR=65	Examiner stopped at 1:00 after SM reported H=5 (total PU=52, RPE=16, HR=130)	H=3 RPE=6 HR=78

Summary

Implementing HRV measurement during exercise for the military population is important because of the physical demands and high stress of military culture and evidence that cardiac autonomic function (HRV) is altered during physical activity after a concussion. [21] The stepping and push-up exertional tasks were designed to challenge SM performance to reveal impairments after acute mTBI safely while being clinically feasible. Preliminary findings revealed that RSA impairments are seen in our small concussed population and are more pronounced in the recovery periods after exertion, but not during the exertional tasks. Previous studies using tonic HRV measurements have found that RSA is lower under exertional conditions and at rest,[43,161] but tonic measurements alone may not be sufficient to determine the adaptation of a system when demand is placed upon it.[11] Our implementation of phasic measures allows for a more in-depth picture including reactivity and recovery.

The tonic differences in RSA at baseline observed in SMs with mTBI may result from lower self-regulatory resources necessary to foster adaptability during exertion.[195] While we did not find differences between mTBI and HC during exertion or in the rate of reactivity (slope during first minute of exertion) for RSA or HP components, there was a trend-level difference in the rate of reactivity for RSA in the second exertion task where mTBI SMs did not react as quickly. This is likely influenced by the differences in CVC recovery.

Recovery after exercise plays a crucial role in the adaptability necessary to face an event and then return to resting levels. [196] The lower tonic RSA found during recovery likely represent impairments to parasympathetic re-activation in CVC after exertion. In healthy individuals during heart rate recovery, the parasympathetic (vagal) activation begins to dominate the ANS over sympathetic activity as the cardiac autonomic network removes “central command”, which is especially critical to drive rapid decrease in HR.[42,197,198] During passive recovery, parasympathetic reactivation is aided by reduced feedback from muscle mechanoreceptors and resetting baroreflexes to a lower level.[197,199] If mTBI causes CVC impairments, we would expect that PNS reactivation would take longer for SMs with mTBI, which is reflected in the lower RSA during the recovery periods in our findings.

In addition, we found differences in the rate of recovery of vagal control (RSA slope during recovery) at 2 minutes after the start of the recovery period. The slope of HP was also significantly different at 1 and 2 minutes during recovery, demonstrating that SMs with mTBI took longer to recover. Previous studies have used one minute of heart rate recovery to measure immediate effects cardiac parasympathetic outflow [200,201] and 2-3 minutes as a longer measure.[201] This response soon after exercise is described as vagal recovery or “vagal rebound” and reflects the ability of an individual after facing a “stressor” to self-regulate and be prepared to face another stressor,[195] a vital component for ADSM with the high demands of the military.

We described the performance of specific individuals with mTBI on 2 exertional tasks and recovery after exertion. Participants with mTBI were more likely to have symptom exacerbation and with one exception were not able to successfully complete tasks compared to healthy controls as expected. While we expected the push-up task may be more symptom provoking due to the position changes required, both tasks provoked symptoms in all of our mTBI cases. Only two out of eight tasks completed by mTBI participants were successfully finished. The exertional tasks elicited symptoms that were absent at rest even in a SM with more chronic symptoms. Monitoring symptoms (headache, vertigo, photophobia, balance, dizziness, nausea, visual changes, etc.) and HRV before, during, and after an exertional task is a way clinicians can assess physiological recovery and prescribe activity.[167] CVC recovery has been positively correlated to performance outcomes (cognitive, prone rifle shooting) indicating a clear relevance for the military,[195,202] but future research is needed in how this can be implemented feasibly in the clinic.

These findings highlight the need for continued data collection and research in the recovery periods of individuals with acute mTBI so we can age match with healthy SMs. Physiological measures may be used alongside symptom report and clinician opinion in return to activity decisions. As a simple, noninvasive measure of ANS balance, HRV could act as an objective marker of recovery and may be a valuable addition in clinical care. Furthermore, standardized exertional assessments that are ecologically valid for military populations can be utilized by primary care managers to guide return to activity or return to duty decisions. Performance on such an exertional task can also help clinicians prescribe appropriate levels of activities, guide progressive return to activity, and may have utility as a predictor of duration of symptoms.

Aim 3

To compare two short clinically feasible exertional tasks that are relevant for military populations in terms of tolerability and self-reported symptoms during exertion.

Results

Due to the small N in our mTBI group, for this analysis we included our total study population (N=29) to compare tasks in terms of successful completion and symptom report.

The results from the logistic regression models with GEE showed no significant difference between the two exertional tasks (Step or push-up task) on predicting a participant's success of task (completion of step task, 60 pts on APFT for push-ups, p=0.78). The odds ratio for task success was 0.79 (95% CI, 0.214-2.98) and in our mTBI group there was no observational difference between task success (1 mTBI case successfully completed both tasks). In addition, linear regression showed task type was a not a predictor of symptom severity (95% CI, [-.94-.67], p= 0.73). Task type may influence RPE as linear regression showed that the push-up task may lead to a higher self-report RPE (95% CI, [-.24-.12], p= 0.07) and when looking at only the healthy participants there was a significant effect (p=.03, 95% CI, [-2.8-.11]). There was no difference in maxHR between tasks (95% CI, [-4.0 -12.6], p= 0.30)

Summary

In summary, our total study population had similar "successful" completion rates and symptom reports in both the step task and push-up. Both tasks provoked symptoms in a similar number of SMs (8 for push-up, 7 for step). However, the push-up task was more symptom provoking in our small cohort of mTBI cases, leading to discontinuation in three of our five cases (safety measure of >2 symptom increase), a "pounding" headache in the fourth, and the addition of new symptoms in the fifth. Healthy participants reported a higher RPE level in the push-up task when compared to the step task, but within the mTBI group there was no RPE difference between tasks. In addition, to these self-report and observational measures, there were no HR max differences between tasks.

The clinical relevance of these findings is that both tasks evoke a similar exertional response and could be performed safely by our participants with acute mTBI. While symptoms were exacerbated in both tasks, they mostly resolved during the recovery periods. The differences in duration of each task with the push-up task being much shorter likely influence why the higher RPE is not correlated with a higher recorded HR. The push-up task was not as standardized as the metronome pacing stepping task was that likely led to the differences in RPE. Yet, the brevity of the push-up task is advantageous in a clinical environment.

STUDY LIMITATIONS

As with any scientific study, the work has limitations. First, this study is not designed to follow individuals longitudinally; therefore we cannot draw conclusions about how task performance predicts recovery time. We could, however, examine any ANS and CVC dysfunction in resting, reactivity to exertion, and recovery after exertion within individuals with mTBI. Second, due to the limited number of mTBI participants enrolled to date, our statistical analysis could not control for confounds like age, sleep, physical fitness, and caffeine intake that could affect HRV[11,97] or other group differences. We are continuing to collect data and can control for these variables as numbers increase. During testing, we controlled for order effects by counter-balancing the sequence of exertional tasks with the matched mTBI performing the same order as the corresponding HC participant, which will be an advantage when we can sex and age match in our analysis. In addition, large between-subject variation is seen in many HRV components.[203] Our study design included within-subject analysis of HRV component changes through exertion before the between-subject comparisons of total change. In line with the HRV Task Force guidelines,[147] we minimized HRV limitations by implementing an editing standard of no more than 5% of total IBIs. With the many kinds of HRV analysis completed in the literature, time-domain analysis could be done in the future as an exploratory analysis and allow for comparisons between studies focusing on time-domain.

FUTURE STUDIES

Currently, an ongoing study in collaboration with the Intrepid Spirit Center at Fort Bragg is continuing data collection of SMs with acute mTBI with our testing protocol to investigate group differences with increased statistical power and ability to control for confounding variables like age, sleep, and caffeine. Also, in collaboration with University of Buffalo and Fort Bragg another study will build on this preliminary data and utilize the same HRV platform to investigate response to a six minute step task compared to the BCTT. Collaboration with DVBIC and military clinicians will improve the utility of our clinically feasible, exertional tasks by examining ways to implement objective physiological measures. In addition, the standardized, simple exertional task protocols we developed may be included as examples in updated DVBIC guidelines for military PCP treating acute mTBI. Further research, on the relationship of CVC dysfunction with different kinds of mTBI symptoms (and comorbidity of PTS and/or chronic pain) will provide insight on if and CVC plays a role in cognitive or emotional symptoms as proposed by the "Vagal Tank Theory".[195] Longitudinal studies where individuals with mTBI are tested at multiple time points will elucidate if or how HRV measures act as a marker of recovery after an acute mTBI.

CHAPTER 5: MANUSCRIPT 1 - THE DEVELOPMENT OF EXERTIONAL TASKS WITH PHYSOLOGICAL MEASURES AND UTLITY WITHIN MILITARY CONCUSSION

INTRODUCTION

Concussion or mild traumatic brain injury (mTBI) is a prevalent injury in civilians, athletic, & military populations alike. Over 380,000 service-members (SMs) have sustained a mTBI since 2000.[1] The rate of concussion continues to be significant in the garrison environment as a result of training exercises & non-duty activities of a young active population. MTBI results in a variety of symptoms that limit activity. Returning to normal activity too soon as well as prolonged rest have both been shown to increase symptom duration.[26–28] Clinicians commonly determine duty readiness based on the absence of symptoms and return to "normal" performance on clinical assessments that may have ceiling effects for military service members.[37]

The Defense and Veterans Brain Injury Center (DVBIC) has developed clinical recommendations for military primary care managers and rehabilitation providers for treatment and management of mTBI that incorporate current evidence, but at times rely on expert consensus for specific practice recommendations.[52–55] The Progressive Return to Activity Clinical Recommendation for Primary Care Providers outlines a five-stage activity progression, similar to sports concussion consensus return-to-play recommendations. The PRA recommends the use of an exertional test before return to activity and return to duty decisions. However, actual implementation of exertion testing is difficult, and there are no standardized exertional assessments that are clinically feasible or validated for primary care providers (PCP).

Patient self-report of symptoms serve as the primary measure that clinicians use to recommend return-to-activity,[29] but evidence shows that physiological deficits may persist beyond self-report symptom resolution.[30,31] The cause of concussive symptoms is likely multifactorial, but one possible contributor to impairments is autonomic nervous system (ANS) dysfunction.[3,4] The ANS drives interactive communication between the cardiac and the regulatory neural systems (i.e., the body and the brain) that may be disrupted after mTBI.[14,97] Regulatory ANS function can be assessed by the analysis of heart rate variability (HRV), which is the variation in time between successive heartbeats. HRV can serve as a proxy for 'top–down' integration of the brain mechanisms that guide flexible control of behavior with peripheral physiology and can provide insight on stress and overall health.[11,156] Higher HRV is associated with better emotion regulation and stress adaptability.[11,145,204] Therefore impaired HRV after concussion may be an indicator of deficits in how effectively resources underlying self-regulation are mobilized,[195] which may be correlated to symptom severity. HRV has the potential to be a target for intervention in mTBI through biofeedback.[14,205]

HRV incorporates input from the both the sympathetic and parasympathetic nervous systems, but also baroreceptors chemoreceptors. One critical component- Respiratory Sinus Arrhythmia (RSA, also known as high frequency, HF HRV), has been validated as a representative measure of parasympathetic input or vagal tone.[44,156] The current "gold standard" for HRV measurement requires electrocardiogram (ECG),[147] as the sequence of times between R-peaks can provide a non-invasive measure of the neural regulation of the heart,[148] but ECG is not always feasible. Multiple studies use other recording methods that are less expensive,[149] including the use of high quality of HR monitors like the Polar H10. Polar HR IBIs are reliable compared to ECG in a resting state and under exertional conditions,[40,150,151] yet some studies found lower reliability under higher exertion conditions.[152] While evidence suggests that concussion temporarily disrupts autonomic control of cardiovascular function[16] with abnormalities in HRV present in mTBI,[6,17–19] HRV responses after mTBI have been variable, especially at rest.[8] It may be necessary to induce physical stress to observe subtle ANS and cardiovascular dysfunction. [20] In addition, many studies have used wide ranges of time since mTBI, which may influence HRV findings. [9,10,43]

The use of exertional testing to identify possible ANS dysfunction after concussion is a reasonable approach in clinical practice.[21] Currently the only validated exertional task investigating the cardiovascular function in acute and prolonged recovery after mild traumatic brain injury is the Buffalo Concussion Treadmill Task (BCTT).[22] While this approach offers an advantage with standardized test procedures, it is not always clinically feasible given the time and equipment required, so that it is best implemented by rehabilitation providers. In the military context, individuals with concussion are typically seen by primary care providers for the first month post-injury. PCPs are encouraged to use exertional testing[23] to guide return to activity and duty, but are limited by time, space, and equipment,[24,25] necessary for use of the BCTT. A more field expedient test of exertion would be beneficial to aid primary care provider examination and inform the progressive return to activity process. The use of a reliable and commercially available HR monitor could improve clinical feasibility and implementation.

The purpose of this study was to develop clinically feasible exertional tasks and assess if an objective physiological measure like HRV could be implemented during the testing protocol. We tested healthy adults including servicemembers (SMs) in two different exertional conditions: a stepping and a push-up task. Clinical feasibility was determined by meeting standards of duration, space and equipment consistent with the time and resources available for a routine concussion appointment with a military primary care manager.[25,37,38] We used a modified 6 minute Chester Step Test, a graded step test developed for use in quantifying occupational aerobic capacity that has been tested with emergency service providers.[32,33] This step task is progressively increases speed every two minutes, similar to the BCTT[34] and HRV has been successfully collected during a stepping task.[39] The second exertional task was performance of push-ups for two minutes. The pushup task is a component of the current Army Physical Fitness Test (APFT), with clear military and functional health relevance,[35,36] but has not been researched after concussion. We hypothesized that HRV would be measurable using clinically available equipment (PolarH10) and reliable compared to ECG "gold standard" before, during after exertional tasks. We also hypothesized that both exertional tasks would be feasible based on participant completion and the exertional levels and physiological responses expected.

METHODS

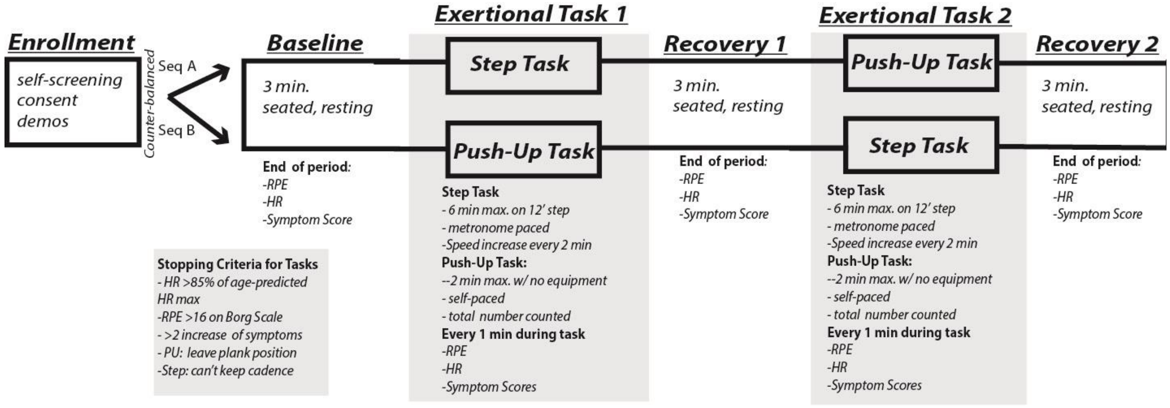
Participants

All participants were healthy adults between the ages of 18-45 who were active, exercising at least three times a week and a subset were affiliated with the United States Marine Corps, currently serving in Eastern North Carolina at a recruiting station. Exclusion criteria were (1) any medical condition or injury that limits ability to perform a Physical Training (PT) session or moderate exertion of stepping or push-ups for 10 minutes, (2) history of moderate to severe TBI. They could have a concussion history if it had been a minimum of one year since most recent injury. Recruitment was limited by level of participation in physical activity and an age range because it is more representative of the active-duty military population. Screening occurred via a "self-screening" procedure where inclusion/exclusion and study procedures were explained in person through briefings and interested individuals could contact research team. All testing procedures were approved by University of North Carolina at Chapel Hill Institutional Review Board (IRB), #17-0429. All participants provided written consent prior to any data collection. Volunteers were free to opt out based on age, physical limitations, activity tolerance, or medical history at any time during any phase of the testing procedures.

Testing Procedures

The experimental design included 1 testing session lasting approximately 45-60 minutes. We continuously recorded heart rate (HR) and inter-beat intervals (IBIs) with two heart-rate monitors for the entire session (Figure 1), starting with a 3 minute baseline in a seated position. After baseline, one exertional task was completed followed by a 3 minute rest in a seated position, then the other exertional task, followed by another 3 minute seated recovery period. The order of the exertional tasks was counterbalanced. During baseline and recovery periods, participants were instructed to relax and could read a selection of magazines. During baseline and recovery periods, participants were instructed to relax and could read a selection of magazines. During both exertional tasks we monitored heart-rate real time via Bluetooth, and assessed rate of perceived exertion (RPE) and concussion related symptoms every minute.

Figure 1: Layout of Testing Session



Self-Report Measures

Participants completed a demographic questionnaire including questions on concussion history and military experience. Factors that may influence HRV were documented including sleep, pain, and caffeine drinks. Rate of perceived exertion (RPE) using the Borg Scale, a 6-20 scale reflecting subjective measure of workload, was used to document self –reported exertion in relation to actual HR during exercise(60-200).[167] Symptoms were assessed using a 0-10 Likert scale focusing on headache, dizziness, nausea, light/sound sensitivity, and fogginess. Throughout the session we recorded verbal RPE and symptom scores at the end of Baseline, Recovery 1, and Recovery 2 and also every minute during each exertional task. Since we only tested healthy adults, we did not expect our exertional tasks to cause much symptom exacerbation.

Heart Rate Recording

In order to examine the reliability of HRV measurement we employed the "gold standard" Faros180 ECG monitor and the more clinically feasible Polar H10 monitor during testing. The Polar H10 HR monitor (Polar Electro Oy, Kempele, Finland) and Faros180 device (Mega Electronics Ltd., Pioneerinkatu, Finland) were used to record HR and IBIs. Participants wore the Polar H10 around their chest and the Faros180 connected by three lead electrodes to the right and left collarbone and left ribcage. The exertional range for heart rate (60-85% of predicted HRmax) was monitored using HRmax estimations from the Fox and Haskell's[188] (HRmax = 220 − age) equation. This equation is simple, commonly used, part of the BCTT protocol,[34] and one of two HRmax equations recommended for use in military populations for graded exercise tests.[189]

Stopping Criteria

Similar safety measures from the BCTT were applied in our protocol to halt either test based on signs of excessive participant stress.[120] The examiner would stop testing if the HR was greater than 85% of predicted HR max, the RPE on the Borg scale was >16, the participant reported an increase >2 on the symptom scale over baseline reported values, or the examiner perceived that testing was unsafe. The participant was also instructed that they could discontinue testing at any time if they deemed it necessary.

Step Task

The step task was a maximum of six minutes in duration and only required a 12-inch step and a metronome (via smartphone app). Every two minutes the stepping pace (metronome bpm) increased as a participant would step up and down a 12-inch step with their preferred leg up first, the other leg up, followed by preferred leg down, then the other one. At the start of the task the metronome was set at 80 beats per minute (bpm) (equaling 20 steps per minute). At two minutes the metronome was increased to 100 bpm (25 steps per minute) and at four minutes the pace increased to 120 bpm (30 steps per minute). The test was discontinued for the general stopping criteria and also if the participant could not keep up with the pace. This exertional step task was adapted from the Chester Step Test protocol,[33] which has been validated to estimate aerobic capacity in a healthy population. The error of measurement is sufficiently small and suggests that this method is well suited to monitoring changes in aerobic capacity in rehab settings.[190]

Push-up Task

The push-up task was a maximum of two-minutes in length where participants were instructed to complete as many push-ups as possible or as many as they can for two minutes without releasing from plank. This is especially relevant for military populations since it is part of the Army Physical Fitness Test.[35] The test was discontinued for the stopping criteria and also if the participant released from plank position to rest at any point. The total number of push-ups was counted on a hand-held lap counter by the examiner.

Data Processing and Reduction

Data collected from the Polar H10 were reduced from the heart rate electrical signal to an IBI value by the devices. The Faros180 recorded a complete ECG waveform at 1 kHz. Inter-beat intervals (IBI), which is the time between consecutive heartbeats expressed in milliseconds, were derived from detected R peaks in ECG using the Cardio Peak-Valley Detector (CPVD)[191] to derive the IBI event series. The CPVD is a LabVIEW™ based algorithm that extracts peaks or valleys of different physiological waves, such as the ECG, PPG, and respiration.

Prior to analysis, each sequence of IBIs was first synchronized automatically, then manually inspected to ensure proper alignment of the IBI series (e.g., the IBIs from the Polar H10 and the Faros180 derived IBIs). Each aligned sequence was then transformed into a 2 Hz equally sampled time-series by linear interpolation. This step was involved in the extraction of HRV parameters, and also prevents the two series from becoming de-coupled.

The unedited IBI file was visually inspected and edited offline with CardioEdit software (developed in the Porges laboratory and implemented by researchers trained in the Porges laboratory). Editing consisted of integer arithmetic (i.e., dividing intervals between heart beats when detections of R-wave from the ECG were missed or adding intervals when spuriously invalid detections occurred). The resulting normal RR intervals were used in analysis when abnormal beats, like ectopic beats (heartbeats that originate outside the right atrium’s sinoatrial node) had been removed.[12]

HRV frequency components were calculated with CardioBatch software (Brain-Body Center, University of Illinois at Chicago), which implemented the Porges-Bohrer metric [154]. This metric was neither moderated by respiration, nor influenced by nonstationarity, and reliably generated stronger effect sizes than other commonly used metrics of RSA (steps are described in depth by Porges et al. [192] and validated in Lewis et al.[154] RSA uses a third-order, 21 point moving polynomial filter (MPF) applied to the 2 Hz IBI time series to remove low frequency oscillations and slow trend. The residual detrended output of the MPF was filtered with a bandpass filter with cut-off frequencies that removes variance not related to spontaneous breathing in adults (0.12 to 0.40 Hz), but takes into account increased breathing rate with exercise (0.12-1.0 Hz). The filtered detrended output was divided into sequential 30-second epochs and the variance within each epoch was transformed by a natural logarithm (ln(ms2)) to decrease skewness. The mean of these epoch values was used as the estimate of RSA for the specific segment. LF uses a third-order, 51 point moving polynomial filter (MPF) applied to the 2 Hz IBI trend to remove extremely low frequency oscillations and slow trend. The residual detrended output of the MPF was filtered with a Kaiser FIR windowed filter with cut-off frequencies (0.06 to 0.10 Hz). The filtered detrended output is divided in 30 second epochs and the variance within each epoch is transformed with a natural logarithm (ln(ms2)), the mean of the epochs values is used as an estimate of LF for the segment[193]. Heart Period was derived from the mean IBI for each epoch used in frequency component analysis. Data variables include: 1) Average Heart Rate 2) Respiratory Sinus Arrhythmia (i.e., RSA or high frequency HRV defined by the frequencies of spontaneous breathing (.12-.4 Hz), 3) Low Frequency HRV (i.e., i.e., occurring within the frequencies of spontaneous vasomotor and blood pressure oscillations; .06-.10 Hz), and 4) Heart Period (total HRV).

Data Analysis

Means, standard deviations, medians, interquartile ranges, and 95% confidence intervals were calculated for all demographic and questionnaire data where appropriate. Alpha will be set a priori at $a < 0.05$ for all statistical analyses. Only participants with complete data will be analyzed for each specific aim. Normality was assessed for all dependent variables using the Shapiro-Wilk test.

Reliability and accuracy of the Polar H10 generated IBI values compared to with the IBI values generated by the Faros180 ECG signals was analyzed using Bland–Altman (B-A) plots and Generalized Estimating Equations (GEE). Comparison of independent measurements was facilitated by visualizing the distribution between the mean measurement and the difference.[194] B-A plots enable the determination of agreement between two sensors, by plotting the mean between pair of measurements against its difference. Visual inspection of the B–A plots is used to identify systematic biases and possible outliers. Paired *t*-tests evaluated whether the differences between the signals were biased (i.e., one signal source generating longer or shorter values). B–A plots and the *t*-test were performed on IBIs collected from all participants during all tasks. Scatter plot and linear regression analyses were used to visualize and calculate the level of convergence between the Polar H10 and Faros180. A strong correlation of threshold of $R^2=0.9$ or higher of IBI time series was determined as a target representing strong agreement. Parameters from Mukaka's (40) paper were used to interpret the size of the correlation coefficients. For each HRV component measure we used linear regression models with GEE to estimate group mean differences (and 95% CIs) for HR monitor methods (Polar H10 vs Faros) and session component (e.g., BL, R1, R2, ST). This allowed us to evaluate if the method of HR measurement had any effect on the analysis of HRV components.

Clinical and physiological feasibility included observational measures as the primary means of analysis. Clinical feasibility was assessed by participant completion (based on safety stopping criteria) of the tasks meeting the primary care manager appointment standards and if HRV could be recorded by a HR monitor and components analyzed at baseline, during exertion, and throughout recovery. Physiological responses were assessed using HR and RPE measurements. HR was measured during both tasks with the exertional range as the primary target for a successful exertional task. Self-reported RPE (Borg Scale) between 12 and 16 (moderate exertion range) during the tasks was a secondary measure of physiological response.

RESULTS

Participants

A total of fifteen healthy adults completed our testing protocol. Thirteen of the participants were active reservists for the United States Marine Corps. Four of the Marine participants had a history of concussion and nine had been deployed serving an average of 2.8 deployments (SD=0.8). Full demographics are presented in Table 1 and 2.

Table 1. Demographic characteristics of Aim 1 Participants. Values are n (%) or mean (SD).

Characteristic	N=15
Age in years	29.33 (6.36)
Sex	
Women	2 (13.3%)
Men	13 (86.7%)
Race/Ethnicity	
Caucasian	7 (46.7%)
Hispanic/Latino	4 (26.7%)
African American	2(13.3%)
Native American	2(13.3%)
Education	
High School	1 (6.7%)
Trade School	1 (6.7%)
Some college/ Associate's Degree	8 (53.3%)
Bachelor's Degree	4 (26.7%)
Advanced Degree	1 (6.7%)
Military Affiliation	
USMC	13 (86.7%)
None	2 (13.3%)

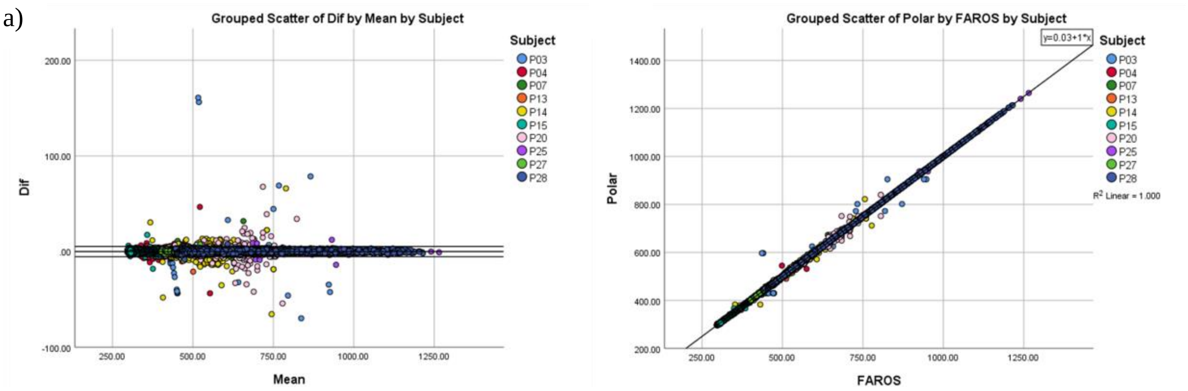
Table 2. Military and Health History of Aim 1 Servicemembers. Values are n (%) or mean (SD),

Characteristic	**N=13**
Time Serving	10.0(5.5)
Military Rank/ Pay Grade	
E1-E5	4 (30.8%)
E6-E9	6 (46.1%)
O1-O3	3 (23.1%)
Deployment History	
Yes	9 (69.2%)
No	4 (30.8%)
Concussion History	
Yes	4 (30.8%)
No	9 (69.2%)
Behavioral Health History	
Combat Stress	1(7.7%)
Post-Traumatic Stress	2 (15.3%)
Anxiety	2 (15.3%)
Depression	1(7.7%)
Caffeine (drinks/ supplements in last 24 hrs.)	1.9 (2.0)
Sleep (hrs. in last 24 hrs.)	5.7 (1.2)

Reliability and Accuracy of PolarH10

Ten participants had complete data for both the PolarH10 and the Faros 180 devices after a Bluetooth issue was identified and resolved. The Faros180 had difficulty in detecting HR peaks during push-ups and required more than 5% editing of total IBIs (beyond the recommended editing standard from HRV Task Force guidelines,[147]) and therefore were excluded from the reliability analysis. Visual inspection of the B–A plot located in the a) panel of Figure 2 indicated excellent agreement and minimal bias between the sequential IBIs measured with PolarH10 and Faros180 (color coded by participant). The B–A plots suggested that error magnitude was driven by a few participants and the IBI differences were closer to zero on the left side with shorter IBIs (higher exertion). A scatterplot with regression analyses contrasting the sensor pair is illustrated in the b) panel of Figure 2. The linear regression of RSA between PolarH10 and Faros180 (ECG) provide excellent fit to the IBI data with R^2 of 0.984 for the model of y= 0.99x+5.23.

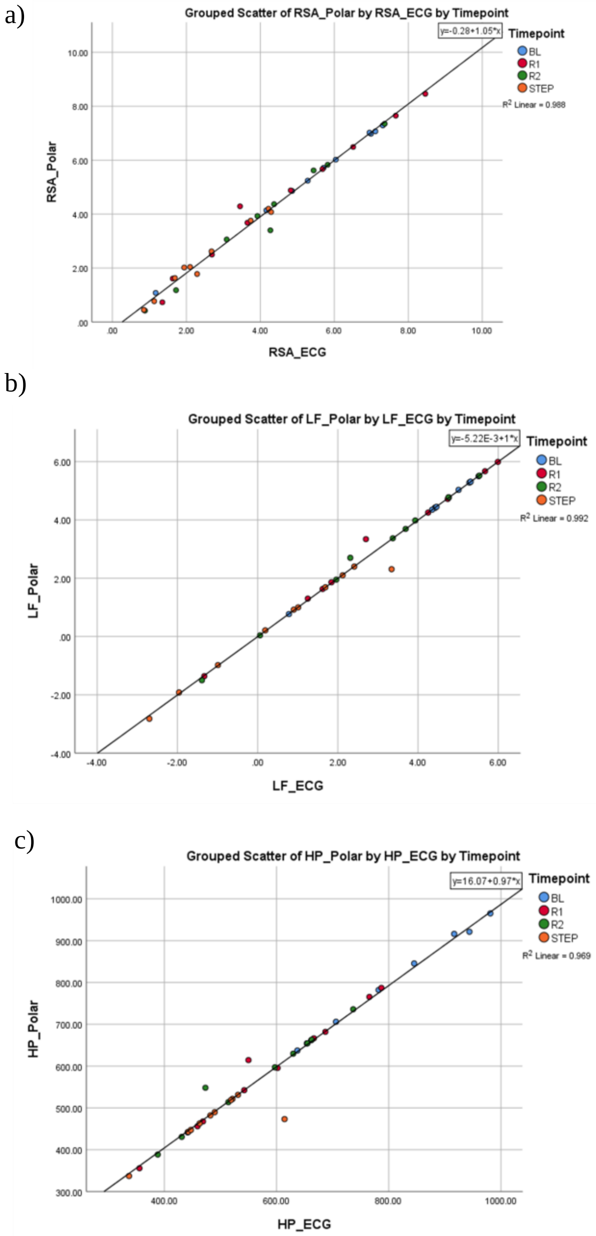
Figure 2: Bland–Altman and scatter plot for inter-beat interval (IBI) from the Faros180 (ECG) and PolarH10, a) Plot of the IBI differences vs the means for the Faros180 and PolarH10. lines indicate the 95% confidence interval. b) Scatter plot of th os vs PolarH10 IBIs



After HRV analyses was completed for the IBIs from both sensors, a scatterplot with regression analysis (Figure 3) contrasting the derived HRV components from the sensor pair confirmed excellent fit with R^2 above 0.90. GEE was used to demonstrate the sensitivity of both sensors regarding the change across timepoints in each HRV parameter. For RSA, sensor type was not a significant predictor (Z = 1.81, p-value = 0.07) showing that for our protocol both methods of HR recordings yielded RSA component results that were not significantly different from each other. The exertion Step task compared to other time points (BL, R1, R2, Step) was a significant predictor of lower RSA (BL: Z = 1.99, p-value = 0.046 R1: Z = 4.78, p-value = <0.001, R2: Z = 3.07, p-value = 0.002) with estimates of 0.98, 2.05, and 1.23 greater than the Step value respectively. Similarly, for LF, sensor type was not a significant predictor (Z = 0.03, p-value = 0.29) of LF value supporting the reliability of the Polar10. Yet, the Step task was a significant predictor of lower LF compared to other time points (BL, R1, R2) was a significant predictor (BL: Z = 7.61, p-value = <0.001 R1: Z = 6.59, p-value = <0.001, R2: Z = 5.18, <0.001) with estimates of 2.36, 2.35, and 1.76 respectively. For HP, sensor type was not a significant predictor (Z = 1.91, p-value = 0.06) but Step task was a significant predictor compared to other time points (BL, R1, R2) was a significant predictor (BL: Z = 7.77, p-value =

<0.001 R1: Z = 4.33, p-value = <0.001, R2: Z = 3.67, p-value= 0.002) with estimate of 284.07, 123.92, and 103.12 respectively with the Step task causing a decrease in HP. Figure 4 shows how BL, Step, and Rest directly after step compare between the sensors in RSA, LF, and HP.

Figure 3: Scatterplots between Sensors for HRV components, color coded by timepoint a) respiratory sinus arrhythmia (RSA), b) Low-frequency (LF), c) Heart-Period (HP)



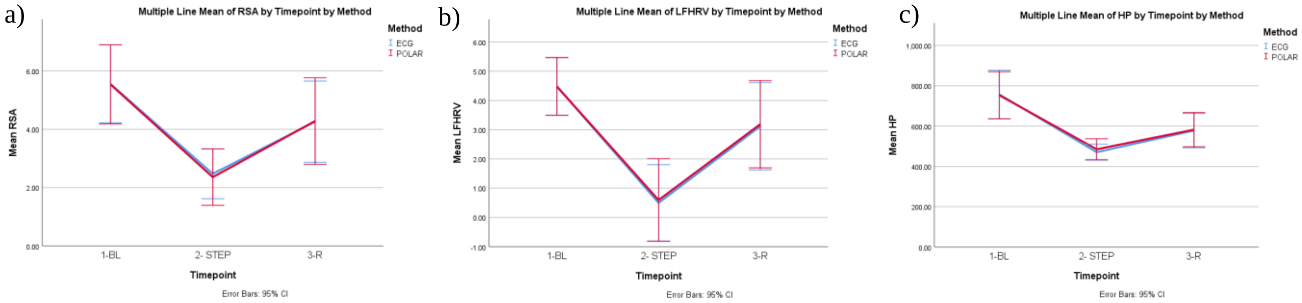
Clinical and Physiological Feasibility

All fifteen participants were able to complete both tasks as instructed without the examiner having to stop based on safety criteria. None of the participants reported symptom exacerbation during either task. HRV analysis was feasible for all of the phases (BL, ST, R1, PU, R2) based on IBI recordings from the commonly available PolarH10.

Both the stepping and push-up task evoked an appropriate exertional physiological response. All participants reached the exertional range (60-85% of age predicted HRmax.) during the six minute step test and the two minute push-ups. During the stepping task all participants reported a RPE between

12 and 16 at least once during the task. Fourteen of fifteen participants reported a RPE in the exertional range (12 to 16) for the push-up task.

Figure 4: Mean of HRV measures at Baseline, Exertion, and Rest after Exertion for Faros180 (ECG) and PolarH10. a) Respiratory sinus arrhythmia (RSA), b) Low Frequency (LF). c) Heart Period (HP). Exertional task is stepping task and rest is recovery period right after step task.



DISCUSSION

The development of a clinically feasible, standardized exertional task for PCMs to administer to SMs after an acute mTBI is an important step in the treatment and management of mTBI within the military in line with current DVBIC guidelines. Our two exertional tasks were ecologically valid for SMs as they build on familiar tasks of patrolling and push-ups and a similar stepping (CST) and push-up (AFPT) task has been utilized to assess aerobic and strength capacity.[33,35] While we tested a majority of Marines, who do not complete the APFT, push-ups are a core training component and can be performed during their USMC Physical Fitness Test.[206] Testing our exertional task protocols in healthy participants allowed us to ensure feasibility, assess adequate physiological response, characterize HR recovery, make protocol improvements, and confirm reliability of a more affordable and clinically available HR monitor.

We found the PolarH10 recordings of beat-to-beat heart rate data for the exertional protocol collected through Bluetooth capabilities to be accurate and reliable compared to the gold standard ECG recordings. Hernado et al. found HR monitor and ECG methods to be interchangeable when analyzing HRV at rest,[40] yet we found a higher correlation under exertion. We also found excellent reliability and agreement indices of the HRV components between sensors.

Both the stepping and push-up task were feasible to perform during a PCP appointment, based on our pre-defined standards with a duration of less than ten minutes, space requirement of a standard PCM exam room (~ 12’ x 12’), and minimal and easily accessible equipment. Besides the common PolarH10 HR monitor, the step task requires a 12” step and metronome app while the push-up task only requires a hand counter. Both tasks were easily administrated by one tester and could be completed in our healthy population without stopping for safety reasons. Previous studies have tested mTBI targeted assessments in healthy individuals prior to completing testing in a clinical cohort.[177,207] The addition of a clinically available HR monitor to provide an objective physiological measure could increase utility for PCPs.

All of the participants demonstrated an appropriate HR exertion range during each task showing that these tasks were difficult enough to cause a physiological stress response. RPE ratings also showed that tasks were sufficiently challenging with the one participant rating below 12 on the Borg RPE scale for push-ups only completing the task for 30 seconds before choosing to stop. Both of our exertional tasks are of greater difficulty than current commonly used concussion balance assessments with the goal of minimizing ceiling effects.[37]

Exploratory analyses showed there was a HRV effect for the stepping task compared to the baseline and recovery time periods showing that HR monitors could sufficiently detect changes in all three HRV components induced by brief exertion. Similar to previous studies we found a decrease in RSA when under exertion, consistent with the parasympathetic withdrawal that occurs upon initiation of exercise.[197,199] We also found a decrease in the LF HRV component under exertion. Since LF includes variable input, no conclusion on ANS input can be drawn, but there is evidence that it also decreases in moderate exertion influenced by parasympathetic withdraw. [208] HP, a measure of Total HRV, was also significantly lower during the exertional task, an expected result since this measure is the inverse of HR.[209]

As with any scientific study, our study had limitations. First, this study focused on the development of exertional tasks within a healthy population, therefore, future studies need to investigate tolerance of these exertional tasks for individuals who have sustained a mTBI and if any HRV impairments can be detected comparing injured SMs to healthy controls. Second, comparisons between Polar H10 and Faros 180 did not include the push-up task due to concerns with over-editing. While the reliability analysis between HR monitor methods for one exertional task could not be completed, exertional levels from out other task (step-task) showed that the PolarH10 was reliable compared to the ECG “gold standard”. Also, only 10 participants were used in reliability calculations due to technical difficulties and missing data for devices.

Feasibility testing in a healthy population allowed improvements to be implemented into the protocol for future studies. For instance, the duration of the baseline and recovery time periods was increased from three to five minutes. Previous studies have used 2-3 minute baseline recording consistent with our protocol, but the HRV Task Force recommends five minute HR recordings for HRV analyses.[147] Although three minute recovery between tasks was sufficient for these healthy participants to return to RPE of 6, we expect that individuals with mTBI may need longer to recover as previous studies show that a higher RPE is reported with the same HR when comparing mTBI and healthy controls.[42] While we are most interested in the first minute of recovery when parasympathetic input increases, the longer duration will allow us to investigate time differences in the duration recovery.[200]

Both of our exertional tasks are clinical feasible in terms of space, duration and equipment and evoke an appropriate HR response in healthy participants. The use of clinically available HR monitors utilizing Bluetooth technology with straightforward administration increases feasibility for PCP. The implementation of standardized exertional tasks that includes an objective physiological measure can improve the standard of care for military mTBI. Monitoring symptoms (headache, dizziness, nausea, light/sound sensitivity, fogginess, etc.), RPE, and HR throughout an exertional task is a way clinicians can assess physiological recovery and prescribe activity.[167] The treatment and management of mTBI remains a priority for DVBIC and the armed forces and further research needs to facilitate clinical implementation.

CHAPTER 6: MANUSCRIPT 2 - HEART RATE VARIABILITY AS A PHYSIOLOGICAL MEASURE OF AUTONOMIC NERVOUS SYSTEM IMPAIRMENTS IN SERVICEMEMBERS AFTER CONCUSSION: A PILOT STUDY

INTRODUCTION

Military medical clinicians are currently challenged to objectively assess the spectrum of vulnerabilities associated with mild traumatic brain injury (mTBI) in active duty service members (ADSM). The Department of Defense (DOD) defines mTBI as “an injury to the brain resulting from an external force and/or acceleration/deceleration mechanism from an event such as a blast, fall, direct impact, or motor vehicle accident which causes an alteration in mental status typically resulting in the temporally related onset of symptoms such as headache, nausea, vomiting, dizziness/balance problems, fatigue, insomnia/sleep disturbances, drowsiness, sensitivity to light/noise, blurred vision, difficulty remembering, and/or difficulty concentrating”.[2] Along with common cognitive, vestibular, and visual symptoms, concussions are also associated with exertional and physiological changes in other organ systems including the autonomic nervous system (ANS). [3,4]

The Autonomic Nervous System is a vital contributor to vascular and cardiac regulation, functions without conscious voluntary control. The ANS plays a role in regulating blood pressure, temperature, respiratory systems, gastrointestinal systems, and heart rate during rest and in response to stressors.[5] The ANS includes the excitatory sympathetic (SNS) and inhibitory parasympathetic nervous systems (PNS).[13] Parasympathetic activity is also known as cardiac vagal control and higher levels are associated with higher executive performance, better stress management and emotional regulation, better social functioning, and better overall health.[45,195,204] Cardiac vagal control (CVC) refers to the efficiency of the PNS or more specifically functioning of the vagus nerve and its contribution to cardiac functioning. [210,211] The Central Autonomic Network that includes the cerebral cortex, amygdala, hypothalamus, and brainstem centers regulates CVC.[128,195] MTBI may cause disruptions to this brain-heart connection [14], which has been found in more severe TBI. [15,129,212]

Subtle impairments of the central autonomic network may induce cardiovascular autonomic changes after mTBI.[136,137] Observations after concussion suggest the presence of reduced PNS activity, overactive SNS, and less efficient responses to autonomic challenges when compared to healthy controls.[6,7] This lack of vagal efficiency may also last beyond symptom resolution. [9,10] Although the cause of concussive symptoms is likely multifactorial, one possible contributor to impairments is CVC dysfunction,[3,4] which has been proposed to be a physiological summary indicator of self-regulation including executive function, and emotion and stress management. [195] This Vagal Tank Theory postulates that different levels and change patterns (i.e., direction and magnitude) of CVC can demonstrate adaptive or maladaptive self-regulation according to the situation.[195] With a physical stressor like exercise, a healthy individual would have rapid CVC reactivity or parasympathetic withdrawal at the initiation of exercise. With higher levels of activity a larger withdrawal is associated with better self-regulation performance.[155,210] The intensity and duration of exercise affects the response of CVC with an increase in time or intensity leading to increases SNS control of heart rate with the resetting of baroreflexes to a higher level and increased input from muscle mechanoreceptors and thermoregulation feedback loops.[199] At the end of exercise, the CVC change from task to resting can be described cardiac vagal recovery. During the first minute of heart rate recovery, the rapid HR decline is due to increased vagal control and is not affected by exercise intensity or sympathetic blockade[200] and in athletics longer recovery (i.e. two minutes) is often a training target [213]. The faster one's ability to return to baseline levels or higher after exercise, the higher the CVC and the better suited an individual is to face and recover from a new demand.[195]

CVC and regulatory ANS function can be assessed by the analysis of heart rate variability (HRV), which is the variation in time between successive heartbeats.[11,12] The variability of these inter-beat intervals (IBIs) is considered a marker of ANS balance, as both branches work together to optimize heart output to situational demands,[3,12] but the fast acting vagus nerve is the primary influencer. Heart Period (HP) represents the average IBI over a period of time and is a measure of "total HRV". HP is sometimes considered the inverse of heartrate,[201] but is more precise while HR is an estimate that is normalized to time (i.e., 60 s).[209] Frequency domain HRV analysis uses principal components analysis to determine the two primary rhythmic frequency elements while eliminating noise.[153–155,209] The high frequency (HF) oscillation, also coined Respiratory Sinus Arrhythmia (RSA), is associated with respiratory oscillation.[44] RSA has been validated as a representative measure of parasympathetic input.[45] The slower frequency rhythm (low frequency LF) is theorized to capture baroreceptor and peripheral vasomotor activity that regulates blood pressure but includes input from both the PNS and SNS.[156,157]

Table 1: Heart Rate Variability Components Description

HRV component	Characteristics	Translation to ANS
Heart Period (HP)	average IBI over a period of time	Flexibility/balance of ANS Measure of total HRV
Respiratory Sinus Arrhythmia (RSA) or High Frequency (HF)	high-frequency band (0.15–0.4 Hz)	Parasympathetic input, Measure of cardiac vagal control
Low Frequency (LF)	low-frequency band (0.04–0.15 Hz)	PNS, SNS, baroreceptor & peripheral vasomotor activity that regulates blood pressure

Previous studies have found abnormalities in HRV in concussed individuals under different conditions (e.g. rest, isometric handgrip exercise, aerobic exercise),[9,43,137] but HRV responses after mTBI have been variable, especially at rest,[8] suggesting it may be necessary to induce physical stress to observe subtle ANS and cardiovascular dysfunction.[20] Evidence supports that cardiac autonomic function (HRV) is altered during physical activity after a concussion.[21] The majority of HRV studies after mTBI have analyzed HRV at specific timepoints (tonic measures) under different conditions, yet equally important is the rate of change of HRV components (phasic measures) which may determine how well individuals adapt to a situation.[195] Based on the “reactivity hypothesis”, cardiovascular response to a stressor has been useful in predicting certain disease states and monitoring athletic performance.[197] The use of exertional testing to identify possible CVC dysfunction is a reasonable approach in clinical practice[21] and is commonly used in sports concussion. The current Defense and Veterans Brain Injury Center guidelines recommend the use of an exertional task prior to return to duty after concussion,[214] however there are no validated measures of exertion for this purpose in the military population.

As a simple, noninvasive measure of ANS balance, HRV could serve as a marker of recovery and may be a valuable biomarker in clinical care. Currently patient symptom report is the primary way clinicians gauge recovery, but self-report of symptoms is known to be somewhat unreliable due to under- or over-reporting. In the military population reporting is further influenced by operational needs, command pressure, or other aspects of warrior culture and demands.[47] The purpose of this study was to investigate proposed CVC dysfunction in servicemembers with mTBI [21] during resting, reactivity, and recovery; which all represent different levels of adaptability. [195] Our quasi-experimental, known-group, single site study utilized two previously developed, clinically feasible exertional tasks to elicit ANS responses that have been tested in a healthy military population and include HRV measures (Prim, unpublished). Both tasks evoked a physiological ($\geq$60% age predicted HR max) and self-reported

(RPE $\geq$12 on Borg Scale) exertional response in healthy SMs. Respiratory Sinus Arrhythmia (RSA), a validated measure of parasympathetic tone,[44] was our primary candidate for investigating CVC impairment after concussion during resting, reactivity, and recovery. We hypothesized that the exertional conditions of both tasks would provoke symptoms and CVC deficits within the concussed population (compared to healthy individuals) that would last into recovery period.

METHODS

Participants

Participants in this study were active duty service-members (men or women) from Fort Bragg, North Carolina. There were two groups (1) SMs who had sustained an acute mTBI and (2) Healthy Controls (HC). MTBI participants were ADSM that satisfied the following criteria: (1) diagnosed with acute mTBI within the last week, (2) 18-45 years of age, (3) first mTBI in last 12 months, (4) no clinical evidence indicating greater than mild TBI, (5) minimal symptoms at rest reported prior to scheduling testing (<2 on a global symptom scale). HC participants were ADSM that satisfied the following criteria: (1) eligible for deployment, (2) any prior concussions greater than one year post-injury with no ongoing symptoms.

Identification and recruitment of mTBI participants occurred in collaboration with primary care providers at the Department of Brain Injury Medicine at the Intrepid Spirit Center or at Robinson Health Clinic. Providers identified individuals who had sustained an acute concussion and a researcher provider information about the study. Consent, screening, and enrollment could occur at an initial appointment; however, testing was not scheduled until the individual reported absent or mild daily symptoms at rest. Symptoms were tracked daily using a global symptom scale (Appendix 1) that included headache, dizziness, nausea, light/sound sensitivity, and fogginess and once symptoms subsided a testing session was schedule based on SM availability. This test was scheduled only if within two weeks of the initial injury. HC participants were recruited from SMs who had expressed interest in participating in the study after hearing inclusion criteria and filled out contact cards at briefings arranged by the DVBIC Regional Education Coordinator. All testing procedures were approved by Womack Army Medical Center (WAMC) and The US Army Regional Health Command- Atlantic (RHC-A) IRB, #2019-001.

Testing Protocol

The study protocol included one testing session of 45-60 minutes. All testing took place at the Intrepid Spirit Center at Fort Bragg. After providing written informed consent, participants would complete a demographic intake form, the Neurobehavioral Symptom Inventory (NSI), a widely used self-report mTBI assessment [185,186] and the Defense and Veterans Pain Rating Scale (DVPRS) to assess pain. Consent and survey completion were all done while seated (15-20 minutes) to allow for HR to stabilize helping control for previous activities earlier in the day. Throughout the whole session, participants wore a Polar H10 HR monitor (Polar Electro Oy, Kempele, Finland) around their chest that recorded heart rate (HR) and inter-beat intervals (IBIs) continuously. The testing protocol included a baseline rest period, a stepping and push-up task with rest periods between each exertional task. Rest was always done in sitting. Starting with a 5 minute baseline rest, one exertional task was completed, followed by a 5 minute rest, then the other exertional task, followed by another 5 minute rest. The order of the exertional tasks was counterbalanced.

Exertional Tasks

The stepping and push-up tasks were designed to challenge SM performance physiologically after acute mTBI safely. Implemented safety standards similar to those used in the validated Buffalo Concussion Treadmill Task were applied.[120] During exertional tasks heart-rate was monitored in real time via Bluetooth. In addition, rate of perceived exertion- RPE (Borg Scale, 6-20 with 12-16 representing moderate exertion) and symptoms on a 0-10 Likert scale were assessed each minute. Rate of perceived exertion (RPE), a subjective measure of workload, allowed us to investigate its relation to actual HR during exercise.[167] The symptom scale included headache (H), dizziness (D), Light/sound Sensitivity (S), Nausea (N), and Fogginess (F). The examiner stopped testing if exercise HR was greater than 85% of predicted HR max, the RPE on the Borg scale was >16, the participant reported an increase >2 on the symptom scale, or the examiner perceived that testing was unsafe. The participant was also instructed that they could discontinue testing at any time if needed. If a participant was unable to complete the first task due to concussive symptom exacerbation that did not improve in the 5 minutes of rest between tasks, the second task was not completed.

The step task was a maximum of 6 minutes with 3 2-minute phases that gradually increased exertion requirements. The participant stepped up and down a 12-inch step with the pace of a metronome, with their preferred leg up first, the other leg, then preferred leg down followed by the other leg. Participants were instructed they could change the leading leg as desired. With each beat of the metronome one leg movement was expected. The pace began at 80 beats per minute (bpm) equating to 20 steps with each foot and increased to 100bpm for minutes 3 and 4, and to 120 bpm for minutes 5 and 6. The test was discontinued in accordance with established stopping rules or if the participant was not stepping consistently with the metronome. Successful completion of this task was measured by being able to complete the full six minutes.

The push-up task was a maximum of 2-minutes in length. Participants were instructed to complete push-ups for up to 2 minutes at their own pace and the number of push-ups were counted by a researcher. This is especially relevant for military populations since it is part of the Army Physical Fitness Test (APFT) and push-ups remain a component for the new Army Combat Fitness Test (ACFT) [215]. The test was discontinued based on stopping rules or if the participant relaxed from the plank position to rest at any point. Successful completion of this task was measured by completion of a score of 60 on the APFT push-up age-adjusted scoring, the minimum for passing Advanced Individual Training (AIT) [216].

Data Processing and HRV Analysis

Data collected from the Polar H10 were reduced from the heart rate electrical signal to an IBI value by the devices. Bluetooth transmission allowed for direct transfer of the Polar H10 data to the laptop with time logs. Prior to analysis, each sequence of IBIs was first synchronized automatically, then manually inspected to ensure proper alignment of the IBI series with the timelog. The unedited IBI file was visually inspected and edited offline with CardioEdit software (developed in the Porges laboratory and implemented by researchers trained in the Porges laboratory). Editing consisted of integer arithmetic (i.e., dividing intervals between heart beats when detections of R-wave from the ECG were missed or adding intervals when spuriously invalid detections occurred). The remaining normal RR intervals were used in analysis when abnormal beats, like ectopic beats (heartbeats that originate outside the right atrium's sinoatrial node) were removed.[12] All editing was completed by two researchers (JP, MD) independently and analyzed separately to ensure reliability.

HRV frequency components were calculated with CardioBatch software (Brain-Body Center, University of Illinois at Chicago), which implements the Porges-Bohrer metric [154]. This metric is neither moderated by respiration, nor influenced by nonstationarity, and reliably generates stronger effect sizes than other commonly used metrics of RSA (steps are described in depth by Porges et al. [192] and validated in Lewis et al).[154] To derive RSA, a third-order, 21 point moving polynomial filter (MPF) was applied to the 2 Hz IBI time series to remove low aperiodic baselines and slow oscillations. The residual detrended output of the MPF was bandpass filtered and the heart period variance in the frequency band associated with spontaneous breathing including an increase of breathing associated with exercise was quantified (0.12 to 1.0 Hz). This output was divided into sequential 20-second epochs and the variance within each epoch was transformed by a natural logarithm (ln(ms2)), the mean of these epoch values was used as the estimate of RSA for the specific segment.

Data Analysis

***Quantitative*:** Means, standard deviations, medians, interquartile ranges, and 95% confidence intervals were calculated for all demographic and questionnaire data where appropriate. Alpha was set *a priori* at $a < 0.05$ for all statistical analyses. Only participants with complete data were analyzed for each specific aim. Normality was assessed for all dependent variables using the Shapiro-Wilk test.

The variables of primary interest were the HRV measures including RSA, and HP during each of the timepoints of testing protocol and the slope of both measures during beginning of exertion (1 minute) and of recovery (1 and 2-minute). The slope was used to calculate the rate of cardiac vagal and heart period reactivity and recovery. Independent t-tests were used to measure differences between groups at the following timepoints: baseline, exertional (push-up and step task), and recovery (rest 1 and rest 2) and differences in slope. In addition, we completed exploratory analysis on differences between groups on task success and symptoms during tasks. Following best practices, all statistical estimates included 95% confidence intervals (C.I.s).

***Qualitative*:** All mTBI cases are described as a case series with observational descriptions on task performance and clinical presentation.

RESULTS

Quantitative: Participants

A total of 29 participants completed the testing protocol including 4 SMs with acute concussion and 25 healthy controls. Six of the HC participants reported a concussion history and one was excluded from healthy control analysis due to exhibiting mTBI symptoms during the exertion tasks. Full demographics are presented in Table 1.

Table 2. Demographic Characteristics of Servicemembers that Performed Testing Protocol

Characteristic	Healthy Controls N=25	mTBI N=4	p-value
Age in years	25.7 (5.9)	31.5 (8.7)	0.10[1]
Sex (Male)	25 (100%)	4 (100%)	1.00[2]
Race/Ethnicity			
Caucasian	14 (56%)	2 (50%)	
African American	5 (20%)	0 (0%)	0.381[2]
Hispanic	3 (12.0%)	2 (50%)	
Asian/Pacific Islander	2 (8.0%)	0 (0%)	
Other	1 (2.0%)	0 (0%)	
Education			
High School	9 (36%)	1 (25%)	0.008[2]
Associate's Degree/ Some college	11 (44%)	2 (50%)	
Bachelor's Degree	1 (4%)	1 (25%)	
Advanced Degree	4 (16%)	0 (0%)	
Years in military	5.1 (5.5)	9.0 (5.4)	0.20[1]
Been Deployed (Y)	8 (32%)	3 (75%)	0.10[2]
Neurobehavioral Symptom Inventory (NS)) Total	5.5 (8.6)	24.3 (13.3)	<0.001[1]
Defense and Veterans Pain Rating Scale (DVPRS) Total Functional Score	2.4 (4.1)	8.5 (7.0)	0.02[1]
0-10 Numeric Pain Rating Scale (#1 on DVPRS)	0.56 (1.0)	1.5 (1.3)	0.11[1]

Table 1. NOTE. Values are n (%), mean(SD). [1]t-Test, [2]Chi-Square, * p-value=<.05

Heart Rate Variability

Tonic Measures

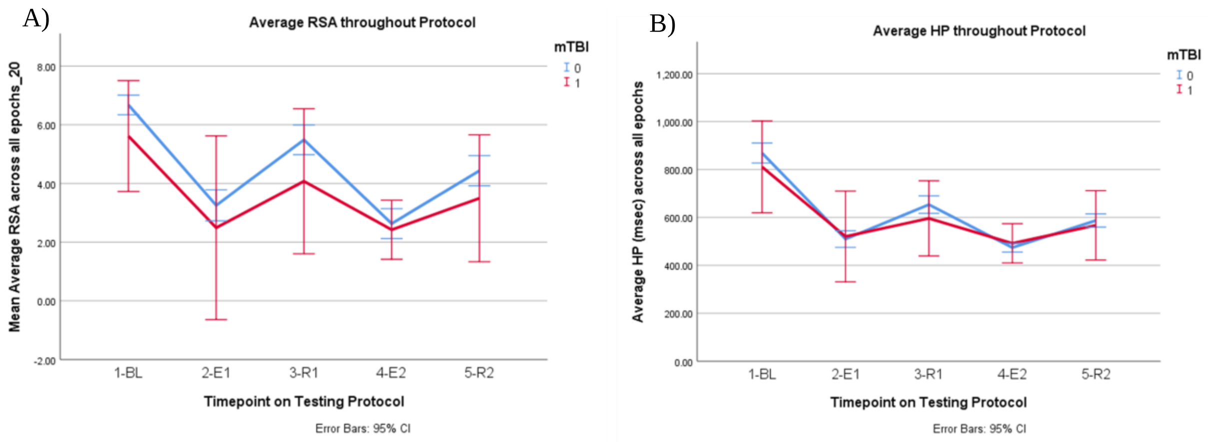
At baseline, there was a significant difference in mean RSA between our mTBI (M=5.62, SD=0.79) and HC (M=6.67, SD= 1.19) group; t(26) =2.311, p-value=0.02. There were no significant differences in HP between mTBI and HC groups at baseline (Table 2). Under exertional conditions, there were no significant differences on any of our HRV measures between groups.

Table 3: Group Differences in Tonic Heart Rate Variability Measures at Different Timepoints
$^{\#}$=Independent T-tests, * p-value=<0.05

Variable	**Time point**	**Group**	**M(SD)**	**Mean difference (95% CI)$^{\#}$**
Respiratory Sinus Arrhythmia (RSA) or High Frequency (HF) HRV	Baseline	HC	6.64 (0.79)	1.03 (.078-1.97)*
		mTBI	5.61 (1.19)	
	Exertional Tasks	HC	2.95 (1.27)	0.49(-.51-1.50)
		mTBI	2.45 (0.86)	
	Rest Periods	HC	4.89(1.29)	1.11(0.10-2.11)*
		mTBI	3.79(1.39)	
Heart Period (HP)	Baseline	HC	861.09 (93.5)	50.2(-58.13-158.53)
		mTBI	810.88 (93.64)	
	Exertional Tasks	HC	500.69 (53.22)	-14.58(-69.04-39.89)
		mTBI	552.01 (51.28)	
	Rest Periods	HC	612.79(75.55)	31.31(-28.28-90.90)
		mTBI	581.49(89.14) *	

During the recovery periods, there was a significant difference in RSA between mTBI (M=3.78, SD= 1.39) and HC (M=5.03, SD=1.28) groups; t(54) =2.521, p-value=0.015. There were no differences on mean HP measures between groups during the recovery periods. Figure 1 shows the mean HRV measures for each group at each testing timepoint.

Figure 1: Mean HRV Measures at Testing Timepoints for mTBI and Healthy Controls. A) Respiratory Sinus Arrhythmia (RSA), B) Heart Period (HP). 1-BL: Baseline, 2-E1: first exertional task, 3-R1: first rest period, 4-E2: second exertional task, 5-R2: second rest period



Reactivity

There were no significant differences on the rate of cardiac vagal reactivity to exertional task measured by the slope of RSA nor rate of heart period reactivity measured by slope of HP during first minute of exertion between groups (Table 3). When looking at only second task reactivity (slope of RSA first minute during exertion), the mTBI group (M=-0.017, SD=0.049) and HC group (M=-0.058, SD=0.036) exhibited trend-level differences (t(25)=-1.98, p-value=0.058). Two HC did not complete push-up task for a duration long enough to calculate slope (1:00 allowed for 3 epochs).

Recovery

There were significant differences on rate of heart period recovery after exertional task measured by the slope of HP during first minute after exertional task between groups (HP t(52)=3.41, p-value=0.001; RSA t(52)=1.95, p-value=0.056) with HC SMs having a steeper HP slope indicating faster recovery than mTBI SMs (Table 3). This difference was found in cardiac vagal recovery (slope of RSA) when examining a longer recovery duration of two minutes and still present in rate of HP recovery. (RSA t(52)=2.18, p-value=0.03; HP t(52)=3.32, p-value=0.002).

Table 4: Group Differences in Phasic Heart Rate Variability Measures during Reactivity and Recovery $^{\#}$=Independent T-tests, * p-value=<0.05

Variable	**Time point**	**Group**	**M(SD)**	**Mean dif(95% CI)**
Respiratory Sinus Arrhythmia (RSA) or High Frequency (HF)	Rate of Reactivity (slope of 1 min)	HC	-0.054(0.04)	-.024 (-0.06—0.01)
		mTBI	-0.030(0.05)	
	Rate of Recovery (slope of 1 min)	HC	0.037(0.04)	0.031(-0.001-0.062)
		mTBI	0.006(0.03)	
	Rate of Recovery (slope of 2 min)	HC	0.027(0.02)	0.016(0.002-0.03)*
		mTBI	0.011(0.02)	
Heart Period (HP)	Rate of Reactivity (slope of 1 min)	HC	-3.336(1.53)	-.592(-1.82-0.619)
		mTBI	-2.744(1.28)	
	Rate of Recovery (slope of 1 min)	HC	2.18(1.15)	2.10(0.86-3.32)*
		mTBI	0.084(3.25)	
	Rate of Recovery (slope of 2 min)	HC	1.98(0.78)	1.79(0.71-2.87)*
		mTBI	0.73(3.3)	

Exertional Symptoms

Fisher's exact test was used to compare task success and symptom exacerbation between groups. For task success (step task completion, 60 on push-up AFPT score), the Fisher's Exact test was significant (p=<0.001) between mTBI and HC with an odds ratio of 18.43 (3.08-110.23). For symptom exacerbation. Fisher's Exact test was significant (p=<.001) and all mTBI participants reported onset or worsening of symptoms during exertional tasks, despite reporting a level of symptoms that suggested ability to return to activity. In addition, there was no difference in maximum RPE between mTBI (M=13.76, SD=2.4) and HC (M=14.1, SD=2.5) groups, t(54) =-0.39, p-value=0.69.

Case Description

A total of 4 mTBI participants completed testing protocol. Since the number of subjects was limited, we have included observational descriptions of each case. The order of exertional tasks was age and gender matched to a HC. In addition, a healthy control who had concussion related exertional issues is also presented as a case. All 5 participants sustained their mTBI while completing training duties of airborne operations. Descriptions of the cases are presented in Table 4.

In addition to the observational measures the tests provided, one SM reported his surprise on how “symptomatic” he still was and inquired if we could share this information with his command. The second case had previously reported being asymptomatic for three consecutive days prior to testing, but endorsed a headache upon arrival to testing session since he had just stopped taking his headache medication. The third case reported a “pounding” headache after stopping during the push-up task, but when asked to re-score symptom on the symptom scale he score it at 2/10 because it was tolerable.

Overall the healthy SM population was able to successfully complete both tasks consistent with our criteria (88% push-ups, 84% step). Three SMs did not complete enough push-ups to get an age-adjusted score of 60 on the AFPT, but continued performing push-ups for the entire 2 minutes. Four SMs did not complete the Step task, one was stopped during testing because of a reported RPE of 17 at 5:00, 2 had a HR greater than 85% of the age-predicted HR max (at 4:00 and 5:00) and one was unable to keep up with the step cadence (age 41, with significant knee pain). At the end of the rest periods 76% of the HC reported a RPE of 6 and the remaining SMs reported either 7 or 8. In addition, the push-up task caused symptoms in three SMs (N,H,F- all scores of 1), while the stepping task provoked symptoms in two (H, D-scores of 1-2).

Table 5: Case Descriptions of mTBI Participants. The symptom scale included headache (H), dizziness (D), Light/sound Sensitivity (S), Nausea (N), and Fogginess (F).

Subjects	Days Post Injury	NSI	DVPRS Total (#1)	Self-report RTD	Days of reporting min. sym.	Resting Baseline Values	First Task	Step Task Observations	Rest 1 Values	Push-Up Task Observations	Rest 2
Male, 32	5	6	6(1)	Y	4	H=1 RPE=6 HR=90	Step	Examiner stopped at 5:30 b/c HR exceeded 85% age-pred. Max. (H=1, RPE=11, HR=165)	H=1 RPE=10 HR=108	SM performed push-ups for 1:20 before stopping with the total# met standard for successful completion (total PU=38, H=2, RPE=12, HR=150)	H=1, RPE=8 HR=110
Male, 22	9	30	16(3)	N	2	H=1, N=2, S= 1 RPE=7 HR=82	Push-up	Examiner stopped at 4:00 b/c N increased from 2 to 5, RPE=17, and SM could not keep up with cadence (H=3, S=3, HR= 155)	H=2, N=2, S=3 RPE=9 HR=102	Examiner stopped at 1:00 after SM reported RPE=17 (total PU=44, H=3, HR=145)	H=4, N=4, S=2 RPE=11 HR=102
Male, 29	11	37	0 (0)	Y	4	F= 2 RPE=6 HR=72	Push-up	Examiner stopped at 5:00 b/c D increased from 1 to 4 (N increased to 1, RPE=15, HR=156)	D=1, F=3 RPE=6 HR=86	Examiner stopped at 1:00 b/c D increased from 0 to 3, (RPE=15, HR=117, total PUs=30)	D=1, N=0, F=3 RPE=6-7 HR = 99
Male, 43	13	24	12(2)	N	5	H=4 RPE=6 HR=63	Step	SM completed the full 6:00 (H=3, RPE=15, HR=128), reported N=5 after the end of task	N=4, H=4 RPE=8 HR=73	SM performed push-ups very slowly and stopped at 1:32 (N=4, H=4, D=1, RPE=11, HR=117 total PU=32)	N=4, H=4, D=2 RPE= 7 HR= 76
Male, 28	(2 yrs.)	34	2(0)	Y	(2 yrs.)	sym. =0 RPE=6 HR=64	Push-up	SM completed the full 6:00 (H=4, RPE=14, HR=150)	H=2 RPE=6 HR=65	Examiner stopped at 1:00 after SM reported H=5 (total PU=52, RPE=16, HR=130)	H=3 RPE=6 HR=78

DISCUSSION

Implementing HRV measurement during exercise for the military population is important because of the physical demands and high stress of military culture and evidence that cardiac autonomic function (HRV) is altered during physical activity after a concussion.[21] The stepping and push-up exertional tasks were designed to challenge SM performance to reveal impairments after acute mTBI safely while being clinically feasible. Preliminary findings revealed that RSA impairments are seen in our small concussed population and are more pronounced in the recovery periods after exertion, but not during the exertional tasks. While we hypothesized that a physical stressor may be needed to see CVC impairments in the response that is present after mTBI, we also found differences in baseline conditions. Previous studies using tonic HRV measurements have found that RSA is lower under exertional conditions and at resting,[43,161] but tonic measurements alone may not be sufficient to determine the adaptation of a system when demand is placed upon it.[11] Our implementation of phasic measures allows for a more in-depth picture including reactivity and recovery.

The tonic differences in RSA at baseline may represent that mTBI SMs have less self-regulatory resources that can be used in order to foster adaptability.[195] While we did not find differences between mTBI and HC during exertion or in the rate of reactivity (slope during first minute of exertion) for RSA or HP components, there was a trend-level difference in the rate of reactivity for RSA in the second exertion task where mTBI SMs did not react as quickly. This is likely influenced by the differences in CVC recovery.

Recovery after exercise plays a crucial role in the adaptability necessary to face an event and then return to resting levels.[196] The lower tonic RSA found during recovery likely represent impairments to parasympathetic re-activation in CVC after exertion. In healthy individuals during heart rate recovery, the parasympathetic (vagal) activation begins to dominate the ANS over sympathetic activity as the cardiac autonomic network removes “central command”, which is especially critical to drive rapid decrease in HR.[42,197,198] During passive recovery, parasympathetic reactivation is aided by feedback from muscle mechanoreceptors being stopped and resetting baroreflexes to a lower level.[197,199] If mTBI causes CVC impairments, we would expect that PNS reactivation would take longer for SMs with mTBI, which is reflected in the lower RSA during the recovery periods in our findings.

In addition, we found differences in the rate of recovery of vagal control (RSA slope during recovery) at 2 minutes after the start of the recovery period. The slope of HP was also significantly different at 1 and 2 minutes during recovery, demonstrating that SMs with mTBI took longer to recover. Previous studies have used one minute of heart rate recovery to measure immediate effects cardiac parasympathetic outflow [200,201] and 2-3 minutes as a longer measure.[201] This response soon after exercise is described as vagal recovery or “vagal rebound” and reflects the ability of an individual after facing a “stressor” to self-regulate and be prepared to face another stressor, [195] a vital component for ADSM with the high demands of the military.

Previous studies have found differences in RSA under exertional conditions after concussion[43,161] with mTBI having lower RSA, but tasks have been short in duration and may not provoke a sufficiently large a physiological exertion response to trigger PNS withdrawal and SNS activation as the cardiac autonomic network resets baroreflexes to a lower level.[199] We did not find any difference in HP or RPE during our exertional tasks, contrary to previous findings that found mTBI participants have a slower increase in HR during aerobic exercise and have lower HR at corresponding RPE conditions.[42] Our small sample of mTBI participants, the short duration of the tasks, and conservative safety standards that limited the RPE and HR likely contributed to these null findings. In addition, our mTBI population consists of physically trained active duty servicemembers, not the average patient seen at a civilian clinic.

We extensively described the performance of specific mTBI cases on 2 exertional tasks and recovery after exertion. Participants with mTBI were more likely to have symptom exacerbation and with one exception were not able to successfully complete tasks compared to healthy controls as expected. While we thought the push-up task may be more symptom provoking due to the position changes required, both tasks provoked symptoms in all of our mTBI cases. Only two out of eight tasks completed by mTBI participants were successfully finished. The exertional tasks elicited symptoms that were absent at rest even in a SM with more chronic symptoms. Monitoring symptoms (headache, vertigo, photophobia, balance, dizziness, nausea, visual changes, etc.) and HRV before, during, and after an exertional task is a way clinicians can assess physiological recovery and prescribe activity.[167] CVC recovery has been positively correlated to performance outcomes (cognitive, prone rifle shooting) indicating a clear relevance for the military,[195,202] but future research is needed in how this can be implemented feasibly in the clinic.

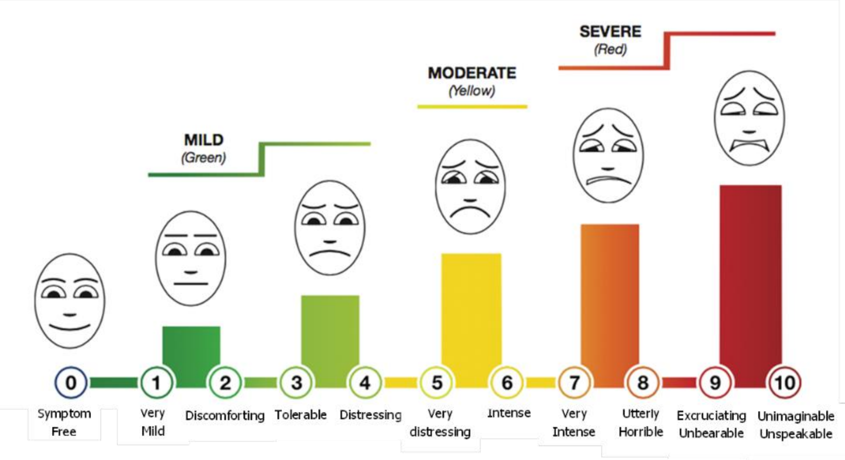
As with any scientific study, the work presented here has limitations. First, all statistical results should be interpreted cautiously given the small sample size and wide age range that may influence the physiological response.[217] In the future, we plan to age match mTBI and HC individuals to address this limitation. We condensed the stepping and pushup task and rest 1 and rest 2 into two timepoints (exertion and rest respectively) to increase our power due to small numbers in the mTBI group. Second, this study was not designed to follow individuals longitudinally; therefore, we cannot draw conclusions about how task performance may predict recovery over time. In line with the HRV Task Force guidelines,[147] we minimized HRV limitations by implementing an editing standard of no more than 5% of total IBIs to avoid over-editing that reduces natural variability. With multiple approaches to HRV analysis in the literature, the frequency domain eliminates random non-rhythmic noise [209] The Porges-Bohrer method for analysis of RSA conforms to the assumptions for parametric analyses and is not moderated by respiration, so the change in breathing rate alone during exertion or recovery is not responsible for RSA changes seen.[154]

Physiological measures may be used alongside symptom report and clinician opinion in return to activity decisions. As a simple, noninvasive measure of ANS balance, HRV could act as an objective marker of recovery and may be a valuable addition in clinical care. Furthermore, standardized exertional assessments that are ecologically valid for military populations can be utilized by primary care managers to guide return to activity or return to duty decisions. Performance on such an exertional task can also help clinicians prescribe appropriate levels of activities, guide progressive return to activity, and may have utility as a predictor of duration of symptoms.

APPENDIX I: SELF-REPORT SCALES DURING TESTING

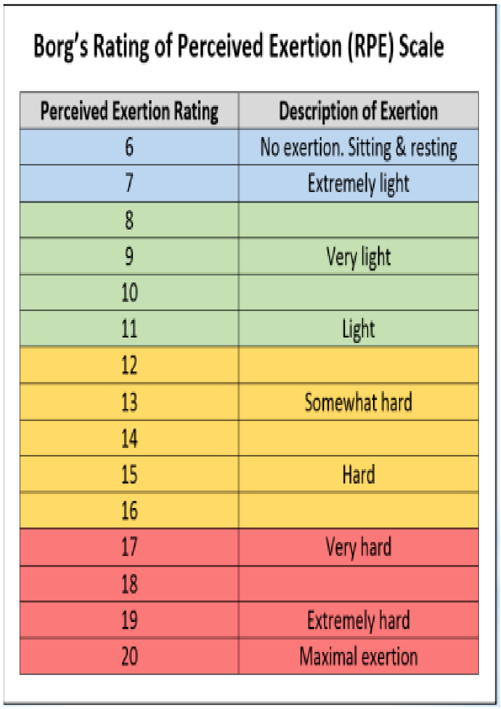
Symptom Scale

Headache, Dizziness, Nausea, Light/sound sensitivity, Fogginess
(feeling “not right” or difficulty concentrating)



Borg RPE

\



Borg’s Rating of Perceived Exertion (RPE) Scale

Perceived Exertion Rating	Description of Exertion
6	No exertion. Sitting & resting
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

APPENDIX II: PRELIMINARY FEASIBILITY RESULTS

Preliminary feasibility results for this study included the testing of active graduate students with military background during task development. These healthy volunteers provided practical and clinical input on task decisions such as step height, speed, and instruction. All five participants reached an exertional HR and RPE level in the final step and push-up protocols.

APPENDIX III: HEARTS INTAKE FORMS

HEARTS Checklist

Date & Time of Consent:__________@__________(Use 24-hour Time Clock format)

Consented By (Staff Initials): ____________

If no for any of the below procedures, please explain in comments below.

Inclusion & Exclusion Criteria Discussed & Eligibility Confirmed: Yes ☐ No ☐

Signed copy of consent given to participant: Yes ☐ No ☐

Initial Intake Form: Yes ☐ No ☐

NSI: Yes ☐ No ☐

DVPRS: Yes ☐ No ☐

Comments:

RedCap Data entry complete: Date:__________________________________Initials:

HEARTS Intake Form

Age: ________

Please answer the following questions that provide information about you & your health history.

General Information

Sex: ☐ Male ☐ Female

2. Which of the following best describes your ethnic background?
   - ☐ Asian/Pacific Islander
   - ☐ Black/African
   - ☐ American Hispanic /
   - ☐ Latino Native
   - ☐ American White/
   - ☐ Caucasian
   - ☐ Bi-racial
   - Other: Please Describe: ☐

What is the highest level of education that you have completed?
- ☐ High school graduate or GED
- ☐ Trade school (Vocational, Technical, or Business School)
- ☐ Some college or Associate's degree (including Community College)
- ☐ Bachelor's degree
- ☐ Graduate or professional degree
- ☐ Other: Please Specify: ☐

Military History

4. What is your branch of military service?
   - ☐ Air Force
   - ☐ Army
   - ☐ Marines
   - ☐ Navy
   - ☐ Coast Guard

5. How long have you been in military service?

|____| Years |____| Months

6. What is your current military pay-grade?
   - ☐ E-1 to E-5
   - ☐ E-6 to E-9
   - ☐ WO-1 to WO-5
   - ☐ O-1 to O-3
   - ☐ O-4 to O-10

7. What is your primary MOS?] ☐

8. Do you currently have any physical training or duty restrictions? NO ☐ YES ☐
IF NO, go on to question 10. If YES go to question 9

9. Check any that apply:

☐ Currently on light or limited duty because of ___________________________________

☐ Have a profile with the following restrictions ____________________________________

____

☐ Performing physical training on my own, not with my unit

☐ Currently serving in a modified role from original MOS

Do you feel physically prepared to begin a combat tour 72 hours from now?
☐ NO
☐ YES

Have you ever been deployed?
☐ NO (If no skip to question 12)
☐ YES

11a. Total number of deployments: ________

Medical History

12. Total number of medically diagnosed concussions or TBIs in your lifetime? ___________

13. Total number of medically diagnosed concussions or TBIs in the past year? ___________

14. What was the date of your most recent concussion/mTBI?

Month _______ Year__________

15. Did that injury happen while performing military duties?
☐ NO ☐ YES

16. What caused the injury?
☐ Airborne Operations
☐ Motor Vehicle Accident
☐ Assault/ Fight
☐ Fall (not sports related)
☐ Sports/ Recreation Activity
☐ Blast/ Explosion
☐ Other: _________________________________

17. Have you ever seen a health care provider for any of the following behavioral health issues?

17a. Combat Stress	☐ NO	☐ YES
17b. Post-traumatic stress	☐ NO	☐ YES
17c. Anxiety	☐ NO	☐ YES
17d. Depression	☐ NO	☐ YES

18. Over the last 2 weeks, how often have you been bothered by the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	☐	☐	☐	☐
Feeling down, depressed or hopeless	☐	☐	☐	☐

19. Over the past week, how many hours of sleep have you averaged per day/night?________

20. Have you used sleep aids in the past 24 hours?

☐ NO

☐ YES

21. How many caffeinated beverages / supplements have you had in the past 24 hours? ________

Neurobehavioral Symptom Inventory (NSI)

Symptom Report

Please rate the following symptoms with regard to how much they have disturbed you **IN THE PAST TWO WEEKS.**

The purpose of this inventory is to track symptoms over time. Please do not attempt to score.

0 = None – Rarely if ever present; not a problem at all

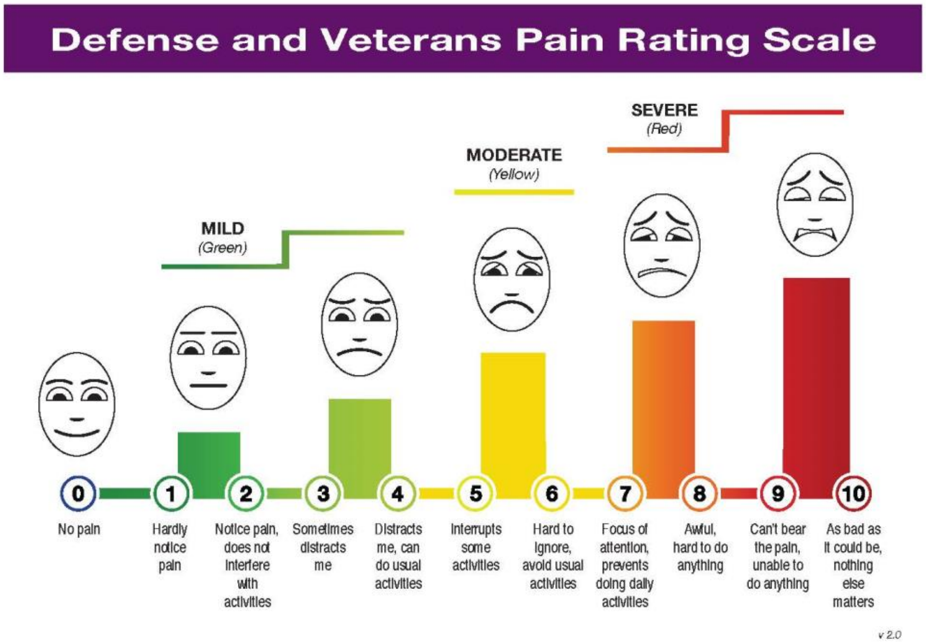
1 = Mild – Occasionally present, but it does not disrupt my activities; I can usually continue what I'm doing; doesn't really concern me.

2 = Moderate – Often present, occasionally disrupts my activities; I can usually continue what I'm doing with some effort; I feel somewhat concerned.

3 = Severe – Frequently present and disrupts activities; I can only do things that are fairly simple or take little effort; I feel I need help.

4 = Very Severe – Almost always present and I have been unable to perform at work, school or home due to this problem; I probably cannot function without help.

Symptom	**0**	**1**	**2**	**3**	**4**
a. Feeling dizzy	☐	☐	☐	☐	☐
b. Loss of balance	☐	☐	☐	☐	☐
c. Poor coordination, clumsy	☐	☐	☐	☐	☐
d. Headaches	☐	☐	☐	☐	☐
e. Nausea	☐	☐	☐	☐	☐
f. Vision problems, blurring, trouble seeing	☐	☐	☐	☐	☐
g. Sensitivity to light	☐	☐	☐	☐	☐
h. Hearing difficulty	☐	☐	☐	☐	☐
i. Sensitivity to noise	☐	☐	☐	☐	☐
j. Numbness or tingling on parts of my body	☐	☐	☐	☐	☐
k. Change in taste and/or smell	☐	☐	☐	☐	☐
l. Loss of appetite or increased appetite	☐	☐	☐	☐	☐
m. Poor concentration, can't pay attention, easily distracted	☐	☐	☐	☐	☐
n. Forgetfulness, can't remember things	☐	☐	☐	☐	☐
o. Difficulty making decisions	☐	☐	☐	☐	☐
p. Slowed thinking, difficulty getting organized, can't finish things	☐	☐	☐	☐	☐
q. Fatigue, loss of energy, getting tired easily	☐	☐	☐	☐	☐
r. Difficulty falling or staying asleep	☐	☐	☐	☐	☐
s. Feeling anxious or tense	☐	☐	☐	☐	☐
t. Feeling depressed or sad	☐	☐	☐	☐	☐
u. Irritability, easily annoyed	☐	☐	☐	☐	☐
v. Poor frustration tolerance, feeling easily overwhelmed by things	☐	☐	☐	☐	☐



1. **Which number above best describes you pain during the past 24 hours? _______**

DOD/VA PAIN SUPPLEMENTAL QUESTIONS

For clinicians to evaluate the biopsychosocial impact of pain

1. Circle the one number that describes how, during the past 24 hours, pain has interfered with your usual ACTIVITY:

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

2. Circle the one number that describes how, during the past 24 hours, pain has interfered with your SLEEP:

0 1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

3. Circle the one number that describes how, during the past 24 hours, pain has affected your MOOD:

0 1 2 3 4 5 6 7 8 9 10

Does not affect Completely affects

4. Circle the one number that describes how, during the past 24 hours, pain has contributed to your STRESS:

0 1 2 3 4 5 6 7 8 9 10

Does not contribute Contributes a great deal

**Reference for pain interference: Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 23(2): 129-138, 1994.* *v 2.*

APPENDIX IV: HEARTS SCORING FORMS

Study ID: Rater: Date:

Sequence: A B Age:

HEARTS: Step Scoring

Time	RPE	Symp. Type	Symp. Score	HR (approx.)
Prior to start				
	Start at 80 bpm			
1:00				
2:00				
	Change to 100 bpm			
3:00				
4:00				
	Change to 120 bpm			
5:00				
6:00				

Did SM complete the task? __Yes

______No (subject stopped)
Comments:

______No (examiner stopped)

- ○ heart rate exceeding 85% of predicted max.
- ○ Can’t keep up with step cadence
- ○ RPE >16
- ○ symptom exacerbation: an increase of >2 points on the Likert scale from resting

Time	RPE	Symp. Type	Symp. Score	HR (approx.)
Post Testing				

Study ID: Rater: Date:

Sequence: A B Age:

HEARTS: Push-Up Scoring

Time	RPE		Symptom	HR (approx.)
Prior to start				
1:00				
2:00				

Total Push-Up: ________

Did SM complete the task? __Yes

______No (subject stopped)
Comments:

______No (examiner stopped)

- ○ heart rate exceeding (moderate vs vigorous exertion 70/85%
- ○ RPE > 16
- ○ symptom exacerbation: an increase of more than 2 points on the Likert scale from resting

HR max. Resource

Age	60% of max	85% of max.
20	130	170
22	128.7	168.3
25	126.75	165.75
28	124.8	163.2
30	123.5	161.5
35	120.25	157.25
40	117	153
45	113.75	148.75

Symptom Resource

Symptom	Abbrev.
Headache	H
Dizziness	D
Nausea	N
Light/Sound Sensitivity	S
Fogginess	F

REFERENCES

1. Houry D, Florence C, Baldwin G, Stevens J, McClure R. The CDC Injury Centers Response to the Growing Public Health Problem of Falls Among Older Adults. *Am J Lifestyle Med*. 2016;10(1):74-77. doi:10.1177/1559827615600137

2. Verma SK, Willetts JL, Corns HL, Marucci-Wellman HR, Lombardi DA, Courtney TK. Falls and fall-related injuries among community-dwelling adults in the United States. Haddad JM, ed. *PLoS One*. 2016;11(3):e0150939. doi:10.1371/journal.pone.0150939

3. Bergen G, Stevens MR, Burns ER. Falls and fall injuries among adults aged ≥65 years - United States, 2014. *Morb Mortal Wkly Rep*. 2016;65(37):993-998. doi:10.15585/mmwr.mm6537a2

4. Adams P, Martinez M, Vickerie J, Kirzinger W. Summary health statistics for the U.S. population: National Health Interview Survey, 2010. *Vital Heal Stat*. 2011;10(251):1-117.

5. Burns ER, Stevens JA, Lee R. The direct costs of fatal and non-fatal falls among older adults — United States. *J Safety Res*. 2016;58:99-103. doi:10.1016/j.jsr.2016.05.001

6. Florence CS, Bergen G, Atherly A, Burns E, Stevens J, Drake C. Medical Costs of Fatal and Nonfatal Falls in Older Adults. *J Am Geriatr Soc*. 2018;66(4):693-698. doi:10.1111/jgs.15304

7. Hoffman GJ, Hays RD, Shapiro MF, Wallace SP, Ettner SL. The Costs of Fall-Related Injuries among Older Adults: Annual Per-Faller, Service Component, and Patient Out-of-Pocket Costs. *Health Serv Res*. 2017;52(5):1794-1816. doi:10.1111/1475-6773.12554

8. Ambrose AF, Paul G, Hausdorff JM. Risk factors for falls among older adults: A review of the literature. *Maturitas*. 2013;75(1):51-61. doi:10.1016/j.maturitas.2013.02.009

9. Hughes CC, Kneebone II, Jones F, Brady B. A theoretical and empirical review of psychological factors associated with falls-related psychological concerns in community-dwelling older people. *Int Psychogeriatrics*. 2015;27(7):1071-1087. doi:10.1017/S1041610214002701

10. Allison LK, Painter JA, Emory A, Whitehurst P, Raby A. Participation Restriction, Not Fear of Falling, Predicts Actual Balance and Mobility Abilities in Rural Community-Dwelling Older Adults. *J Geriatr Phys Ther*. 2013;36(1):13-23. doi:10.1519/JPT.0b013e3182493d20

11. Bertera EM, Bertera RL. Fear of Falling and Activity Avoidance in a National Sample of Older Adults in the United States. *Health Soc Work*. 2008;33(1):54-62. doi:10.1093/hsw/33.1.54

12. Fletcher PC, Guthrie DM, Berg K, Hirdes JP. Risk Factors for Restriction in Activity Associated With Fear of Falling Among Seniors Within the Community. *J Patient Saf*. 2010;6(3):187-191. doi:10.1097/PTS.0b013e3181f1251c

13. Moyer VA. Prevention of Falls in Community-Dwelling Older Adults: U.S. Preventive Services Task Force Recommendation Statement. *Ann Intern Med*. 2012;157:197-204.

14. Sherrington C, Michaleff ZA, Fairhall N, et al. Exercise to prevent falls in older adults: an updated systematic review and meta-analysis. *Br J Sports Med*. 2016;51(24):1750-1758. doi:10.1136/bjsports-2016-096547

15. Robertson MC, Campbell AJ, Gardner MM, Devlin N. Preventing injuries in older people by preventing falls: a meta- analysis of individual-level data. *J Am Geriatr Soc*. 2002;50(5):905-911.

16. Gormley KJ. Falls prevention and support: Translating research, integrating services and promoting the contribution of service users for quality and innovative programmes of care. *Int J Older People Nurs*. 2011;6(4):307-314. doi:10.1111/j.1748-3743.2011.00303.x

17. Shubert TE, Altpeter M, Busby-Whitehead J. Using the RE-AIM Framework to translate a research-based falls prevention intervention into a community-based program: Lessons Learned. *J Safety Res*. 2011;42(6):509-516. doi:10.1016/j.jsr.2011.09.003

18. Arcury TA, Preisser JS, Gesler WM, Powers JM. Access to transportation and health care utilization in a rural region. *J Rural Heal*. 2004;21(1):31-38. doi:10.1111/j.1748-0361.2005.tb00059.x

19. Li F, Eckstrom E, Harmer P, Fitzgerald K, Voit J, Cameron KA. Exercise and fall prevention: Narrowing the research-to-practice gap and enhancing integration of clinical and community practice. *J Am Geriatr Soc*. 2016;64(2):425-431. doi:10.1111/jgs.13925

20. National Academies of Sciences Engineering and Medicine. *Health-Care Utilization as a Proxy in Disability Determination*. Washington, D.C.: National Academies Press; 2018. doi:10.17226/24969

21. Shubert TE, Goto LS, Smith ML, Jiang L, Rudman H, Ory MG. The Otago Exercise Program: Innovative delivery models to maximize sustained outcomes for high risk, homebound older adults. *Front Public Heal*. 2017;5(March):54. doi:10.3389/fpubh.2017.00054

22. Shubert TE, Smith ML, Goto L, Jiang L, Ory MG. Otago Exercise Program in the United States: Comparison of 2 implementation models. *Phys Ther*. 2017;97(2):187-197. doi:10.2522/ptj.20160236

23. Li F, Harmer P, Fitzgerald K. Implementing an Evidence-Based Fall Prevention Intervention in Community Senior Centers. *Am J Public Health*. 2016;106(11):2026-2031. doi:10.2105/AJPH.2016.303386

24. Hawley-Hague H, Roden A, Abbott J. The evaluation of a strength and balance exercise program for falls prevention in community primary care. *Physiother Theory Pract*. 2017;33(8):611-621. doi:10.1080/09593985.2017.1328721

25. Renfro M, Bainbridge DB, Smith ML. Validation of evidence-based fall prevention programs for adults with intellectual and/or developmental disorders: A modified Otago exercise program. *Front Public Heal*. 2016;4:261. doi:10.3389/fpubh.2016.00261

26. Mercer VS, Zimmerman MY, Schrodt LA, Palmer WE, Samuels V. Interprofessional education in a rural community-based falls prevention project: The CHAMP experience. *J Phys Ther Educ*. 2014;28(2):35-45.

27. Shubert TE, Smith ML, Jiang L, Ory MG. Disseminating the Otago Exercise Program in the United States: Perceived and actual physical performance improvements from participants. *J Appl Gerontol*. 2018;37(1):79-98. doi:10.1177/0733464816675422

28. Rossiter-Fornoff JE, Wolf SL, Wolfson LI, Buchner DM. A cross-sectional validation study of the FICSIT common data base static balance measures. Frailty and Injuries: Cooperative Studies of Intervention Techniques. *J Gerontol A Biol Sci Med Sci*. 1995;50(6):M291-M297. doi:10.1093/gerona/50A.6.M291

29. Podsiadlo D, Richardson S. The timed "Up and Go" test: A test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142-148.

30. Jones C, Rikli R, Beam W. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. *Res Q Exerc Sport*. 1999;70(2):113-119.

31. Mat S, Ng CT, Tan PJ, et al. Effect of Modified Otago Exercises on Postural Balance, Fear of Falling, and Fall Risk in Older Fallers With Knee Osteoarthritis and Impaired Gait and Balance: A Secondary Analysis. *PM R*. 2018;10(3):254-262. doi:10.1016/j.pmrj.2017.08.405

32. Robertson DA, Savva GM, Kenny RA. Frailty and cognitive impairment-A review of the evidence and causal mechanisms. *Ageing Res Rev*. 2013;12(4):840-851. doi:10.1016/j.arr.2013.06.004

33. Chen HT, Lin CH, Yu LH. Normative physical fitness scores for community-dwelling older adults. *J Nurs Res*. 2009;17(1):30-41. doi:10.1097/JNR.0b013e3181999d4c

34. Lin M, Hwang ÃH, Hu M, et al. Psychometric Comparisons of the Timed Up and Go, One-Leg Stand, Functional Reach, and Tinetti Balance Measures in Community-Dwelling Older People. *J Am Geriatr Soc*. 2004;52(8):1343-1348. doi:10.1111/j.1532-5415.2004.52366.x

35. Robertson MC, Devlin N, V PS, Gardner MM, Buchner DM, Campbell AJ. Economic evaluation of a community based exercise programme to prevent falls. *J Epidemiol Community Health*. 2001;55:600-606.

36. Thomas S, Mackintosh S, Halbert J. Does the "Otago exercise programme" reduce mortality and falls in older adults?: a systematic review and meta-analysis. *Age Ageing*. 2010;39(6):681-687. doi:10.1093/ageing/afq102

37. Lamb SES, Jorstad-Stein E, Hauer K, Jørstad-Stein EC, Hauer K, Becker C. Development of a common outcome data set for fall injury prevention trials: The Prevention of Falls Network Europe consensus. *J Am Geriatr Soc*. 2005;53(9):1618-1622. doi:10.1111/j.1532-5415.2005.53455.x

38. Gillespie LD, Robertson MC, Gillespie WJ, et al. Interventions for preventing falls in older people living in the community. Gillespie LD, ed. *Cochrane Database Syst Rev*. 2012;2(CD007146):CD007146. doi:10.1002/14651858.CD007146.pub3

39. Avin KG, Hanke TA, Kirk-Sanchez N, et al. Management of falls in community-dwelling older adults: clinical guidance statement from the Academy of Geriatric Physical Therapy of the American Physical Therapy Association. *Phys Ther*. 2015;95(6):815-834. doi:10.2522/ptj.20140415 [doi]

40. Guirguis-Blake JM, Michael YL, Perdue LA, Coppola EL, Beil TL. Interventions to Prevent Falls in Older Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. *JAMA*. 2018;319(16):1705-1716. doi:10.1001/jama.2017.21962

41. Stevens JA, Phelan EA. Development of STEADI: A Fall Prevention Resource for Health Care Providers. *Health Promot Pract*. 2013;14(5):706-714. doi:10.1177/1524839912463576

42. Stevens JA. *A CDC Compendium of Effective Fall Interventions: What Works for Community-Dwelling Older Adults. Second Edition.* Vol 2nd ed. Atlanta, ,GA: Centers for Disease Control and Prevention; 2010.

43. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Tilyard MW, Buchner DM. Randomised controlled trial of a general practice programme of home based exercise to prevent falls in elderly women. *BMJ*. 1997;315(7115):1065-1069. doi:10.1136/bmj.315.7115.1065

44. Campbell AJ, Robertson MC, Gardner MM, Norton RN, Buchner DM. Falls prevention over 2 years: A randomized controlled trial in women 80 years and older. *Age Ageing*. 1999;28(6):513-518. doi:10.1093/ageing/28.6.513

45. Campbell A, Robertson M, Gardner M, Norton R, Buchner D. Psychotropic medication withdrawal and a home-based exercise program to prevent falls: a randomized, controlled trial. *J Am Geriatr Soc*. 1999;47(7):850-853. doi:10.1111/j.1532-5415.1999.tb03843.x

46. Robertson MC, Gardner MM, Devlin N, Mcgee R, Campbell AJ. Effectiveness and economic evaluation of a nurse delivered home exercise programme to prevent falls. 2: Controlled trial in multiple centres. *Bmj*. 2001;322(March):1-5. doi:10.1136/bmj.322.7288.701

47. Campbell A, Robertson M. Otago exercise programme to prevent falls in older adults. *Otago Med Sch Univ Otago, New Zeal*. 2003.

48. Gardner MM, Buchner DM, Robertson MC, Campbell AJ. Practical implementation of an exercise-based falls prevention programme. *Age Ageing*. 2001;30:77-83. doi:10.1093/ageing/30.1.77

49. Binns E. The Otago exercise programme: do strength and balance improve? 2005.

50. Liu-Ambrose T, Donaldson MG, Ahamed Y, et al. Otago home-based strength and balance retraining improves executive functioning in older fallers: A randomized controlled trial. *J Am Geriatr Soc*. 2008. doi:10.1111/j.1532-5415.2008.01931.x

51. Campbell AJ, Robertson MC, Grow SJ La, et al. Randomised controlled trial of prevention of falls in people aged ≥75 with severe visual impairment: the VIP trial. *BMJ*. 2005;331(7520):817. doi:10.1136/bmj.38601.447731.55

52. Shier V, Trieu E, Ganz DA. Implementing exercise programs to prevent falls: systematic descriptive review. *Inj Epidemiol*. 2016;3:16. doi:10.1186/s40621-016-0081-8

53. Shubert TE, Smith ML, Ory MG, et al. Translation of the Otago Exercise Program for adoption and implementation in the United States. *Front public Heal*. 2014;2:152. doi:10.3389/fpubh.2014.00152

54. Shubert TE, Smith ML, Schneider EC, Wilson AD, Ory MG. Commentary: Public health system perspective on implementation of evidence-based fall-prevention strategies for older adults. *Front public Heal*. 2016;4:252. doi:10.3389/fpubh.2016.00252

55. Smith ML, Towne SDJ, Herrera-Venson A, et al. Delivery of fall prevention interventions for at-risk older adults in rural areas: Findings from a national dissemination. *Int J Environ Res Public Health*. 2018;15(12):2798.

56. United States Census Bureau (Institution). 2013-2017 American Community Survey 5-Year Estimates. factfinder.census.gov. Published 2017. Accessed August 9, 2019.

57. Stevens JA, Burns E. A CDC Compendium of Effective Fall Interventions: What Works for Community-Dwelling Older Adults. 3rd ed. 2015:885-896. doi:10.1016/j.apmr.2006.04.005

58. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12(3):189-198.

59. Powell LE, Myers AM. The activities-specific balance confidence (ABC) scale. *Journals Gerontol Ser A Biol Sci Med Sci*. 1995;50(1):M28-M34. doi:10.1093/gerona/50A.1.M28

60. Botner EM, Miller WC, Eng JJ. Measurement properties of the Activities-specific Balance Confidence Scale among individuals with stroke. *Disabil Rehabil*. 2005;27(4):156-163. doi:10.1080/09638280400008982

61. Myers AM, Powell LE, Maki BE, Holliday PJ, Brawley LR, Sherk W. Psychological

indicators of balance confidence: relationship to actual and perceived abilities. *J Gerontol A Biol Sci Med Sci*. 1996;51(1):M37-M43. doi:10.1093/gerona/51A.1.M37

62. Lamarche L, Zaback M, Gammage KL, Klentrou P, Adkin AL. A method to investigate discrepancies between perceived and actual balance in older women. *Gait Posture*. 2013;38(4):888-893.

63. Beauchamp MK, Harrison SL, Goldstein RS, Brooks D. Interpretability of Change Scores in Measures of Balance in People With COPD. *Chest*. 2016;149(3):696-703. doi:10.1378/chest.15-0717

64. Vellas BJ, Wayne SJ, Romero L, Baumgartner RN, Rubenstein LZ, Garry PJ. One-leg balance is an important predictor of injurious falls in older persons. *J Am Geriatr Soc*. 1997;45(6):735-738.

65. Freiberger E, De vreede P, Schoene D, et al. Performance-based physical function in older community-dwelling persons: A systematic review of instruments. *Age Ageing*. 2012;41(6):712-721. doi:10.1093/ageing/afs099

66. Treacy D, Hassett L. The Short Physical Performance Battery. *J Physiother*. 2018;64(1):61. doi:10.1016/j.jphys.2017.04.002

67. Guralnik JM, Simonsick EM, Ferrucci L, et al. A Short Physical Performance Battery Assessing Lower Extremity Function: Association With Self-Reported Disability and Prediction of Mortality and Nursing Home Admission. *J Gerontol*. 1994;49(2):M85-M94. doi:10.1093/geronj/49.2.M85

68. Cho B, Scarpace D, Alexander NB. Tests of Stepping as Indicators of Mobility , Balance , and Fall Risk in Balance-Impaired Older Adults. *J Am Geriatr Soc*. 2004;52(7):1168-1173.

69. Herman T, Giladi N, Hausdorff JM. Properties of the “Timed Up and Go” test: More than meets the eye. *Gerontology*. 2011;57(3):203-210. doi:10.1159/000314963

70. Wrisley DM, Kumar N. Functional gait assessment: Concurrent, discriminative, and predictive validity in community-dwelling older adults. *Phys Ther*. 2010;90(4):1-13. doi:10.2522/ptj.20090069

71. Shumway-Cook A, Brauer S, Woollacott M. Predicting the Probability for Falls in Community-Dwelling Older Adults Using the Timed Up and Go Test. *Phys Ther*. 2000;32(suppl 2):450-456. doi:10.1093/ptj/80.9.896

72. Bischoff HA, Stähelin HB, Monsch AU, et al. Identifying a cut-off point for normal mobility: A comparison of the timed “up and go” test in community-dwelling and institutionalised elderly women. *Age Ageing*. 2003;32(3):315-320. doi:10.1093/ageing/32.3.315

73. Lusardi MM, Fritz S, Middleton A, et al. Determining Risk of Falls in Community

Dwelling Older Adults. *J Geriatr Phys Ther*. 2017;40(1):1-36. doi:10.1519/JPT.0000000000000099

74. Phelan EA, Mahoney JE, Voit JC, Stevens JA. Assessment and Management of Fall Risk in Primary Care Settings. *Med Clin North Am*. 2015;99(2):281-293. doi:10.1016/j.mcna.2014.11.004

75. Lee J, Geller AI, Strasser DC. Analytical review: Focus on fall screening assessments. *PM R*. 2013;5(7):609-621. doi:10.1016/j.pmrj.2013.04.001

76. Wright AA, Cook CE, Baxter GD, Dockerty JD, Abbott JH. A Comparison of 3 Methodological Approaches to Defining Major Clinically Important Improvement of 4 Performance Measures in Patients With Hip Osteoarthritis. *J Orthop Sport Phys Ther*. 2011;41(5):319-327. doi:10.2519/jospt.2011.3515

77. Meretta BM, Whitney SL, Marchetti GF, Sparto PJ, Muirhead RJ. The five times sit to stand test: Responsiveness to change and concurrent validity in adults undergoing vestibular rehabilitation. *J Vestib Res Equilib Orientat*. 2006;16(4/5):233-243.

78. Bohannon RW. Test-Retest Reliability of the Five-Repetition Sit-to-Stand Test: A Systematic Review of the Literature Involving Adults. *J Strength Cond Res*. 2011;25(11):3205-3207. doi:10.1519/JSC.0b013e318234e59f

79. McCarthy EK, Horvat MA, Holtsberg PA, Wisenbaker JM. Repeated chair stands as a measure of lower limb strength in sexagenarian women. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2004;59(11):1207-1212. doi:10.1093/gerona/59.11.1207

80. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav Res Methods*. 2007;39(2):175-191. doi:10.3758/BF03193146

81. Page P. Beyond statistical significance: clinical interpretation of rehabilitation research literature. *Int J Sports Phys Ther*. 2014;9(5):726-736.

82. Houry D, Florence C, Baldwin G, Stevens J, McClure R. The CDC Injury Center’s response to the growing public health problem of falls among older adults. *Am J Lifestyle Med*. 2016;10(1):74-77. doi:10.1177/1559827615600137

83. Liu SW, Obermeyer Z, Chang Y, Shankar KN. Frequency of ED revisits and death among older adults after a fall. *Am J Emerg Med*. 2015;33(8):1012-1018. doi:10.1016/j.ajem.2015.04.023

84. Sherrington C, Tiedemann A. Physiotherapy in the prevention of falls in older people. *J Physiother*. 2015;61(2):54-60. doi:10.1016/j.jphys.2015.02.011

85. Stubbs B, Brefka S, Denkinger MD. What Works to Prevent Falls in Community-Dwelling Older Adults? Umbrella Review of Meta-analyses of Randomized Controlled Trials. *Phys Ther*. 2015;95(8). doi:10.2522/ptj.20140461

86. Carande-Kulis V, Stevens JA, Florence CS, Beattie BL, Arias I. A cost–benefit analysis of three older adult fall prevention interventions. *J Safety Res*. 2015;52:65-70. doi:10.1016/j.jsr.2014.12.007

87. Campbell AJ, Robertson MC. Comprehensive Approach to Fall Prevention on a National Level: New Zealand. *Clin Geriatr Med*. 2010;26(4):719-731. doi:10.1016/j.cger.2010.06.004

88. NCOA. *State Policy Toolkit for Advancing Fall Prevention: Select Resources*.; 2017.

89. Kaniewski M, Stevens JA, Parker EM, Lee R. An introduction to the Centers for Disease Control and Prevention's efforts to prevent older adult falls. *Front Public Heal*. 2015;2(119):1-3.

90. Benavent-Caballer V, Rosado-Calatayud P, Segura-Ortí E, Amer-Cuenca JJ, Lisón JF. The effectiveness of a video-supported group-based Otago exercise programme on physical performance in community-dwelling older adults: a preliminary study. *Physiother (United Kingdom)*. 2016;102(3):280-286. doi:10.1016/j.physio.2015.08.002

91. Arcury TA, Gesler WM, Preisser JS, Sherman J, Spencer J, Perin J. The effects of geography and spatial behavior on health care utilization among the residents of a rural region. *Health Serv Res*. 2005;40(1):135-155. doi:10.1111/j.1475-6773.2005.00346.x

92. Glasgow RE, Klesges LM, Dzewaltowski DA, Estabrooks PA, Vogt TM. Evaluating the impact of health promotion programs: Using the RE-AIM framework to form summary measures for decision making involving complex issues. *Health Educ Res*. 2006;21(5):688-694. doi:10.1093/her/cyl081

93. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: The RE-AIM framework. *Am J Public Health*. 1999;89:1322-1327.

94. Smith ML, Ory MG, Larsen R. Older women in a state-wide, evidence-based falls prevention program: Who enrolls and what benefits are obtained? *Women's Heal Issues*. 2010;20(6):427-434. doi:10.1016/j.whi.2010.07.003

95. Lopez MN, Charter RA, Mostafavi B, Nibut LP, Smith WE. Psychometric properties of the Folstein Mini-Mental State Examination. *Assessment*. 2005;12(2):137-144. doi:10.1177/1073191105275412

96. Podsiadlo DD. The timed "Up & Go": A test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39(2):142-148.

97. Lachman ME, Howland J, Tennstedt S, Jette A, Assmann S, Peterson EW. Fear of falling and activity restriction: the survey of activities and fear of falling in the elderly (SAFE). *J Gerontol B Psychol Sci Soc Sci*. 1998;53(1):P43-50.

98. Painter JA, Allison LK, Dhingra P, Daughtery J, Cogdill K, Trujillo LG. Fear of falling

and its relationship with anxiety, depression, and activity engagement among community-dwelling older adults. *Am J Occup Ther*. 2012;66:169-176. doi:10.5014/ajot.2012.002535

99. Greenberg SA. Analysis of measurement tools of fear of falling for high-risk, community-dwelling older adults. *Clin Nurs Res*. 2012;21(1):113-130. doi:10.1177/1054773811433824

100. Falvey JR, Gustavson AM, Price L, Papazian L, Stevens-Lapsley JE. Dementia, Comorbidity, and Physical Function in the Program of All-Inclusive Care for the Elderly. *J Geriatr Phys Ther*. 2019;42(2):E1-E6. doi:10.1519/JPT.0000000000000131

101. Beato M, Dawson N, Svien L, Wharton T. Examining the Effects of an Otago-Based Home Exercise Program on Falls and Fall Risks in an Assisted Living Facility. *J Geriatr Phys Ther*. 2018;0(0):1. doi:10.1519/jpt.0000000000000190

102. Cigolle CT, Ha J, Min LC, et al. The epidemiologic data on falls, 1998-2010: More older Americans report falling. *JAMA Intern Med*. 2015;175(3):443-445. doi:10.1001/jamainternmed.2014.7533

103. Orces CH. Emergency department visits for fall-related fractures among older adults in the USA: a retrospective cross-sectional analysis of the National Electronic Injury Surveillance System All Injury Program, 2001-2008. *BMJ Open*. 2013;3:1-8. doi:10.1136/bmjopen-2012-001722

104. Web-based Injury Statistics Query and Reporting System (WISQARS). Centers for Disease Control and Prevention, National Center for Injury Prevention and Control. www.cdc.gov/injury/wisqars. Published 2017.

105. Scholl L, Seth P, Kariisa M, Wilson N, Baldwin ; Grant. Drug and Opioid-Involved Overdose Deaths-United States, 2013-2017. *Morb Mortal Wkly Rep*. 2019;67:1419–1427.

106. National Center for Injury Prevention and Control (Institution). *Tools to Implement the Otago Exercise Program: A Program to Reduce Falls*. 1st ed. Centers for Disease Control and Prevention

107. Liu X, Villamagna AH, Yoo JW. Sustainable affordability of Otago exercise in the US healthcare system. *Osteoporos Int*. 2017;28:2733-2734. doi:10.1007/s00198-017-4055-7

108. Shubert TE, Smith ML, Prizer LP, Ory MG. Complexities of fall prevention in clinical settings: a commentary. *Gerontologist*. 2014;54(4):550-558. doi:10.1093/geront/gnt079

109. Jones DL, Starcher RW, Eicher JL, Wilcox S. Adoption of a Tai Chi Intervention, Tai Ji Quan: Moving for Better Balance, for Fall Prevention by Rural Faith-Based Organizations, 2013–2014. *Prev Chronic Dis*. 2016;13:160083. doi:10.5888/pcd13.160083

110. Smith ML, Towne SD, Herrera-Venson A, et al. Dissemination of Chronic Disease Self-Management Education (CDSME) Programs in the United States: Intervention Delivery

by Rurality. *Int J Environ Res Public Health*. 2017;14(6). doi:10.3390/ijerph14060638

111. Costello E, Kafchinski M, Vrazel J, Sullivan P. Motivators, Barriers, and Beliefs Regarding Physical Activity in an Older Adult Population. *J Geriatr Phys Ther*. 2011;34(3):138-147. doi:10.1519/JPT.0b013e31820e0e71

112. Rosenblatt NJ, Grabiner MD. Relationship between obesity and falls by middle-aged and older women. *Arch Phys Med Rehabil*. 2012;93(4):718-722. doi:10.1016/j.apmr.2011.08.038

113. McMahon SK, Lewis B, Oakes JM, Wyman JF, Guan W, Rothman AJ. Assessing the effects of interpersonal and intrapersonal behavior change strategies on physical activity in older adults: A factorial experiment. *Ann Behav Med*. 2017;51(3):376-390. doi:10.1007/s12160-016-9863-z

114. Laddu DR, Wertheim BC, Garcia DO, et al. Associations Between Self-Reported Physical Activity and Physical Performance Measures Over Time in Postmenopausal Women: The Women’s Health Initiative. *J Am Geriatr Soc*. 2017;65(10):2176-2181. doi:10.1111/jgs.14991

115. Campbell A, Borrie M, Spears G. Risk factors for falls in a community-based prospective study of people 70 years and older. *J Gerontol*. 1989;44(4):M112–M117.

116. Hanke T, Martin S. Posture and balance. In: Cech DJ, Martin S, eds. *Functional Movement Development Across the Lifespan*. 3rd ed. St. Louis, MO: Elsevier Saunders; 2012:263-287.

117. Bohannon RW, Bubela DJ, Magasi SR, Wang Y-C, Gershon RC. Sit-to-stand test: Performance and determinants across the age-span. *Isokinet Exerc Sci*. 2010;18(4):235-240. doi:10.3233/IES-2010-0389

118. McMahon SK, Wyman JF, Belyea MJ, Shearer N, Hekler EB, Fleury J. Combining Motivational and Physical Intervention Components to Promote Fall-Reducing Physical Activity Among Community-Dwelling Older Adults: A Feasibility Study. *Am J Heal Promot*. 2016;30(8):638-644. doi:10.4278/ajhp.130522-ARB-265

119. Tennstedt S, Howland J, Lachman M, Peterson E, Kasten L, Jette A. A randomized, controlled trial of a group intervention to reduce fear of falling and associated activity restriction in older adults. *J Gerontol B Psychol Sci Soc Sci*. 1998;53(6):P384-92. doi:10.1093/geronb/53B.6.P384

120. Cummings S, Nevitt M, Kidd S. Forgetting falls: the limited accuracy of recall of falls in the elderly. *J Am Geriatr Soc*. 1988;36(7):613-616.

121. Smith AS, Trevelyan E. In some states, more than half of older residents live in rural areas. United States Census Bureeau. https://www.census.gov/library/stories/2019/10/older-population-in-rural-america.html. Published 2019.

122. Battaglia C, Glasgow RE. Pragmatic dissemination and implementation research models, methods and measures and their relevance for nursing research. *Nurs Outlook*. 2018;66(5):430-445. doi:10.1016/j.outlook.2018.06.007

123. Schwenk M, Lauenroth A, Stock C, et al. Definitions and methods of measuring and reporting on injurious falls in randomised controlled fall prevention trials: a systematic review. *BMC Med Res Methodol*. 2012;12(1):50. doi:10.1186/1471-2288-12-50

124. Tinetti ME, Williams CS. Falls, injuries due to falls, and the risk of admission to a nursing home. *N Engl J Med*. 1997;337(18):1279-1284. doi:10.1056/NEJM199710303371806

125. Alexander BH, Rivara FP, Wolf ME. The cost and frequency of hospitalization for fall-related injuries in older adults. *Am J Public Health*. 1992;82(7):1020-1023. doi:10.2105/AJPH.82.7.1020

126. Ayoung-Chee P, McIntyre L, Ebel BE, MacK CD, McCormick W, Maier R V. Long-term outcomes of ground-level falls in the elderly. *J Trauma Acute Care Surg*. 2014;76(2):498-503. doi:10.1097/TA.0000000000000102

127. Ayoung-Chee PR, Rivara FP, Weiser T, Maier R V., Arbabi S. Beyond the hospital doors: Improving long-term outcomes for elderly trauma patients. *J Trauma Acute Care Surg*. 2015;78(4):837-843. doi:10.1097/TA.0000000000000567

128. Deshpande N, Metter EJ, Lauretani F, Bandinelli S, Guralnik J, Ferrucci L. Activity restriction induced by fear of falling and objective and subjective measures of physical function: A prospective cohort study. *J Am Geriatr Soc*. 2008;56(4):615-620. doi:10.1111/j.1532-5415.2007.01639.x

129. Kumar A, Carpenter H, Morris R, Iliffe S, Kendrick D. Which factors are associated with fear of falling in community-dwelling older people? *Age Ageing*. 2014;43(1):76-84. doi:10.1093/ageing/aft154

130. Li F, Fisher KJ, Harmer P, McAuley E, Wilson NL. Fear of falling in elderly persons: Association with falls, functional ability, and quality of life. *Journals Gerontol - Ser B Psychol Sci Soc Sci*. 2003;58(5):283-290. doi:10.1093/geronb/58.5.P283

131. Scheffer AC, Schuurmans MJ, Van dijk N, Van der hooft T, De rooij SE. Fear of falling: Measurement strategy, prevalence, risk factors and consequences among older persons. *Age Ageing*. 2008;37(1):19-24. doi:10.1093/ageing/afm169

132. Evitt CP, Quigley PA. Fear of falling in older adults: a guide to its prevalence, risk factors, and consequences. *Rehabil Nurs*. 2004;29(6):207-210.

133. Liu JYW. The severity and associated factors of participation restriction among community-dwelling frail older people: an application of the International Classification of Functioning, Disability and Health (WHO-ICF). *BMC Geriatr*. 2017;17(1):43. doi:10.1186/s12877-017-0422-7

134. Gross MT, Mercer VS, Lin F-C. Effects of Foot Orthoses on Balance in Older Adults. *J Orthop Sport Phys Ther*. 2012;42(7):649-657. doi:10.2519/jospt.2012.3944

135. Arnadottir SA, Mercer VS. Effects of footwear on measurements of balance and gait in women between the ages of 65 and 93 years. *Phys Ther*. 2000;80(1):17-27.

136. Rubenstein LZ. Falls in older people: Epidemiology, risk factors and strategies for prevention. *Age Ageing*. 2006;35(SUPPL.2):37-41. doi:10.1093/ageing/afl084

137. Hu J, Xia Q, Jiang Y, Zhou P, Li Y. Risk factors of indoor fall injuries in community-dwelling older women: A prospective cohort study. *Arch Gerontol Geriatr*. 2015;60(2):259-264. doi:10.1016/j.archger.2014.12.006

138. Muir SW, Berg K, Chesworth B, Klar N, Speechley M. Quantifying the magnitude of risk for balance impairment on falls in community-dwelling older adults: a systematic review and meta-analysis. *J Clin Epidemiol*. 2010;63(4):389-406. doi:10.1016/j.jclinepi.2009.06.010

139. Smith ML, Jiang L, Prizer LP, et al. Health indicators associated with falls among middle-aged and older women enrolled in an evidence-based program. *Women's Heal Issues*. 2014;24(6):613-619. doi:10.1016/j.whi.2014.08.004

140. Lord SR, Menz HB, Tiedemann A. A physiological profile approach to falls risk assessment and prevention. *Phys Ther*. 2003;83(3):237-252. doi:10.1056/nejm198812293192604

141. Deandrea S, Lucenteforte E, Bravi F, Foschi R, La Vecchia C, Negri E. Risk Factors for Falls in Community-dwelling Older People. *Epidemiology*. 2010;21(5):658-668. doi:10.1097/EDE.0b013e3181e89905

142. Tromp AM, Pluijm SMF, Smit JH, Deeg DJH, Bouter LM, Lips P. Fall-risk screening test: A prospective study on predictors for falls in community-dwelling elderly. *J Clin Epidemiol*. 2001;54(8):837-844. doi:10.1016/S0895-4356(01)00349-3

143. Stel VS, Smit JH, Pluijm SMF, Lips P. Balance and mobility performance as treatable risk factors for recurrent falling in older persons. *J Clin Epidemiol*. 2003;56(7):659-668. doi:10.1016/S0895-4356(03)00082-9

144. Verghese J, Wang C, Allali G, Holtzer R, Ayers E. Modifiable Risk Factors for New-Onset Slow Gait in Older Adults. *J Am Med Dir Assoc*. 2016;17(5):421-425. doi:10.1016/j.jamda.2016.01.017

145. Donoghue OA, Cronin H, Savva GM, O'Regan C, Kenny RA. Effects of fear of falling and activity restriction on normal and dual task walking in community dwelling older adults. *Gait Posture*. 2013;38(1):120-124. doi:10.1016/j.gaitpost.2012.10.023

146. Inacio M, Ryan AS, Bair WN, Prettyman M, Beamer BA, Rogers MW. Gluteal muscle composition differentiates fallers from non-fallers in community dwelling older adults.

BMC Geriatr. 2014;14(1):1-8. doi:10.1186/1471-2318-14-37

147. Horlings CGC, van Engelen BGM, Allum JHJ, Bloem BR. A weak balance: The contribution of muscle weakness to postural instability and falls. *Nat Clin Pract Neurol*. 2008;4(9):504-515. doi:10.1038/ncpneuro0886

148. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: A systematic review and meta-analysis. *J Am Geriatr Soc*. 2004;52(7):1121-1129. doi:10.1111/j.1532-5415.2004.52310.x

149. Lord SR, Clark RD, Webster IW. Physiological factors associated with falls in an elderly population. *J Am Geriatr Soc*. 1991;39:1194-1200. doi:10.1111/j.1532-5415.1991.tb03574.x

150. Campbell AJ, Robertson MC. Fall prevention: Single or multiple interventions? Single interventions for fall prevention. *J Am Geriatr Soc*. 2013. doi:10.1111/jgs.12095-2

151. Shubert TE. Evidence-Based Exercise Prescription for Balance and Falls Prevention. *J Geriatr Phys Ther*. 2011;34(3):100-108. doi:10.1519/JPT.0b013e31822938ac

152. Talley KMC, Wyman JF, Gross CR. Psychometric properties of the activities-specific balance confidence scale and the survey of activities and fear of falling in older women. *J Am Geriatr Soc*. 2008;56(2):328-333. doi:10.1111/j.1532-5415.2007.01550.x

153. Richardson K, Bennett K, Kenny RA. Polypharmacy including falls risk-increasing medications and subsequent falls in community-dwelling middle-aged and older adults. *Age Ageing*. 2015;44(1):90-96. doi:10.1093/ageing/afu141

154. Warner M, Schenker N, Heinen MA, Fingerhut LA. The effects of recall on reporting injury and poisoning episodes in the National Health Interview Survey. *Inj Prev*. 2005;11(5):282-287. doi:10.1136/ip.2004.006965

155. Perry L, Kendrick D, Morris R, et al. Completion and return of fall diaries varies with participants' level of education, first language, and baseline fall risk. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2012;67 A(2):210-214. doi:10.1093/gerona/glr175

156. Chaudhuri S, Thompson H, Demiris G. Fall Detection Devices and their Use with Older Adults: A Systematic Review. *J Geriatr Phys Tehr*. 2014;37(4):178-196. doi:10.1519/JPT.0b013e3182abe779.Fall

157. Aziz O, Klenk J, Schwickert L, et al. Validation of accuracy of SVM-based fall detection system using real-world fall and non-fall datasets. *PLoS One*. 2017;12(7):1-11. doi:10.1371/journal.pone.0180318

158. Duncan PW, Weiner DK, Chandler J, Studenski S. Functional reach: a new clinical measure of balance. *J Gerontol*. 1990;45(6):M192-7.

159. Berg KO, Wood-Dauphinee SL, Williams JI, Maki B. Measuring balance in the elderly:

validation of an instrument. *Can J Public Health*. 1992;83 Suppl 2:S7-11.

160. Shumway-Cook A, Baldwin M, Polissar NL, Gruber W. Predicting the probability for falls in community-dwelling older adults. *Phys Ther*. 1997;77(8):812-819. doi:N/A

161. Savva GM, Donoghue OA, Horgan F, O'Regan C, Cronin H, Kenny RA. Using timed up-and-go to identify frail members of the older population. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2013;68(4):441-446. doi:10.1093/gerona/gls190

162. Barry E, Galvin R, Keogh C, et al. Is the Timed Up and Go test a useful predictor of risk of falls in community dwelling older adults: a systematic review and meta- analysis. *BMC Geriatr*. 2014;14(1):14. doi:10.1186/1471-2318-14-14

163. Berg KO, Maki BE, Williams JI, Holliday PJ, Wood-Dauphinee SL. Clinical and laboratory measures of postural balance in an elderly population. *Arch Phys Med Rehabil*. 1992;73(11):1073-1080. doi:0003-9993(92)90174-U [pii]

164. Trueblood P, Hodson-Chennault N, McCubbin A, Youngclarke D. Performance and impairment-based assessments among community dwelling elderly: Sensitivity and specificity. *Issues on Aging*. 2001;24(1):1-6.

165. Lord SR, Murray SM, Chapman K, Munro B, Tiedemann A. Sit-to-stand performance depends on sensation, speed, balance, and psychological status in addition to strength in older people. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2002;57(8):539-543. doi:10.1093/gerona/57.8.M539

166. Murphy MA, Olson SL, Protas EJ, Overby AR. Screening for Falls in Community-Dwelling Elderly. *J Aging Phys Act*. 2003;11:63-78.

167. Rikli RE, Jones CJ. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. *Gerontologist*. 2013;53(2):255-267. doi:10.1093/geront/gns071

168. Gerdhem P, Ringsberg KAM, Åkesson K, Obrant KJ. Clinical history and biologic age predicted falls better than objective functional tests. *J Clin Epidemiol*. 2005;58(3):226-232. doi:10.1016/j.jclinepi.2004.06.013

169. Heitmann DK, Gossman MR, Shaddeau SA, Jackson JR. Balance performance and step width in noninstitutionalized, elderly, female fallers and nonfallers. *Phys Ther*. 1989;69(11):923-931. doi:10.1093/ptj/69.11.923

170. Weiner DK, Duncan PW, Chandler J, Studenski SA. Functional reach: a marker of physical frailty. *J Am Geriatr Soc*. 1992;40(3):203-207.

171. Rockwood K, Awalt E, Carver D, MacKnight C. Feasibility and measurement properties of the Functional Reach and the Timed Up and Go tests in the Canadian Study of Health and Aging. *Journals Gerontol Ser A Biol Sci Med Sci*. 2000;55A(2):M70-M73.

172. Duncan PW, Studenski S, Chandler J, Prescott B. Functional reach: predictive validity in a sample of elderly male veterans. *J Gerontol*. 1992;47(3):M93-8. doi:10.1093/geronj/47.3.M93

173. Lajoie Y, Gallagher SP. Predicting falls within the elderly community: Comparison of postural sway, reaction time, the Berg balance scale and the Activities-specific Balance Confidence (ABC) scale for comparing fallers and non-fallers. *Arch Gerontol Geriatr*. 2004;38(1):11-26. doi:10.1016/S0167-4943(03)00082-7

174. Thorbahn LB, Newton RA. Use of the Berg Balance Test to predict falls in elderly persons. *Phys Ther*. 1996;76(6):576-583; discussion 584-5.

175. Balasubramanian CK. The community balance and mobility scale alleviates the ceiling effects observed in the currently used gait and balance assessments for the community-dwelling older adults. *J Geriatr Phys Ther*. 38(2):78-89. doi:10.1519/JPT.0000000000000024

176. Scott V, Votova K, Scanlan A, Close J. Multifactorial and functional mobility assessment tools for fall risk among older adults in community, home-support, long-term and acute care settings. *Age Ageing*. 2007;36(2):130-139. doi:10.1093/ageing/afl165

177. Shumway-Cook, A. Woollacott M. *Motor Control: Theory and Applications*. Baltimore, MD: Wilkins & Wilkins; 1995.

178. Herman T, Inbar-Borovsky N, Brozgol M, Giladi N, Hausdorff JM. The Dynamic Gait Index in healthy older adults: The role of stair climbing, fear of falling and gender. *Gait Posture*. 2009;29(2):237-241. doi:10.1016/j.gaitpost.2008.08.013

179. Bishop MD, Patterson TS, Romero S, Light KE. Improved fall-related efficacy in older adults related to changes in dynamic gait ability. *Phys Ther*. 2010;90(11):1598-1606. doi:10.2522/ptj.20090284

180. Landers MR, Oscar S, Sasaoka J, Vaughn K. Balance Confidence and Fear of Falling Avoidance Behavior Are Most Predictive of Falling in Older Adults: Prospective Analysis. *Phys Ther*. 2016;96(4):433-442. doi:10.2522/ptj.20150184

181. Tinetti ME, Richman D, Powell L. Falls efficacy as a measure of fear of falling. *J Gerontol*. 1990;45(6):P239-43.

182. Schepens S, Sen A, Painter JA, Murphy SL. Relationship between fall-related efficacy and activity engagement in community-dwelling older adults: a meta-analytic review. *Am J Occup Ther*. 2012;66(2):137-148. doi:10.5014/ajot.2012.001156

183. Moore DS, Ellis R, Kosma M, Fabre JM, McCarter KS, Wood RH. Comparison of the Validity of Four Fall-Related Psychological ... *Res Q Exerc Sport*. 2011;82(3):545-554.

184. Beninato M, Portney LG, Sullivan PE. Using the International Classification of Functioning, Disability and Health as a framework to examine the association between

falls and clinical assessment tools in people with stroke. *Phys Ther*. 2009;89(8):816-825. doi:10.2522/ptj.20080160

185. Cleary K, Skornyakov E. Predicting falls in community dwelling older adults using the Activities-specific Balance Confidence Scale. *Arch Gerontol Geriatr*. 2017;72(December 2016):142-145. doi:10.1016/j.archger.2017.06.007

186. Goodwin VA, Abbott RA, Whear R, et al. Multiple component interventions for preventing falls and fall-related injuries among older people: Systematic review and meta-analysis. *BMC Geriatr*. 2014;14(1). doi:10.1186/1471-2318-14-15

187. Healy TC, Peng C, Haynes MS, McMahon EM, Botler JL, Gross L. The feasibility and effectiveness of translating a matter of balance into a volunteer lay leader model. *J Appl Gerontol*. 2008;27(1):34-51. doi:10.1177/0733464807308620

188. Ory MG, Smith ML, Wade A, Mounce C, Wilson A, Parrish R. Implementing and disseminating an evidence-based program to prevent falls in older adults, Texas, 2007-2009. *Prev Chronic Dis*. 2010;7(6):A130. doi:A130 [pii]

189. Clemson L, Cumming RG, Kendig H, Swann M, Heard R, Taylor K. The effectiveness of a community-based program for reducing the incidence of falls in the elderly: A randomized trial. *J Am Geriatr Soc*. 2004;52(9):1487-1494. doi:10.1111/j.1532-5415.2004.52411.x

190. Welcome to Wisconsin Institute for Healthy Aging | WIHA. Wisconsin Institute for Healthy Aging. https://wihealthyaging.org/. Accessed May 10, 2018.

191. Keall MD, Pierse N, Howden-Chapman P, et al. Home modifications to reduce injuries from falls in the Home Injury Prevention Intervention (HIPI) study: A cluster-randomised controlled trial. *Lancet*. 2015;385(9964):231-238. doi:10.1016/S0140-6736(14)61006-0

192. Drootin M. Summary of the updated american geriatrics society/british geriatrics society clinical practice guideline for prevention of falls in older persons. *J Am Geriatr Soc*. 2011;59(1):148-157. doi:10.1111/j.1532-5415.2010.03234.x

193. Zia A, Kamaruzzaman SB, Tan MP. Polypharmacy and falls in older people: Balancing evidence-based medicine against falls risk. *Postgrad Med*. 2015;127(3):330-337. doi:10.1080/00325481.2014.996112

194. Van Der Cammen TJ, Rajkumar C, Onder G, Sterke CS, Petrovic M. Drug cessation in complex older adults: Time for action. *Age Ageing*. 2014;43(1):20-25. doi:10.1093/ageing/aft166

195. Iyer S, Naganathan V, McLachlan AJ et al. Medication withdrawal trials in people aged 65 years and older: a systematic review. *Drugs Aging*. 2008;25(12):1021-1031. doi:10.2165/0002512-200825120-00004

196. Sherrington C, Whitney JC, Lord SR, Herbert RD, Cumming RG, Close JCT. Effective

Exercise for the Prevention of Falls: A Systematic Review and Meta-Analysis. *J Am Geriatr Soc*. 2008;56(12):2234-2243. doi:10.1111/j.1532-5415.2008.02014.x

197. Close JCT. How can you prevent falls and subsequent fractures? *Best Pract Res Clin Rheumatol*. 2013;27(6):821-834. doi:10.1016/j.berh.2013.12.001

198. Barnett A, Smith B, Lord SR, Williams M, Baumand A. Community based group exercise improves balance and reduces falls in at risk older people: a randomised controlled trial. *Age Ageing*. 2003;32(4):407-414. doi:10.1093/ageing/32.4.407

199. Li F, Harmer P, Fisher KJ, et al. Tai Chi and Fall Reductions in Older Adults: A Randomized Controlled Trial. *Journals Gerontol Ser A Biol Sci Med Sci*. 2005;60(2):187-194. doi:10.1093/gerona/60.2.187

200. van den Berg M, Sherrington C, Killington M, et al. Video and computer-based interactive exercises are safe and improve task-specific balance in geriatric and neurological rehabilitation: A randomised trial. *J Physiother*. 2016;62(1):20-28. doi:10.1016/j.jphys.2015.11.005

201. De Groot GCL, Fagerström L. Older adults' motivating factors and barriers to exercise to prevent falls. *Scand J Occup Ther*. 2011;18(2):153-160. doi:10.3109/11038128.2010.487113

202. Yardley L, Kirby S, Ben-Shlomo Y, Gilbert R, Whitehead S, Todd C. How likely are older people to take up different falls prevention activities? *Prev Med (Baltim)*. 2008;47(5):554-558. doi:10.1016/j.ypmed.2008.09.001

203. Sleet DA, Moffett DB, Stevens J. CDC's research portfolio in older adult fall prevention: A review of progress, 1985-2005, and future research directions. *J Safety Res*. 2008;39(3):259-267. doi:10.1016/j.jsr.2008.05.003

204. Ory MG, Smith ML, Resnick B. Changing behavior throughout the life-course: Translating the success of aging research. *Transl Behav Med*. 2012;2(2):159-162. doi:10.1007/s13142-012-0129-4

205. Shubert TE, Goto LS, Smith ML, Jiang L, Rudman H, Ory MG. The Otago Exercise Program: Innovative Delivery Models to Maximize Sustained Outcomes for High Risk, Homebound Older Adults. *Front Public Heal*. 2017;5(March):54. doi:10.3389/fpubh.2017.00054