2023

Physical Activity and Exercise with Blood Flow Restriction as Medicine During the COVID-19 Pandemic and Beyond

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PHYSICAL ACTIVITY AND EXERCISE WITH BLOOD FLOW RESTRICTION AS MEDICINE DURING THE COVID-19 PANDEMIC AND BEYOND

By

Isaac J. Wedig

A DISSERTATION

Submitted in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

In Integrative Physiology

MICHIGAN TECHNOLOGICAL UNIVERSITY

2023

This dissertation has been approved in partial fulfillment of the requirements for the Degree of DOCTOR OF PHILOSOPHY in Integrative Physiology.

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Acknowledgments

I would like to express my deepest appreciation to my committee members, Dr. Kelly Kamm, Dr. John Durocher, Dr. John McDaniel, and Dr. Erich Petushek, for generously providing their knowledge, expertise, and support. A special thanks to my committee chair and advisor, Dr. Steven Elmer, for his constant guidance, encouragement, and mentorship. I could not have asked for a better academic training to prepare me for my future career as an educator and scientist. I would also like to thank Dr. William Cooke, Dr. Carolyn Duncan, Jess Barish and the Department of Kinesiology and Integrative Physiology for their support. I'm especially grateful for my fellow graduate students and colleagues in the Exercise Physiology Laboratory, Ben Cockfield, Isaac Lennox, Carmen Scarfone, Jamie Phillips, Kyle Wehmanen, Felix Cottet-Puinel, Luke Moore, and Ashley Hawk for their support, continuous feedback, assistance in data collection, and excellent camaraderie. I would be remiss if I did not extend a special thank you to my dear friends Dr. Jessica Bruning and Dr. Joshua Gonzalez for their mentoring and friendship throughout this journey. I am forever in debt to my magnificent parents, Dale and Cindy Wedig, for their unceasing love and support. Thank you for instilling in me the character, morals, and faith that form the foundation of all my accomplishments. I would not be who I am today without you. Above all, I can't begin to express how grateful I am for my fiancée, Sydnie Mazurek, who has supported me through every step of this process. Thank you for your love, patience, and continuous encouragement. I extent a very sincere thank you to all of my research participants who so willingly donated their time and legs to my research. Lastly, this work would not be possible without the Michigan Space Grant Consortium, Blue Cross Blue Shield of Michigan, the Health Research Institute at Michigan Tech, the Portage Health Foundation, and the Michigan Health Endowment Fund who have provided financial support for this work.

Author Contribution Statement

Study 1: **Promoting Physical Activity in Rural Communities During COVID-19 with Exercise Is Medicine® On Campus**

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Study 2: Blood Flow Restriction as a Potential Therapy to Restore Physical Function Following COVID-19 Infection

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Study 3: Development of a Prediction Equation to Estimate Lower-Limb Arterial Occlusion Pressure with a Thigh Sphygmomanometer

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Abstract

During the COVID-19 pandemic, physical activity levels have decreased and sitting time has increased. This is a major concern as physical inactivity increases the risk for severe COVID-19 outcomes. Evidence also indicates that COVID-19 survivors can experience reduced physical function (i.e., ability to complete daily living activities) long after acute illness. Currently, there are no evidence-based guidelines for recovering physical function following COVID-19 infection. Exercise with blood flow restriction (BFR) presents a promising rehabilitation strategy as the benefits of traditional exercise can be achieved using lower intensities. However, several barriers such as cost, access to equipment, and lack of standardized methods limit its use. The goal of this research was to promote and facilitate the use of physical activity as a critical form of medicine during the COVID-19 pandemic and beyond. With study 1, I implemented a community-based program to provide free physical activity resources to the rural Upper Peninsula during the pandemic. Physical activity was promoted through a widespread media campaign and over 260 virtual home-based workouts were delivered to community members using several platforms (i.e., Zoom, Facebook Live, YouTube, TV, DVD). With study 2, I developed a working hypothesis and theoretical framework for using BFR to help restore physical function in those individuals infected with COVID-19. Specifically, I hypothesized that passive BFR modalities can mitigate losses of muscle mass and muscle strength that occur during acute infection and 2) exercise with BFR can serve as an effective alternative to traditional higher intensity exercise for regaining muscle mass, muscle strength, and aerobic capacity during convalescence. With study 3, I collected laboratory-based measures using Doppler ultrasound and anthropometric techniques in healthy adults (n=143) and applied linear regression methods to develop and validate a prediction equation for performing BFR without the need for specialized equipment. Finally, with study 4, I developed and usability tested a web-based application designed to serve as user support tool that aids physical therapists in implementing BFR.

Collectively, my research addressed two major public health problems (COVID-19 and physical inactivity) and sought to enhance accessibility of physical activity and exercise with BFR during the pandemic and beyond.

1 Introduction

1.1 Physical Inactivity

Physical inactivity is the fourth leading cause of death worldwide, contributing to over 3 million deaths annually.[1] As a leading risk factor for non-communicable diseases, physical inactivity increases the risk for cardiovascular disease, obesity, cancer, diabetes, hypertension, bone and joint disease, and depression.[2] Currently, 80% of U.S. adults do not meet the necessary guidelines for aerobic and muscle strengthening exercise [3] and it is estimated that $117 billion in U.S. health care is spent per year due to inadequate levels of physical activity.[4] Given its widespread health and economic impacts, physical inactivity has been defined as a pandemic [5] and suggested to be the biggest public health threat of the 21st century.[6] Despite robust evidence pointing to the role of physical activity in maintaining health, treating disease, and reducing health care costs, it remains an underappreciated modifiable behavior by the medical community, policy makers, and the public at large. Furthermore, physical activity (e.g., walking) presents one of the most affordable and accessible healthcare interventions with potential to be highly effective in modulating health outcomes.

1.2 Physical Inactivity and COVID-19

In March of 2020, coronavirus disease 2019 (COVID-9), the disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared a pandemic by the World Health Organization (WHO). To date, there have been over 760 million cases of COVID-19 reported worldwide and over 6.8 million deaths.[7] During the COVID-19 pandemic, physical activity levels decreased and sedentary behaviors increased.[8] Importantly, several recent systematic reviews and meta-analyses [9-11] indicate that physical inactivity is associated with an increased risk of severe outcomes (i.e., hospitalization, admission to the intensive care unit, and death) in those individuals infected with COVID-19. In a groundbreaking study, Sallis and colleauges [12] reported that

other than advanced age and a history of organ transplant, physical inactivity is the strongest risk factor for hospitalization, admission to the intensive care unit, and death in those individuals infected with COVID-19. Furthermore, physical inactivity increases risk for these outcomes even more than other well established risk factors such as obesity, diabetes, smoking, high blood pressure, and cardiovascular disease. In light of mounting evidence, physical inactivity is now recognized as a major risk factor for severe COVID-19 outcomes by the CDC [13] and the WHO.[14] The synergistic effects of COVID-19 with preexisting public health threats, such as physical inactivity and non-communicable disease, has led several authors to refer to COVID-19 as a syndemic.[15,16] While strategies to manage viral transmission (i.e., hand washing, social distancing, wearing a mask) serve as an important first line of defense, improving healthy living behaviors [17] such as increasing physical activity, may be just as critical to combating COVID-19 (as well as other non-communicable and communicable diseases). Thus, it is imperative that efforts are made by public health authorities to educate the public about the risk of physical inactivity related to COVID-19 and to promote engagement in physical activity during the pandemic. Moreover, when the COVID-19 pandemic subsides, the physical inactivity pandemic is likely to remain and potentially have worsened. Taking immediate widespread action to promote and facilitate physical activity will not only create a population that is more resilient to COVID-19 (and possible future pandemics) but will counteract the future consequences of increasingly sedentary lifestyles.

1.3 Long-term Effects of COVID-19 Infection

In addition to the acute complications of COVID-19 infection, accumulating evidence [18-23] indicates that a variety of symptoms can persist for weeks and/or months following the acute phase of illness. The long-term manifestations of COVID-19 have been referred to as “long COVID”, “post-acute sequelae of COVID-19”, and/or “post-acute COVID-19 condition”. Among the most prevalent reported symptoms are fatigue, dyspnea, cognitive dysfunction, muscle and joint pain, and weakness. Additionally, in a recent systematic review de Olivira

Almeida and colleagues [24] reported that COVID-19 survivors experience impaired physical function and reduced ability to perform activities of daily living up to 6 months following acute illness. For example, authors reported lower performance on functional tests including the 1-min sit-to-stand, 2-min walking, and Short Physical Performance Battery Test as well as lower Barthel Index and Activities of Daily Living Scores. While those individuals with more severe acute illness requiring hospitalization appear to be most affected, impaired physical function has been reported across acute illness severities and affects community recovered individuals with milder cases.[25,26]

Collectively, the chronic manifestations of COVID-19 infection may comprise long-term health and leave those individuals who become infected prone to frailty and disease. Persistent physical function impairments following COVID-19 are associated with lower physical activity levels[27-30] and may increase the risk of frailty,[31] falls and injury,[32] and chronic diseases such as diabetes, obesity, and cardiovascular disease.[33] Furthermore, long-term functional impairments may drastically impact the workforce. A recent report [25] indicated that 50% of British Armed Forces were medically non-deployable at 12-months after COVID-19 infection. Data indicate [18] that 44% of individuals infected with COVID-19 will develop long-term impairments in physical function, meaning that ~300 million people could be affected. As COVID-19 continues to impact the world, the health and economic consequences of long-term symptoms could be astronomical. Currently, there are widespread initiatives,[34] action plans,[35,36] and calls for research [23,37] (e.g., The White House, National Institutes of Health, American Physiological Society) to address the long-term effects of COVID-19 and identify potential treatment strategies. Currently, there are no widely accepted approaches for rehabilitating physical function following COVID-19. Thus, finding effective interventions (e.g., physical activity and exercise) that are safe, cost-effective, and feasible during and following infection is critical.

1.4 Blood Flow Restriction

Exercise with blood flow restriction (BFR) offers an effective approach for increasing muscle size and strength,[38-41]aerobic capacity,[42,43] and physical function [44] in a variety of populations. This modality involves performing exercise with mechanical compression applied to the proximal portion of a limb, typically with a pneumatic cuff, which serves to partially reduce arterial blood flow to the exercising limb while limiting most of the venous return [45-47]. The main advantages of exercise with BFR compared to traditional exercise are: 1) increases in muscle size, strength, and aerobic capacity can be achieved with low exercise intensities,[40,43,44,48] 2) adaptations from BFR occur faster, and 3) muscle size and strength can be increased with aerobic or resistance exercise.[39] Accordingly, BFR offers an alternative option for improving muscle size and strength in populations such as the elderly, those with orthopedic limitations, and various diseased states, for whom higher intensity exercise may be difficult or contraindicated. Additionally, exercise with BFR may be a useful alternative to traditional exercise during the COVID-19 pandemic. Several authors [49,50] have suggested that exercise with BFR provides a feasible means to counteract the negative effects of physical inactivity during the pandemic. Specifically, exercise with BFR could be used as a home-based strategy to maintain and improve skeletal muscle size and strength when access to gyms, fitness facilities, and equipment for performing high intensity exercise is limited. Additionally, with limited access to healthcare during the pandemic, this modality has been suggested as a therapy to aid in the home-based management of musculoskeletal conditions.[51] Lastly, authors [52] have proposed the use of exercise with BFR for the treatment of intensive care acquired weakness in those individuals suffering from severe COVID-19 illness. Collectively, exercise with BFR represents a viable alternative to achieve the benefits of traditional exercise in a wide variety of populations during the COVID-19 pandemic and beyond.

1.5 Dissertation Overview

The overarching goal of this research is to facilitate the use of physical activity as a critical form of medicine during the COVID-19 pandemic and beyond. To accomplish this, I conducted a series of 4 studies spanning the spectrum of translational science. For study 1, I promoted and facilitated physical activity in the Upper Peninsula community during the pandemic through implementation of a population-based physical activity program. For study 2, I developed a working hypothesis and theoretical framework for the use of BFR as a therapy to restore physical function in those individuals infected with COVID-19. For study 3, I conducted a laboratory-based study to develop a prediction equation for implementing exercise with BFR without the need for expensive equipment. Lastly, for study 4, I developed and usability tested a web-based application to aid practitioners in the clinical implementation of exercise with BFR. Collectively, this research address two major public health problems (i.e., COVID-19 and physical inactivity) and enhances accessibility of an effective form of exercise that can be used during the pandemic and beyond (i.e., exercise with BFR). An overview of this work is shown in Figure 1.1. This research was supported by 1) graduate student fellowships through the Blue Cross Blue Shield of Michigan, Michigan Space Grant Consortium, Health Research Institute of Michigan Technological University, Portage Health Foundation, and 2) a community health grant from the Michigan Health Endowment Fund.

1.5.1 Study 1

Efforts to promote physical activity during the pandemic are especially important in rural communities where residents are the least physically active [53] and have high susceptibility to severe COVID-19 outcomes.[54] However, there are many barriers to implementing physical activity in these communities. Access to both the infrastructure that facilitates physical activity (e.g., fitness centers, outpatient rehabilitation clinics, parks, recreational facilities) and the availability of credentialed fitness professionals is severely limited and even more so during the COVID-19 pandemic. While resources in rural communities are sparse, locally

situated colleges and universities can play an important role in promoting and facilitating physical activity for their surrounding communities. The purpose of this study was to leverage Exercise is Medicine® on Campus (EIM-OC) at Michigan Technological University to provide critical physical activity resources to Michigan's rural Upper Peninsula during the COVID-19 pandemic. I led a team of students, faculty, and fitness professionals to: 1) promote physical activity through a widespread media campaign (i.e., website, social media, radio, newspaper, TV, public townhall) and 2) deliver virtual home-based workouts to community members using several platforms (i.e., Zoom, Facebook Live, YouTube, TV, DVD). Together, these efforts demonstrate the extent to which EIM-OC increased physical activity infrastructure (e.g., promotion and resources for engaging in physical activity) during a critical time of need for our rural and underserved community. Work from this study resulted in the construction of several infographics that were published in: 1) the *British Journal of Sports Medicine* [55] (Appendix B) and a home-based cardiac rehabilitation booklet [56] , 2) the *Baylor University Medical Center Proceedings* [57] (Appendix C), and 3) the *Mayo Clinic Proceedings* [58] and *Kinesiology Review* [59] (Appendix D). A manuscript of this work has been published [60] in the *ACSM Health and Fitness Journal* (Chapter 2).

1.5.2 Study 2

Accumulating evidence indicates that COVID-19 survivors display reduced muscle mass and muscle strength [28,61-63] and aerobic capacity,[64] which contribute to impairments in physical function that can persist for months after the acute phase of illness. Accordingly, strategies to restore muscle mass, muscle strength, and aerobic capacity following infection are critical to mitigating the long-term consequences of COVID-19. The application of BFR presents a promising therapy that could be utilized throughout different phases of COVID-19 illness to restore physical function. The purpose of this study was to provide a working hypothesis and theoretical framework for how BFR may be utilized to aid in the rehabilitation of those individuals infected with COVID-19. Specifically, I

hypothesize that: 1) use of passive BFR modalities can mitigate losses of muscle mass and muscle strength that occur during acute infection and 2) exercise with BFR can serve as an effective alternative to traditional higher intensity exercise for regaining muscle mass, muscle strength, and aerobic capacity during convalescence. In addition to restoring physical function, I highlight how the various applications of BFR may also serve as a targeted therapy to address the underlying pathophysiology of COVID-19 and provide benefits to numerous organ systems affected by the disease. Lastly, I propose a theoretical framework with which BFR could be implemented throughout the progression from acute illness to outpatient rehabilitation with the goal to improve short and long-term outcomes in COVID-19 survivors. This work encourages consideration of the potential therapeutic benefits of BFR to treat not only COVID-19 but similar pathologies and cases of acute critical illness. A manuscript of this work has been submitted for publication in *Medical Hypotheses* (Chapter 3).

1.5.3 Study 3

It is recommended that cuff pressures during BFR be selected based upon arterial occlusion pressure (AOP) or the minimum amount of pressure required to occlude arterial blood flow to the limb.[65] However, high costs associated with the necessary equipment to assess AOP and implement BFR limit its accessibility to clinicians, coaches, and athletes. The purpose of this study was to develop a practical approach (i.e., regression equation to estimate AOP) to implementing lower body exercise with BFR. For this lab-based study I utilized Doppler ultrasound, Biodex dynamometry, and anthropometric techniques in a large sample of healthy adults (n=143). Specifically, for part 1 of this study, I utilized multiple linear regression to explore sociodemographic, anthropometric, and hemodynamic variables that constitute predictors of AOP when applying an inexpensive thigh sphygmomanometer as a restrictive device. I hypothesized that thigh circumference and femoral systolic blood pressure would be the main predictors and explain approximately 40% of the variability in AOP. For part 2, I utilized the predictor variables identified in part 1 to develop and validate a

prediction equation that estimates AOP. Collectively, a validated prediction equation paired with an inexpensive cuff offers a practical method for implementing exercise with BFR in the lower body.

1.5.4 Study 4

Emerging evidence indicates that exercise with BFR may be an effective alternative to traditional exercise in a broad range of clinical populations including those living with hypertension,[66] cardiovascular disease,[67-72] diabetes,[73,74] renal dysfunction,[75,76] and most notably in those with musculoskeletal conditions.[77-80] Accordingly, exercise with BFR is now endorsed by the American Physical Therapy Association [81] and used in rehabilitation.[82] Despite its growing use in rehabilitation settings, implementation of BFR remains challenging for practitioners [83] for several reasons. First, most interventions have been focused on healthy individuals and applied in controlled laboratory settings. Second, methods used to implement exercise with BFR vary widely [84] and include the use of different types of equipment (i.e., pneumatic cuffs, elastic wraps), a wide range of applied cuff pressures (e.g., 100-240mmHg), and a variety of procedures for determining cuff pressure (i.e., arbitrarily selected, based on systolic blood pressure, based on limb circumference, perceived tightness). Finally, BFR methodology used in clinical settings [82] may be lagging behind current evidence-based guidelines. Thus, the current gap between research and clinical practice poses a major obstacle to the implementation of BFR in real world settings. The purpose of this study was to develop a web-based application to serve as a user support tool for the implementation of exercise with BFR in clinical settings. A secondary purpose was to conduct preliminary usability testing of the web-based application in physical therapists. Importantly, this user support tool for implementing BFR will help to overcome many of the major barriers that practitioners face to utilizing this modality, thus improving access, safety, and effectiveness of its use in clinical settings.

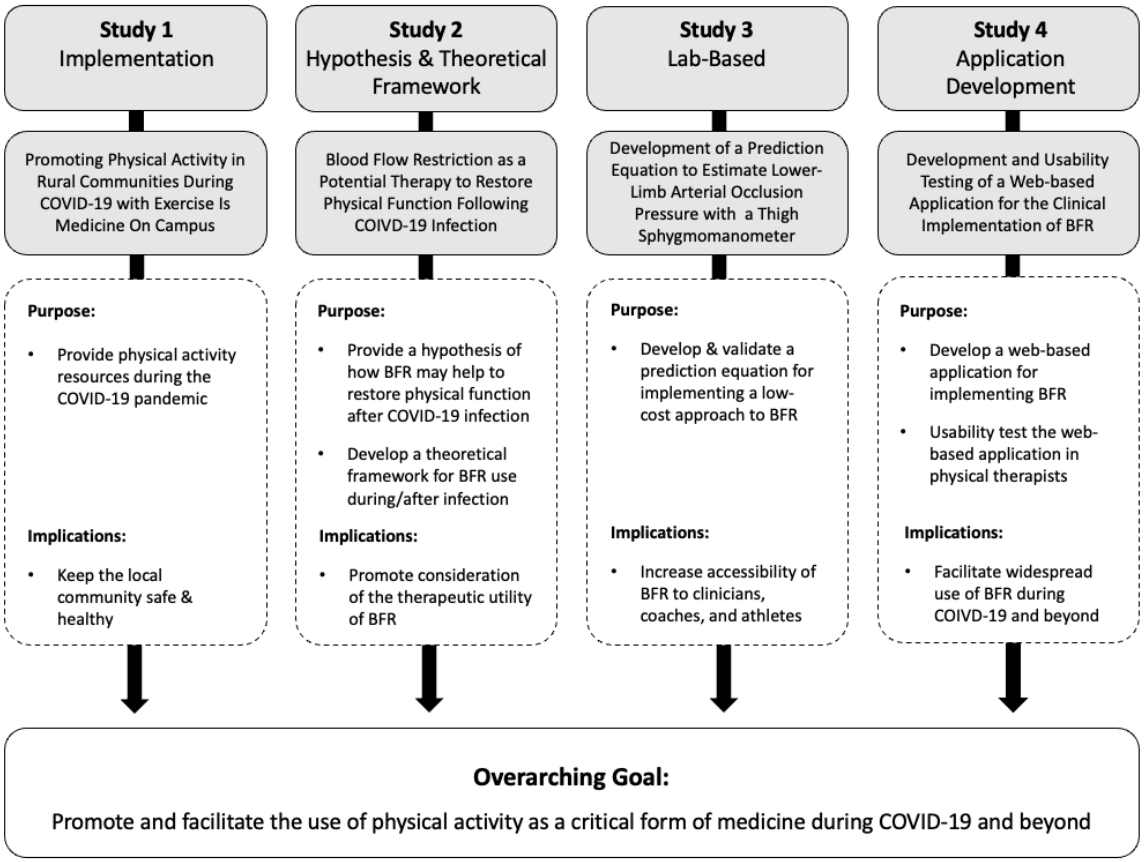

Figure 1.1 Overview of dissertation.

2 Promoting Physical Activity in Rural Communities During COVID-19 with Exercise Is Medicine On Campus®

2.1 Abstract

During the COVID-19 pandemic, physical activity levels have decreased. This is concerning as physical inactivity increases the risk of non-communicable disease and severe outcomes in those individuals infected with COVID-19. Thus, strategies to increase physical activity levels are paramount for keeping communities healthy during the pandemic. Efforts to promote physical activity during the pandemic are especially important in rural communities where residents are the least physically active and have high susceptibility to severe COVID-19 outcomes. However, there are many barriers to implementing physical activity in these communities. Access to both the infrastructure that facilitates physical activity (e.g., fitness centers, outpatient rehabilitation clinics, parks, recreational facilities) and the availability of credentialed fitness professionals is severely limited and even more so during the COVID-19 pandemic. The purpose of this study was to leverage Exercise is Medicine® on Campus (EIM-OC) at Michigan Technological University to provide critical physical activity resources to Michigan's rural Upper Peninsula during the COVID-19 pandemic. A team of students, faculty, and fitness professionals: 1) promoted physical activity through a widespread media campaign (i.e., website, social media, radio, newspaper, TV, public townhall) and 2) delivered over 260 virtual home-based workouts to community members using several platforms (i.e., Zoom, Facebook Live, YouTube, TV, DVD). Together, these efforts highlight the extent to which EIM-OC bolstered physical activity infrastructure during a critical time of need for our rural and underserved community.

2.2 Background

During the COVID-19 pandemic, physical activity levels have decreased for children, adolescents, college students, and adults.[8] This is concerning as physical inactivity and sedentary behavior are risk factors for cardiovascular disease, obesity, cancer, diabetes, hypertension, bone and joint disease, depression, and premature death.[2] Additionally, recent evidence [85] indicates that physical inactivity increases risk for severe outcomes in those individuals who become infected with COVID-19. Thus, strategies to increase physical activity levels are paramount for keeping communities healthy during the pandemic and beyond. Accordingly, call to actions by the American College of Sports Medicine [86] and Physiological Society [87] have urged widespread promotion and implementation of physical activity.

Efforts to promote physical activity during the pandemic are especially important in rural communities, where over 46 million Americans reside. Compared to urban and suburban residents, those living in rural areas have lower physical activity levels.[53] These residents are also older in age and have higher rates of smoking, hypertension, and obesity.[88] Collectively, the intersection of health behavior risk factors and poor access to health care place rural residents at increased susceptibility to severe outcomes when infected with COVID-19.[54] Thus, leveraging the health benefits of physical activity in rural communities is critical to reducing the impact of COVID-19. A barrier for implementing physical activity in rural communities is limited access to both the infrastructure that facilitates physical activity (e.g., fitness centers, outpatient rehabilitation clinics, parks, recreational facilities) and the availability of credentialed fitness professionals that promote and provide physical activity programming. For comparison, in urban areas, large health care systems, universities with allied health and medicine programs, and numerous fitness centers and credentialed professionals deliver health promotion and services including physical activity. Many urban communities also have bicycle and pedestrian routes that promote active commuting to destinations such as schools

and parks that rural areas may not have. Even though rural communities typically possess fewer resources, the U.S. Department of Education [89] identifies over 500 colleges and universities that are located in rural areas. These institutions can play an important role with providing physical activity resources for their surrounding communities. The Upper Peninsula of Michigan makes up ~30% of the state landmass and ~3% of the population. In this commentary, we describe how we leveraged Exercise is Medicine® on Campus (EIM-OC) at Michigan Technological University to provide critical physical activity resources during the pandemic to Michigan's rural Upper Peninsula. Specifically, university health science students and faculty collaborated with local fitness professionals to promote and facilitate physical activity. Given the time sensitive need, our objective was focused on rapid implementation of physical activity resources.

2.3 Rural Community

Michigan Technological University is a small doctoral granting public research university (~7,000 students). The University campus is in Houghton, Michigan (7,870 residents) and the closest major city (>50,000 residents) is over 200 miles away. Major medical facilities (i.e., Hospitals with Level I Trauma Centers, Medical Schools) are several hours away (Figure 2.1). Categorized by the U.S. Health Resources and Services Administration as a Medically Underserviced Area, Houghton is serviced by a regional health department that oversees 5 surrounding counties encompassing over 13,000 mi^2. Moreover, all 15 counties within the Upper Peninsula are classified as "rural remote" according to the U.S. Department of Agriculture.[90] Accordingly, Michigan Technological University was committed to improving health in its rural and underserved community (Figure 2.1) which aligns with the Exercise is Medicine® efforts to develop strategies to promote and facilitate physical activity in underserved populations.

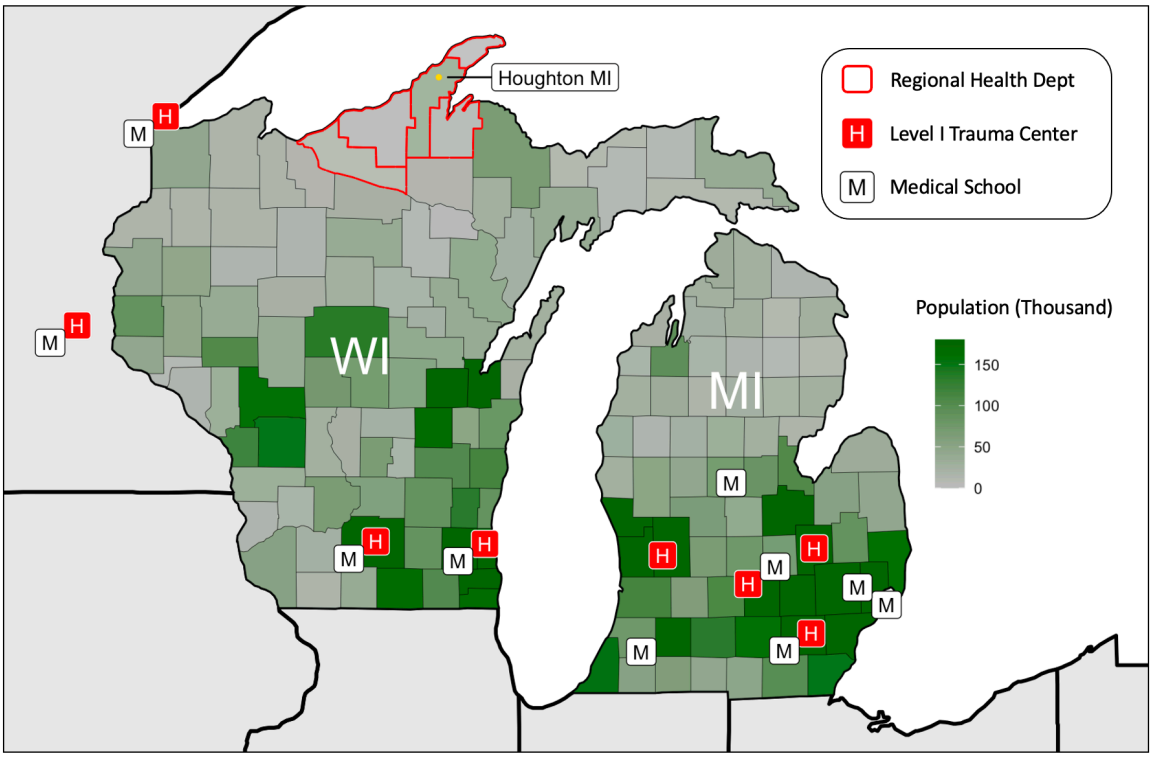

Figure 2.1 Map of the rural area surrounding Michigan Technological University. Map highlights county level population, counties overseen by the regional health department, and the nearest Level I Trauma Centers and medical schools.

2.4 Exercise Is Medicine On Campus

In 2020, the Department of Kinesiology and Integrative Physiology at Michigan Technological University formed its EIM-OC program as an emergency initiative to promote and facilitate physical activity as a protective health strategy during the COVID-19 pandemic, both on campus and in the broader rural community. EIM-OC is a global health initiative that calls upon colleges and universities to promote and increase physical activity on their campuses. Currently, there are over 220 registered EIM-OC colleges and universities worldwide. Importantly, EIM-OC programs have also extended off campus to impact their surrounding communities. The EIM-OC team was comprised of 1) undergraduate students in exercise science, 2) graduate students in kinesiology, integrative physiology, and biology, 3) faculty specializing in exercise physiology

and public health, and 4) university and community-based fitness professionals including strength and conditioning coaches, personal trainers, and fitness instructors. To support our EIM-OC initiative, we initially applied for and received a small science outreach grant. A graduate student team member also applied for and received a graduate student health focused grant. The team also created a crowdfunding page to collect donations from community members to help support costs of delivering the free program. Subsequently, we leveraged these funding resources along with our preliminary work to secure a community health impact grant from a Michigan health foundation. These resources enabled us to aggressively implement and sustain our EIM-OC initiative throughout the pandemic.

2.5 Promotion of Physical Activity

The importance of physical activity during the pandemic was promoted in the community using several platforms (Table 2.1). First, an EIM-OC website specific to the rural Upper Peninsula of Michigan was created. An email list was established and subscribers received monthly emails containing tips for staying physically active during the pandemic. Second, social media accounts (Facebook and YouTube) were created to market and support the EIM-OC initiative. Third, an existing virtual COVID-19 Public Townhall Series was leveraged to keep the community informed during the pandemic. Specifically, the goal of this monthly series was to provide timely and accurate information about COVID-19 while promoting the importance of mitigation strategies to interrupt and halt transmission. The series also gave public health officials, clinicians, educators, EIM-OC team members, and other health and fitness experts in the local community a platform to come together and discuss a range of pandemic-related topics including the role of public health to protect the community, the impact of disease on physical and mental health, health disparities, and adopting healthy living behaviors including physical activity. The series was free to all community members and broadcasted live online (Zoom, Facebook Live) and on local radio and TV. Fourth, the EIM-OC team participated in radio and podcast interviews to

discuss the health benefits of physical activity and to direct listeners to physical activity resources. Fifth, the importance of staying physically active during the pandemic was communicated through newspaper articles and blogs posts. Finally, infographics were created to illustrate the importance of staying physically active during the pandemic and were shared with clinicians and community members.

Table 2.1 Overview of physical activity promotion.

Platform	**Media Channels**	**Purpose**
Website	www.upandmoving.org	House initiative Establish email list Archive workouts
Social Media	Facebook & YouTube accounts	Promote initiative Stream workouts Archive workouts
Community Townhall	Streamed on Zoom, Facebook Live, local radio & TV	Keep community informed during the pandemic Direct viewers to physical activity resources
Radio/Podcast Interviews	Local radio & health foundation podcast	Discuss the health benefits of physical activity Direct listeners to physical activity resources
Newspaper/Science Blog	Local/regional newspaper & national science blog	Communicate importance of physical activity Direct readers to physical activity resources
Infographic	Shared with clinicians & within community	Provide visual illustration of the importance of physical activity Provide recommendations for meeting guidelines during the pandemic

2.6 Community-Based Physical Activity Program

A free physical activity program was made accessible to the community using a number of different platforms (Figure 2.2). Virtual physical activity workouts were delivered live 3x/week (Fall 2020), 6x/week (Spring 2021), 3x/week (Summer and Fall 2021), and 2x/week (Spring 2022) through Zoom and Facebook Live. The home-based workouts were led by an EIM-OC team member, open to any community member, and lasted ~30-45 min. Specifically, workouts included aerobic exercise, resistance exercise using common household items, agility and balance movements, and/or yoga (Figure 2.3). Importantly, adaptations were demonstrated for each movement to accommodate age, individual fitness, and mobility. Community members were encouraged to self-select an intensity that they felt most comfortable with. All live workouts were recorded and archived on the EIM-OC website and YouTube channel where they were available to view at any time. Additionally, live lunchtime movement sessions were offered 1x/week through Zoom. These ~20 min sessions consisted of low-intensity physical activity and stretching to break up sitting. An exercise DVD option was also available upon request that included 4 different home-based workout sessions and could be ordered on the EIM-OC website or by phone. Additionally, 30 min physical activity workouts were aired on our local ABC TV affiliate monthly.

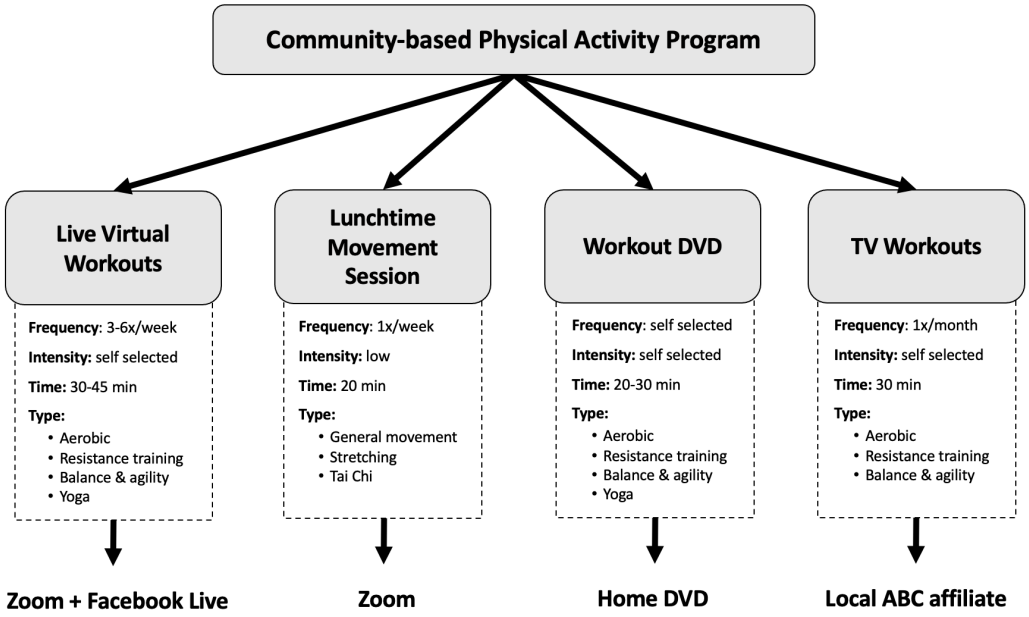

Figure 2.2 Overview of community-based physical activity program.

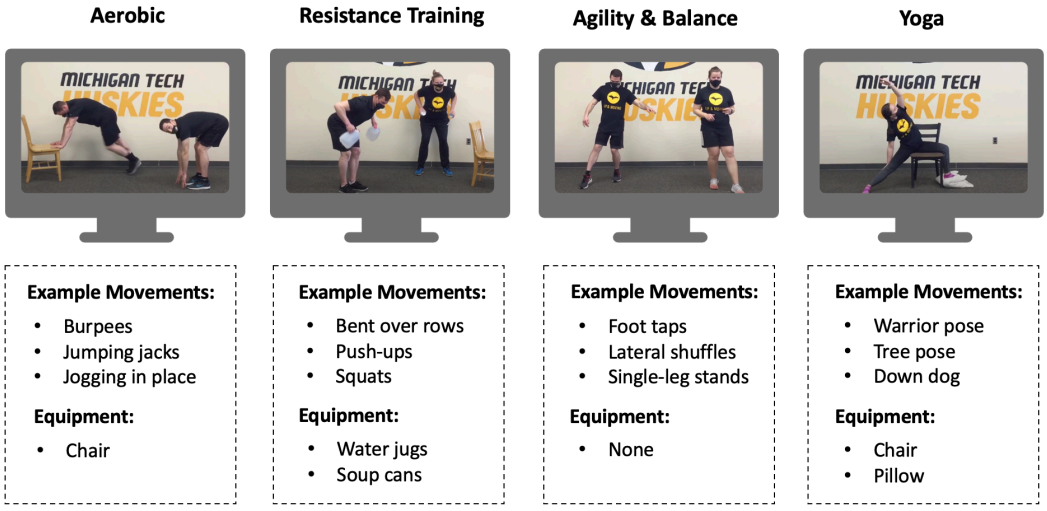

Figure 2.3 Screenshots and descriptions for each of the different virtual workout types.

2.7 Primary Outputs

The EIM-OC team: 1) participated in 2 radio interviews, 1 podcast, and 25 COVID-19 Public Townhalls, 2) contributed to 5 newspaper articles, 3) produced a COVID-19 healthy living TV commercial, and 4) published 2 blog posts on the American Physiological Society's I Spy Physiology Blog. Over an 18-month period, our EIM-OC website had more than 17,000 views and our monthly email gained 134 subscribers. Most notably, promotion of physical activity resulted in 2 physical activity infographics that gained widespread attention. Specifically, our infographic "Promote The 4-W's" (Figure 2.4; left) provided a simple message for the community to **W**ash their hands, **W**ear a mask, and **W**atch their distance, and **W**alk, to stay physically active. This message was featured in the American Kinesiology Association quarterly newsletter and included in a recent publication.[57] A second infographic (Figure 2.4; right) illustrated physical activity as a form of medicine, its health benefits, and how to reach the recommended levels of physical activity safely from home during the pandemic. This infographic was requested by the Michigan Department of Health and Human Services and featured in a home-based cardiac rehabilitation booklet. This infographic was also published [55] and to date, downloaded over 23,000 times, Tweeted 526 times, and cited 17 times. Additionally, both infographics were provided to clinicians and local fitness professionals as a resource to promote the importance of physical activity during the pandemic.

We delivered over 260 guided virtual physical activity workouts (Table 2.2) that could be performed safely from home without the need for specialized equipment. Collectively, these workouts helped adults work towards achieving the recommended amounts of weekly aerobic and muscle strengthening exercise and reduce time spent sitting. Additionally, our virtual physical activity program also was utilized by two remotely taught Michigan Technological University physical education courses. Over an 18-month period, our webpage linking viewers to the live virtual workouts had more than 4,800 views. During this same timeframe, our YouTube channel containing archived workouts received over

4,000 views. To celebrate the 100th virtual workout, a virtual 5 km walk/run/movement event was held on Zoom. The event facilitated a home-based option that accumulated the number of steps required to cover ~5 km. As a result of the EIM-OC team's efforts to promote and facilitate physical activity on campus and in the community, Michigan Technological University received a Silver level designation from the ACSM's EIM-OC program and a special honor for demonstrating creative physical activity adaptations during the COVID-19 pandemic.

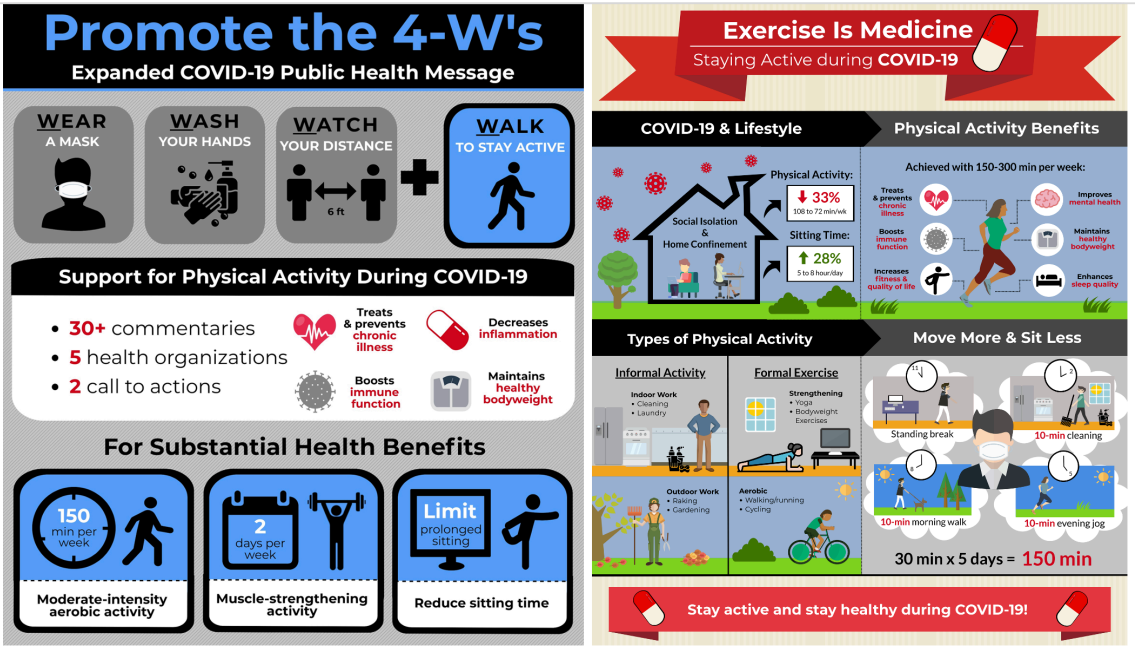

Figure 2.4 Infographics used to promote physical activity during the pandemic. Reprinted from references [55,57]. Used with permission (pending at time of manuscript acceptance to ACSM Health & Fitness Journal).

Table 2.2 Summary of workouts delivered.

Type	Number Delivered
Live Virtual Workouts	212
Aerobic	88
Resistance training	64
Agility & Balance	38
Yoga	22
Lunchtime Movement Sessions	40
TV Workouts	12
Workout DVDs	5
Total	269

2.8 Considerations and Lessons Learned

Our EIM-OC initiative provided physical activity resources to the community quickly during the pandemic. Based on our experiences to date, there were several important considerations and lessons learned. First, through EIM-OC we were able to facilitate collaboration between students, faculty, and fitness professionals. Importantly, this collaborative effort allowed our team to come together and leverage our health and fitness expertise to contribute to the COVID-19 response within our rural and underserviced community. With limited public health resources and a local health care system overburdened with managing COVID-19 our team helped to supply critical messaging about physical activity as a form of medicine and provided resources to keep our community safe and healthy. Further, our website and social media analytics suggest that these resources were accessed by community members.

Second, EIM-OC facilitated widespread public health promotion through several forums (e.g., newspaper, social media, interviews, public town hall, TV commercial, infographics). According to the World Health Organization's

Interventions on Diet and Physical Activity: What Works?,[91] mass media campaigns promoting physical activity are an effective intervention for increasing awareness and prompting positive behavioral change. Similar to our promotional efforts, successful interventions commonly focused on communicating a clear and simple message via many different channels. Increased health promotion through media campaigns could have far reaching effects in rural communities. Increased access to health information may help to improve health literacy, a social determinant of health that tends to be lower in rural populations compared to urban populations.[92] Further, increased awareness about the importance of physical activity and the promotion of local resources may result in more community members seeking help from fitness professionals in the area.

Third, the delivery of a virtual physical activity program was a viable way to offer physical activity resources during the pandemic and may offer numerous benefits to facilitating physical activity beyond the pandemic. Specifically, the workouts were easily broadcasted and archived, providing many different ways for community members to access the program (Zoom, Facebook Live, YouTube, website, TV, DVD). Additionally, it provided a convenient way for community members to access our local fitness professionals from home. By including fitness professionals with a diverse range of interests and skillsets we were able to provide a wide variety of different workout types. Indeed, with some creativity along with common household items, workouts could be delivered similar to those more typical in a gym or fitness center. The virtual platform also aided with university remote physical education instruction thus helping to keep students active even though they were not on campus. In rural communities where access to physical activity infrastructure is limited, guided virtual home-based workouts may provide an option for rural residents to engage in physical activity.

2.9 Limitations and Strengths

We acknowledge that a limitation of our work was that we did not directly assess the effectiveness of our intervention to increase public awareness or improve physical activity levels. However, our objectives were not framed as research questions that would require experimental design and methods to evaluate. Given the critical and time sensitive need for physical activity promotion during a national crisis, we focused exclusively on timely implementation. Under these time constraints we did our best to conduct process type-evaluation and tracked views to our web pages, social media communications and virtual exercise programming. These data helped to provide some level of evaluation and guided our work during real time. As outlined in the MAP-IT framework promoted by Healthy People 2020, a powerful model for planning and evaluating a successful public health intervention includes five steps: 1) **M**obilize, 2) **A**ssess, 3) **P**lan, 4) **I**mplement, and 5) **T**rack. By leveraging EIM-OC to address the need for physical activity promotion and implementing a plan in our rural community, we were able complete the first four steps of this model. Evaluating the effectiveness of our program to impact health behaviors is an important next step, as we believe that this type of virtual physical activity programming will gain increasingly more importance in the future, during both pandemic and non-pandemic times. These types of virtual programs expand the potential for greater reach and impact among persons living in rural areas and/or among older adults and people with disabilities who may not be able to travel to locations were in-person programming and assistance are available.

2.10 Professional Development for Students

The pandemic has negatively impacted educational experiences for students and trainees. Through our EIM-OC initiative several students had the opportunity to contribute to the COVID-19 response in their rural and underserved community while at the same time developing skills related to health promotion and exercise implementation. Indeed, the EIM-OC team doubled in size from Fall 2020 to Spring 2021 to include students interested in a wide range

of different careers within health and fitness. The EIM-OC initiative provided these future professionals with valuable learning experiences beyond the classroom and aided in their professional development during the pandemic. Importantly, EIM-OC will continue to provide an experiential learning and outreach opportunity for our students focused on careers in health science, health fitness, and healthcare.

2.11 Moving Forward

Physical inactivity will present a serious threat to public health for decades to come. Moving forward, EIM-OC at Michigan Technological University will continue to use a collaborative approach involving students, faculty, and fitness professionals to provide physical resources for our rural and underserved community. An important next step is to work with local health care providers to establish physical activity as a vital sign of health and implement an exercise prescription and referral system, which aligns with the vision for EIM. Local fitness professionals involved with our EIM-OC program will be key players in the referral system. We hope that this commentary will encourage fitness professionals to collaborate with EIM-OC programs to promote and facilitate physical activity during the COVID-19 pandemic and beyond.

*An unpublished addendum to Study 1 (Appendix A) includes more description of the population-based framework used to develop and implement the physical activity program

3 Blood Flow Restriction as a Potential Therapy to Restore Physical Function Following COVID-19 Infection

3.1 Abstract

Accumulating evidence indicates that COVID-19 survivors display reduced muscle mass, muscle strength, and aerobic capacity, which contribute to impairments in physical function that can persist for months after the acute phase of illness. Accordingly, strategies to restore muscle mass, muscle strength, and aerobic capacity following infection are critical to mitigating the long-term consequences of COVID-19. Blood flow restriction (BFR), which involves the application of mechanical compression to the limbs, presents a promising therapy that could be utilized throughout different phases of COVID-19 illness to restore physical function. Specifically, we hypothesize that: 1) use of passive BFR modalities can mitigate losses of muscle mass and muscle strength that occur during acute infection and 2) exercise with BFR can serve as an effective alternative to traditional higher intensity exercise for regaining muscle mass, muscle strength, and aerobic capacity during convalescence. In addition to restoring physical function, the various applications of BFR may also serve as a targeted therapy to address the underlying pathophysiology of COVID-19 and provide benefits to numerous organ systems affected by the disease. Consequently, we propose a theoretical framework with which BFR could be implemented throughout the progression from acute illness to outpatient rehabilitation with the goal to improve short and long-term outcomes in COVID-19 survivors. We hope that this work encourages consideration of the potential therapeutic benefits of BFR to treat not only COVID-19 but similar pathologies and cases of acute critical illness.

3.2 Introduction

To date, there have been over 670 million reported cases of coronavirus disease 2019 (COVID-19) and over 6 million deaths worldwide.[7] In addition to the acute complications associated with COVID-19 infection, accumulating evidence [18-22,93] indicates that a variety of symptoms can persist for weeks and/or months following the acute phase of illness (i.e., long COVID, post-acute sequelae of COVID-19 or post-COVID-19 syndrome). Among the most prevalent symptoms are fatigue, dyspnea, cognitive dysfunction, muscle and joint pain, and weakness. Additionally, in a recent systematic review de Olivira Almeida and colleagues [24] reported that COVID-19 survivors experience impaired physical function and reduced ability to perform activities of daily living up to 6 months following acute illness. For example, several authors have reported lower performance on sit-to-stand,[61,94,95] walking,[19,96] and physical performance battery tests [61,94,97] and lower Barthel Index and Activities of Daily Living Scores.[98] While these outcomes have been reported across acute illness severities, individuals with more severe illness requiring hospitalization appear to be most affected.

Physical function is influenced by the integration of multiple organ systems, particularly the musculoskeletal and cardiorespiratory systems. Accordingly, skeletal muscle quality,[99-101] muscular strength,[102-105] and aerobic capacity [99] (i.e., peak oxygen consumption) are important determinants of physical function. Individuals who become critically ill with COVID-19 experience rapid muscle wasting,[63] loss of muscle strength,[61-63] and reduced aerobic capacity [106] during hospitalization. Furthermore, these losses are not recovered months following acute infection. Recently, Ramirez-Velez and colleagues [28] reported muscle and strength loss in COVID-19 survivors at 3-months following acute illness. Several authors [64] have also reported lower aerobic capacity in survivors with some evidence indicating that impairments may persist up to 12 months after initial infection. Together, these data suggest that diminished skeletal muscle mass, muscle strength, and aerobic capacity are likely contributors to long-term impairments in physical function. The mechanisms responsible for these effects

are not well understood and may be multifactorial including factors associated with general critical illness (i.e., extended periods of inactivity, pharmacological therapies, malnutrition) and/or mechanisms specific to COVID-19 pathophysiology (i.e., direct viral infiltration, renin angiotensin system dysregulation, systemic inflammation, and oxidative stress).

Collectively, the chronic manifestations of COVID-19 infection may be comprising long-term health and leaving those individuals who become infected prone to frailty and disease. Persistent physical function impairments following COVID-19 are associated with lower physical activity levels [27-30] and may increase the risk of frailty,[31] falls and injury,[32] and chronic diseases such as diabetes, obesity, and cardiovascular disease.[33] Data indicate [18] that 44% of individuals infected with COVID-19 will develop long-term impairments in physical function, meaning that ~230 million people could be affected. As COVID-19 continues to impact the world, the health and economic consequences of long-term symptoms could be astronomical. Currently, there are no evidence-based strategies for restoring physical function in those individuals suffering from short- to long-term complications following COVID-19. Developing safe, feasible, and cost-effective approaches to mitigate the loss of muscle mass, muscle strength, and aerobic capacity are of paramount importance and align with COVID-19 initiatives.[35-37,107] Based on the unique symptoms, pathophysiology, and challenges associated with COVID-19, innovative rehabilitation approaches are required. Accordingly, the present paper aims to discuss the potential use of blood flow restriction (BFR) as a rehabilitation modality during and following COVID-19 infection to improve physical function.

3.3 Statement of Hypotheses

Our working hypothesis is that implementation of BFR can facilitate recovery of physical function following COVID-19. Specifically, we hypothesize that BFR can be applied during: 1) acute infection in those individuals with critical

illness to mitigate the loss of muscle mass and muscle strength and 2) convalescence in those individuals recovering from critical illness to regain muscle mass, muscle strength, and aerobic capacity. To support these hypotheses, we provide a rationale for how BFR offers a targeted therapy that specifically addresses the underlying pathophysiology of COVID-19 and propose a theoretical framework for how BFR may be implemented throughout the progression from acute illness to outpatient rehabilitation. We hope that this paper encourages discussion and consideration among researchers and clinicians not only about the potential utility of BFR in the treatment of COVID-19 but its application to similar pathologies and cases of acute critical illness.

3.4 Theory of Hypotheses

Recently, several authors [52,108,109] have suggested the use of blood flow restriction (BFR) as a treatment strategy for COVID-19 patients. This modality (Figure 3.1) involves applying mechanical compression to the proximal portion of a limb, typically with a pneumatic cuff, which serves to partially reduce arterial blood flow to the limb while limiting most of the venous return.[45-47] The reduction of arterial and venous blood flow results in localized tissue hypoxia,[110] metabolite accumulation, and cellular swelling [111] within tissues distal to the cuff. Currently, BFR is endorsed by the American Physical Therapy Association and is used in rehabilitation.[82] It has been implemented with a variety of clinical populations including individuals with advanced age,[43,112-114] orthopedic limitations,[77,115,116] critical illness,[117] cardiovascular disease,[67-72] hypertension,[66,118-120] diabetes,[73,74] renal dysfunction,[75,76] and neurological conditions.[121-123] Notably, some of these conditions share similar pathophysiological presentations to COVID-19, characterized by increased levels of inflammation, oxidative stress, autonomic, and endothelial dysfunction.

Most commonly, BFR has been applied in combination with the performance of voluntary exercise, including both resistance exercise (BFR-RE) [38-41] and aerobic exercise (BFR-AE).[42,43,124] Additionally, it has also been

implemented passively in the absence of muscle contraction (BFR-P) [117,125] and in combination with involuntary muscle contraction elicited via neuromuscular electrical stimulation (BFR-NMES).[48,123,126,127] The various applications of BFR may have utility during different phases of acute infection and post-acute recovery from COVID-19. Specifically, we hypothesize that passive applications of BFR (BFR-P and BFR-NMES) can help to mitigate losses in muscle mass and muscle strength during acute COVID-19 illness and that the combination of BFR with exercise (BFR-AE and BFR-RE) can provide a viable way to restore muscle mass, muscle strength, and aerobic capacity to adequate levels during convalescence. Furthermore, BFR may offer a unique therapy that not only facilitates recovery of physical function but specifically addresses the underlying pathophysiology of COVID-19.

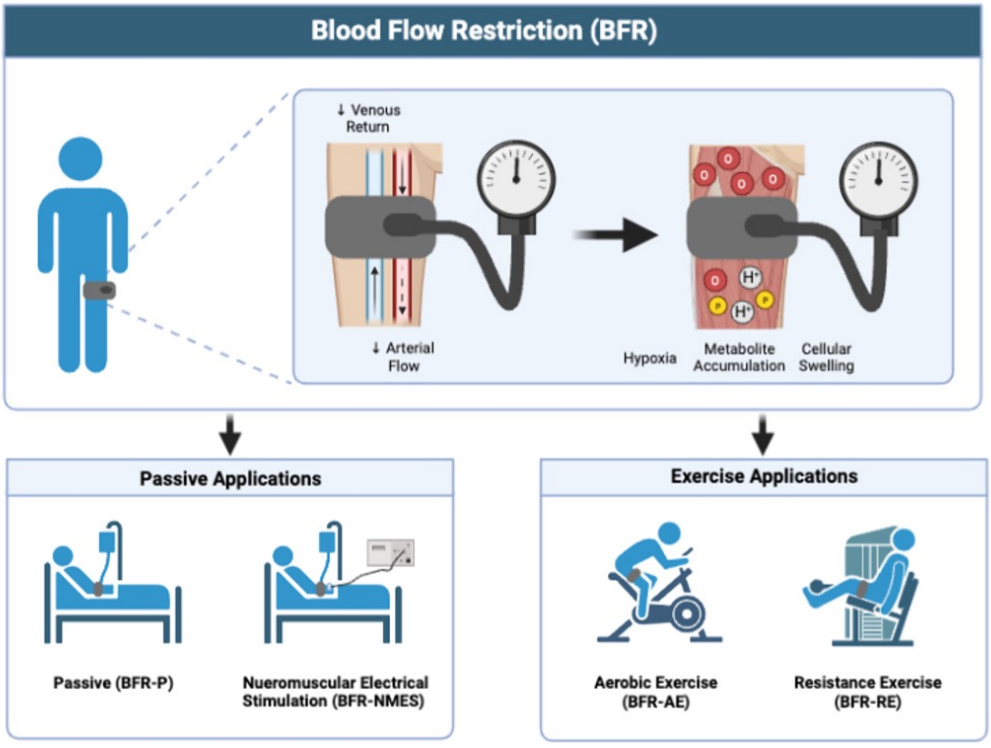

Figure 3.1 Overview of BFR and the different methods of application.

3.5 Evaluation of Hypotheses

3.5.1 Hypotheses 1: Mitigating Muscle and Strength Loss during Acute infection

Muscle and strength loss are common during admittance to the intensive care unit (ICU) [128] and correlate with hospital length of stay [129,130] and physical function after discharge.[131] After 10 days in the ICU, de Andrade-Junior and colleagues [63] reported that COVID-19 patients displayed a 30% reduction in rectus femoris muscle cross-sectional area and a 19% reduction in the thickness of the anterior compartment of the quadriceps muscles. These rates of muscle loss are greater than those reported in other critically ill patients during ICU admission.[132] At hospital discharge, Paneroni and colleagues [61] reported that 80% of COVID-19 patients presented with muscle weakness, displayed quadriceps and biceps brachii muscle strength that were 54 and 69% of predicted values. Furthermore, accumulating evidence indicates that COVID-19 survivors are at an increased risk of developing acute sarcopenia [133] and have a 20% risk of readmittance after initial hospital discharge.[134] Efforts to reduce rates of muscle and strength loss during severe acute COVID-19 infection may improve patient outcomes and reduce the time needed to recover physical function to adequate levels following discharge. However, viable therapies to mitigate the effects of critical illness on skeletal muscle are limited as hospitalized patients typically experience prolonged immobility and have a reduced ability to perform voluntary muscle contractions. As described below, the application of BFR-P and BFR-NMES may help to slow the rate of muscle and strength loss in those individuals hospitalized with severe COVID-19 illness. These modalities may also help to counteract the underlying pathophysiology of COVID-19.

3.5.1.1 BFR-P

Emerging evidence [117,125] indicates that the intermittent application of BFR passively in the absence of muscle contraction mitigates losses in muscle and strength that occur during immobilization. Barbalho and colleagues [117] demonstrated that the addition of BFR to passive mobilization reduced rates of

muscle wasting in elderly coma patients admitted to the ICU. Compared to a control limb receiving passive mobilization alone, the addition of a tourniquet cuff to the proximal thigh during once daily passive mobilization decreased the rate of quadriceps muscle loss by 6% over an 11-day period. Other reports, which have been previously reviewed,[125] indicate that a BFR-P protocol consisting of 5 sets of 5 min restriction and 3 min reperfusion performed twice daily diminished disuse of the knee extensors by 11% following anterior crucial ligament reconstruction [135] and prevented strength losses during 2 weeks of simulated cast immobilization in healthy adults.[136,137]

3.5.1.2 BFR-NMES

Neuromuscular electrical stimulation (NMES) is a technique that consists of generating involuntary muscle contractions using low level electrical currents delivered through electrodes applied to the skin. The addition of NMES to standard care [138,139] in critically ill patients reduces the rate of muscle loss, improves muscle strength, shortens length of stay in the hospital, and improves ability to perform activities of daily living. Some evidence [48,123,126,127] indicates that low-intensity NMES combined with BFR promotes more robust effects on muscle size and strength than low-intensity NMES or BFR performed alone. For example, Gorgey and colleagues [123] reported that 6 weeks of BFR-NMES in individuals living with spinal cord injury increased wrist extensor muscle cross-sectional area and improved electronically evoked wrist extensor torque. Changes in wrist extensor cross-sectional area were 17% greater in the treatment limb receiving BFR-NMES compared to a control limb receiving NMES alone. In another report,[127] BFR-NMES performed twice daily (5 days/week) in the lower-body increased quadriceps muscle thickness and maximal knee extension strength after 2 weeks of training in young males. No changes were observed in a control limb performing NMES alone. Slysz and Burr [126] reported increased knee extensor strength when BFR-NMES was applied 4 times per week for 6 weeks in recreationally active adults. Strength increases with BFR-P and NMES alone did not differ from a control limb receiving no intervention.

Finally, during 14 days of simulated limb unloading, Slysz and colleagues [48] reported that BFR-NMES prevented losses in whole thigh lean mass and increased vastus lateralis muscle thickness. Changes with BFR-P alone were similar to a control group receiving no intervention.

3.5.1.3 Pathophysiology of COVID-19

Endothelial dysfunction has been suggested to be a major pathogenic mechanism of COVID-19 [140-142] and persists for months beyond acute infection.[143] Endothelial dysfunction is associated with numerous chronic diseases [144] as well as risk of future cardiovascular events [145] and likely contributes to long-term symptoms in COVID-19 survivors.[146] In a systematic review and meta-analysis including 292 participants, Gu and colleagues [147] reported that BFR-P protocols, referred to as ischemic preconditioning, augment endothelial function via increased flow mediated dilation. Several authors [148-150] have also reported enhanced microvascular function when implementing similar protocols. Like BFR-P protocols discussed previously, ischemic preconditioning involves the cyclical application of blood flow restriction and reperfusion. However, tourniquets are applied at higher pressures that result in arterial occlusion. A large body of evidence [151] demonstrates that ischemic preconditioning protects tissues from subsequent ischemia and reperfusion injury and that these effects also occur in remote tissues (i.e., remote ischemic conditioning) that are not directly subject to the localized ischemic preconditioning stimulus. Indeed, lung and cardiovascular injury [152] are common with severe COVID-19 illness and ischemic preconditioning may confer a systemic protective effect. The use of ischemic preconditioning in COVID-19 patients has been previously suggested.[109,153-155] Additionally, COVID-19 patients display impaired hemostasis [156] which is characterized by overactivation in the coagulation system with reduced fibrinolytic activity. Accordingly, thrombotic complications are common in COVID-19. Longstanding evidence indicates that vascular compression stimulates the fibrinolytic system without elevating the coagulation cascade [157-161] and has been shown to reduce incidence of deep

vein thrombosis.[162-164] Accordingly, when applied in COVID-19 patients, various BFR-P approaches could potentially help to reduce risk for thrombotic complications. While there is extensive literature supporting the application of BFR-P and its effects on numerous organ systems, reports implementing BFR-NMES are limited. To the best of our knowledge, only one report has investigated the effects of BFR-NMES on vascular function in which the authors [123] demonstrated acute increases in brachial artery flow mediated dilation following BFR-NMES when compared BFR alone. These promising preliminary data suggest that there are vascular benefits with the addition of NMES, however, more work in needed to characterize the effects of this modality.

Low aerobic capacity in COVID-19 survivors, as assessed through an incremental exercise test for determination of VO_{2peak}, has been attributed to both central and peripheral factors.[64] Thus, impairments throughout the oxygen transport pathway are likely present. In addition to potentially enhancing oxygen delivery via improved peripheral vascular function, BFR-P could attenuate reductions in aerobic capacity during critical COVID-19 illness by reducing cardiac deconditioning and improving oxygen kinetics in skeletal muscle. Nakajima and colleagues [165] reported similar hemodynamic responses to that of upright standing when BFR-P was applied to the proximal thighs of participants placed in a 6-degress head-down tilt position. These observations suggest that BFR-P can replicate the cardiac demands of standing and may attenuate cardiac deconditioning and orthostatic intolerance occurring during prolonged bedrest. Additionally, several authors [166-169] have reported that repeated ischemic preconditioning exposure improves local skeletal muscle oxygen dynamics during exercise. Data from Jefferies and colleagues [148] demonstrated that 7 consecutive days of lower-body ischemic preconditioning increased local skeletal muscle oxidative capacity. Together, BFR-P protocols can help preserve skeletal muscle mass and strength during critical illness and offer a systemic therapeutic strategy that can provide benefits to numerous organ systems affected during COVID-19 infection (Figure 3.2; bottom left).

3.5.2 Hypotheses 2: Increasing Muscle Mass, Muscle Strength, and Aerobic Capacity During Convalescence

Exercise training is a promising therapy in the rehabilitation of COVID-19 as it: 1) promotes healthy function in multiple organ systems, 2) effectively treats a variety of diseases that share similar pathophysiological presentations to COVID-19, 3) increases muscle mass, muscle strength, and aerobic capacity, and 4) directly improves physical function. A recent systematic review [170] including 233 COVID-19 survivors found that a combination of resistance and aerobic exercise training following hospital discharge increased muscle strength, physical function, and quality of life. It is important to note that several concerns have been raised about exercise after COVID-19 including the risk of cardiac injury, thromboembolic complications, and post-exertional symptom exacerbation.[171-173] Given these concerns, along with frequently reported symptoms of fatigue, joint and muscle pain, and weakness, exercise prescription in COVID-19 survivors requires careful consideration. Importantly, higher exercise intensities needed to promote increases in muscle size, strength, and aerobic capacity may be challenging or contraindicated. Alternatively, exercise training with BFR could offer a unique approach for COVID-19 survivors to attain the benefits of higher intensity exercise. The main advantages of exercise with BFR compared to traditional exercise are: 1) increases in muscle size, strength, and aerobic capacity can be achieved with low exercise intensities,[40,43,44,48] 2) adaptations from BFR occur faster, and 3) muscle size and strength can be increased with both aerobic and resistance exercise.[39] The following sections provide a brief review on the effects of BFR-AE and BFR-RE on muscle size, muscle strength, and aerobic capacity and highlight unique advantages of these exercise modalities over that of higher intensity exercise in managing the pathophysiology of COVID-19.

3.5.2.1 BFR-AE

The combination of aerobic exercise, such as walking or cycling, with BFR increases muscle size and strength in younger [39] and older adults.[113] Importantly,

these adaptations are achieved at lower exercise intensities (45% heart rate reserve or 40% VO_{2max}) and occur in as early as 3 weeks, sooner than that observed with more traditional higher intensity resistance training. In addition to increases in muscle size and strength, BFR-AE also facilitates increases in aerobic capacity in young adults [42,43] as well as well-trained athletes.[124] Thus, BFR-AE provides an efficient exercise mode that improves both skeletal muscle size and strength as well as aerobic capacity simultaneously. Importantly, a systematic review by Clarkson and colleagues[44] indicated that adaptations occurring with BFR-AE translate to improvements in objective measures of physical function, including the 30-second sit-to-stand, timed up and go, and 6-minute walk test. This modality has been safely applied in individuals living with a variety of diseases including hypertension,[174] end-stage kidney disease,[175] chronic heart failure,[176] and obesity.[177]

3.5.2.2 BFR-RE

Increases in muscle size and strength with the performance of resistance exercise in combination with BFR have been reported in reviews of healthy young [38-41] and older populations,[38,41,113] as well as those individuals with orthopedic limitations.[77] Once again, adaptations from BFR-RE are achieved with lower exercise intensities (20-40% 1RM) and are significantly greater than those attained with lower intensity resistance exercise performed without BFR. While strength increases are lower with BFR-RE compared to higher intensity resistance exercise, increases in muscle size are comparable between modes.[38] Relative to BFR-AE, the magnitude of muscle size and strength improvements with BFR-RE are greater [39] and also translate to improvements in objective measures of physical function.[44,178] Few studies have investigated the effects of BFR-RE on aerobic capacity, however, one report [71] noted significant increases in aerobic capacity when BFR-RE was performed for 3 months in individuals living with ischemic heart disease. Thus, BFR-RE may have the potential to promote cardiovascular adaptations in diseased and less trained populations. Lastly, in addition to improvements in skeletal muscle function, BFR-RE appears

to promote adaptations in bone and connective tissue, with reports indicating positive impacts on bone metabolism [179] and tendon properties.[180,181] This modality has been applied in individuals living with hypertension,[66,118-120] diabetes,[73,74] chronic kidney disease,[75,76] and cardiovascular disease.[67-72]

3.5.2.3 Pathophysiology of COVID-19

Elevated levels of inflammation and oxidative stress have been suggested [141] to play important roles contributing to organ dysfunction with COVID-19. Furthermore, evidence indicates that oxidative stress [182] and inflammation [183] remain elevated beyond acute infection and likely contribute to long-term symptoms. It is important that interventions aimed at restoring muscle mass, muscle strength, and aerobic capacity in COVID-19 survivors do not exacerbate the underlying pathological mechanisms of the disease. Traditional higher intensity exercise can result in acute elevations in oxidative stress, muscle damage, and inflammation.[184] These responses are greatest in individuals that are deconditioned and unaccustomed to exercise. Given the combination of prolonged immobilization, deconditioning, and pre-existing inflammatory and oxidant-antioxidant imbalances, the acute physiological perturbations associated with higher intensity exercise could be deleterious in those recovering from severe COVID-19. Additionally, meta-analyses [185-187] have reported elevated makers of skeletal muscle damage (i.e., creatine kinase, lactate dehydrogenase, myoglobin) associated with COVID-19 infection and several case studies [188-191] have reported rhabdomyolysis in patients. Exercise resulting in further muscle damage and a subsequent inflammatory response could further deteriorate physical function, suppress the immune system, and worsen symptoms.

Several reports [192-195] indicate that lower intensity exercise with BFR results in lower acute elevations in biomarkers of oxidative stress when compared to higher intensity exercise. Additionally, Petrick and colleagues [196] reported that skeletal muscle mitochondrial reactive oxygen species emission rates were acutely decreased 2 hr following lower intensity BFR-RE but not after

the same exercise protocol performed without BFR. Available evidence [65,197-200] suggests that BFR-RE in combination with lower loads results in minimal to no muscle damage based on the absence of prolonged decrements in muscle function, edema, range of motion, and elevation in blood markers of muscle damage. Moreover, significant muscle damage is not reported in studies [201,202] directly investigating the integrity of muscle fibers following BFR-RE. Accordingly, exercise with BFR provides a novel method to increase muscle size, muscle strength, and aerobic capacity which elicits relatively small acute elevations in oxidative stress and damage to skeletal muscle compared to traditional higher intensity exercise. Thus, exercise with BFR provides an alternative way to restore physical function that may be less likely to exacerbate the underlying pathophysiological mechanisms of COVID-19.

A potential mechanism by which COVID-19 promotes systemic pathology, particularly endothelial dysfunction, is interaction of SARS-CoV-2 with the renin angiotensin system (RAS). The principal target of SARS-CoV-2 binding is angiotensin-converting enzyme 2 (ACE2), a membrane bound protein found in numerous tissues throughout the body. The active form of ACE2 opposes the action of the RAS. Specifically, ACE2 degrades Angiotensin I (Ang I) and converts Angiotensin II (Ang II) into Ang (1,7), which exerts vasodilatory and anti-inflammatory effects. With COVID-19 infection, the consumption and downregulation of ACE2 via SARS-CoV-2 binding leaves RAS unopposed, increasing the ratio of ANG II to ANG (1,7) and driving excessive vasoconstriction, inflammation, and oxidative stress. Joshi and colleagues [203] reported that BFR-RE performed in the lower-body substantially increased ACE2 activity and enhanced the ACE2-to-ACE ratio following exercise. Additionally, these authors reported increases in circulating hematopoietic stem/progenitor cells which were associated with three-fold increases in vascular endothelial growth factor receptors. Further, a recent meta-analysis [204] demonstrated that exercise with BFR facilitates greater expression of angiogenesis related factors than exercise performed without BFR. Collectively, this evidence suggests that

exercise with BFR may combat RAS dysregulation in COVID-19 and enhance the adaptive and regenerative capacity of the vascular system. Other data have reported direct benefits of exercise with BFR throughout the vascular tree. In a recent meta-analysis, Pereira-Neto and colleagues [205] reported that 4 or more weeks of BFR-RE improves endothelial function (i.e., flow mediated dilation, reactive hyperemia blood flow, and reactive hyperemia index) and some data [206,207] report enhanced capillary growth.

Among the benefits of exercise is its positive impact on hemostasis. Higher intensity resistance training acutely enhances fibrinolytic activity,[208] increasing tissue plasminogen activator (tPA) and decreasing plasminogen activator inhibitor-1 (PAI-1), without elevating activity in the coagulation system. Evidence indicates similar responses in the fibrinolytic system with the performance of lower intensity exercise with BFR. Nakajima and colleagues [209] reported significant increases in tPA antigen and unchanged PAI-1 activity during lower intensity BFR-RE (30% 1RM) performed after 24 hours of bedrest. Similarly, Clark and colleagues [210] reported a 33% increase in tPA antigen immediately following acute bouts of BFR-RE with no alterations in markers of coagulation. Responses were similar to those observed with higher intensity resistance exercise without BFR. Furthermore, studies [211,212] implementing the chronic performance of BFR-RE have demonstrated decreases in von Willebrand factor (vWF) after 4 weeks. Taken together, these data demonstrate that exercise with BFR provides similar fibrinolytic effects as higher intensity exercise, albeit at lower exercise intensities, and could protect against short and long-term thrombotic complications associated with COVID-19. Collectively, exercise with BFR appears to promote a variety of positive adaptations in the vascular system and may confer several unique benefits to COVID-19 survivors that are not achieved with traditional high-intensity exercise (Figure 3.2; bottom right).

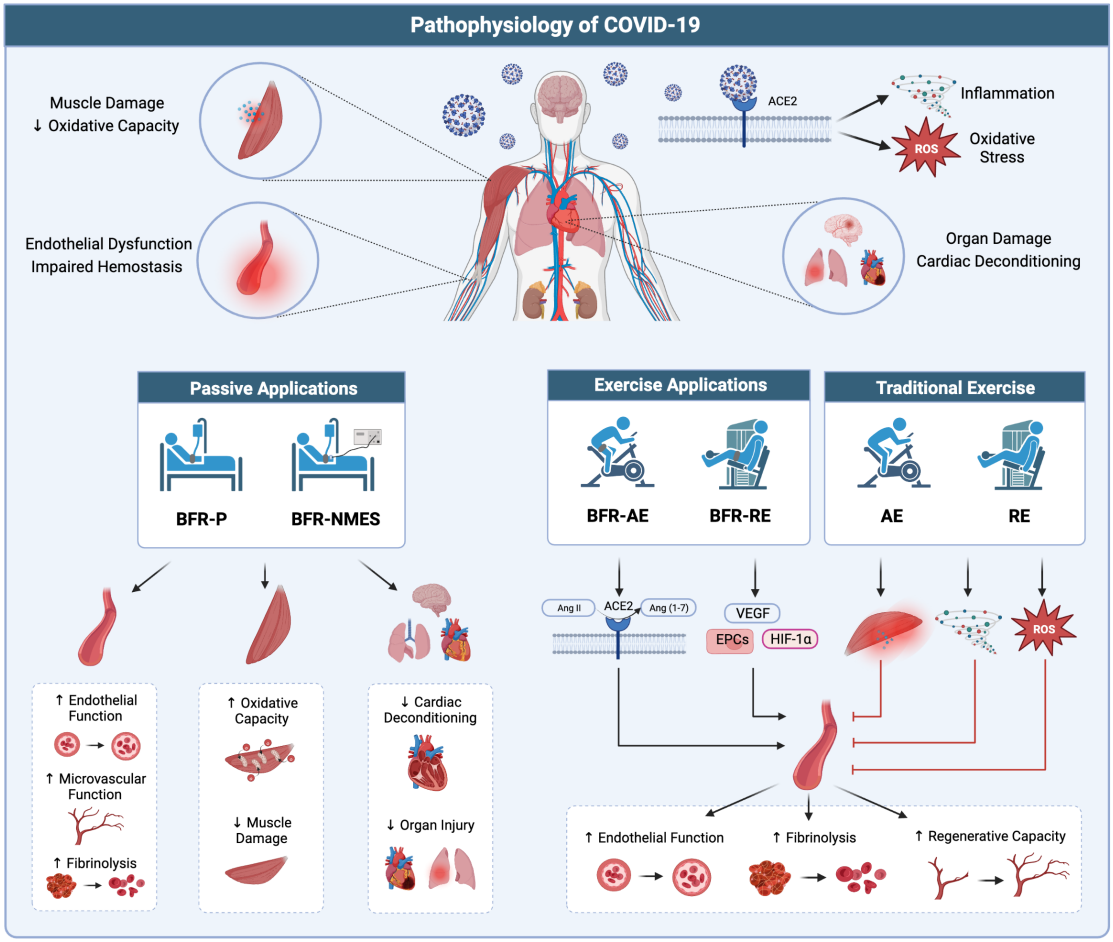

Figure 3.2 Potential therapeutic benefits of BFR in treating the pathophysiology of COVID-19. (Top) Infection with COVID-19 results in widespread organ dysfunction which may be the result of systemic viral infiltration, hyper-inflammation, and oxidative stress. (Bottom left) Passive applications of BFR (BFR-P and BFR-NMES) promote positive effects in the vasculature, skeletal muscle, and vital organs which may serve to combat multiple organ dysfunction occurring with COVID-19. (Bottom right) Exercise applications of BFR (BFR-AE and BFR-RE) promote benefits to the vascular system through increased ACE2 activity, stimulating the release of hematopoietic stem cells, and promoting the expression of factors related to vascular growth and regeneration. Additionally, compared to traditional high-intensity exercise, exercise with BFR results in lower levels of muscle damage, inflammation, and oxidative stress, which could exacerbate the pathophysiological mechanisms of COVD-19 and worsen symptoms.

3.6 Consequences of Hypotheses

We have constructed a theoretical framework for which BFR could be applied to COVID-19 patients throughout the transition from acute illness to outpatient rehabilitation. Our framework (Figure 3.3) was adapted from Leonneke and colleagues [213] and consists of three phases of BFR application. ***Phase I*** consists of applying passive BFR applications (BFR-P and BFR-NMES) during severe acute COVID-19 illness to reduce muscle and strength loss while patients are immobilized. Importantly, these modalities can be implemented early in acute care and do not require active cooperation from the patient. Once capable of mobilization, patients can be progressed to ***Phase II***, which consists of performing BFR-AE to regain muscle mass, muscle strength, and aerobic capacity. Before patients are capable of ambulating, BFR-AE could be performed during early active mobilization activities such as bed mobility, transfers (e.g., supine-to-sit, sit-to-stand), arm ergometry, or supine leg ergometry. Once physically capable, patients can be progressed to more traditional BFR-AE exercise modes including walking and cycling. As patients' mobility and tolerance to exercise increases, they can be progressed to ***Phase III***, which includes the addition of BFR-RE to provide a more robust method for increasing muscle mass and strength. Based on patient progress and physical ability, BFR-RE could be initiated in the post-acute rehabilitation setting or during outpatient rehabilitation. Given the substantial and prolonged decrements in aerobic capacity of COVID-19 survivors, it would be advised to continue BFR-AE during this phase and/or begin integrating higher intensity aerobic exercise without BFR based on patient tolerance. While initial resistance exercise training protocols can focus on BFR-RE exclusively, higher intensity resistance exercise without BFR should be slowly incorporated into the rehabilitation program as tolerated to stimulate additional improvements in muscle strength. Collectively, progression through each phase of BFR application can help to restore physical function and reduce the long-term consequences of severe COVID-19 infection.

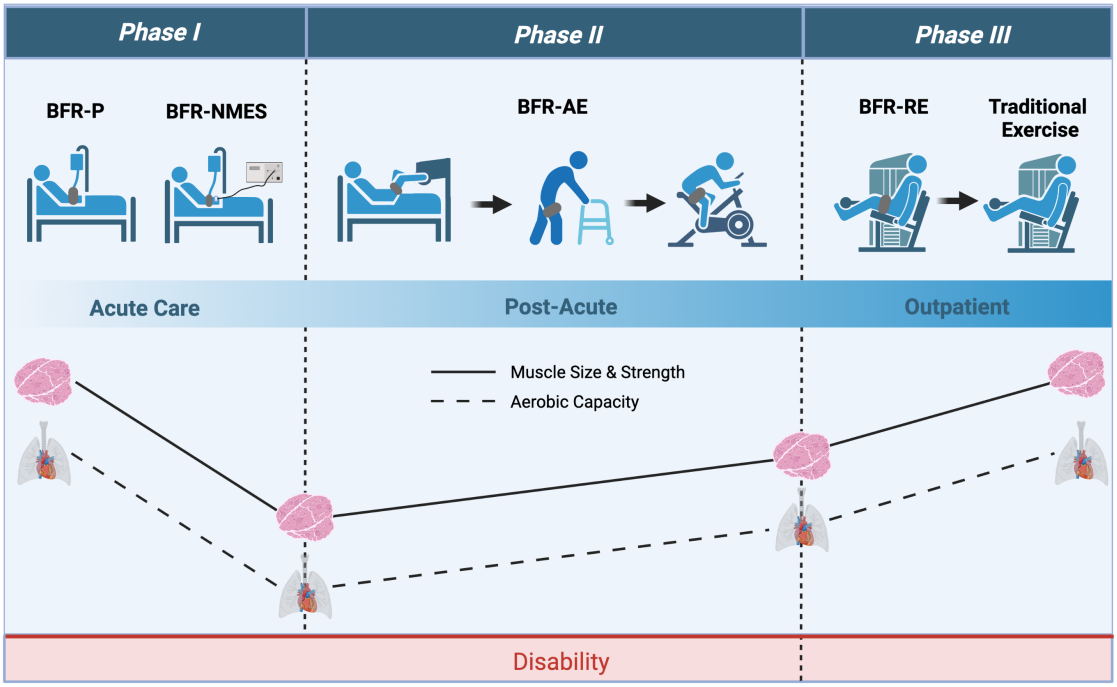

Figure 3.3 Theoretical framework with which BFR could be applied to COVID-19 survivors throughout acute care and outpatient rehabilitation. *Phase I* consists of using passive applications of BFR (BFR-P and BFR-NMES) to prevent losses in muscle mass and strength during acute care. *Phase II* consists of using various modes of BFR-AE to improve muscle mass, muscle strength, and aerobic capacity during post-acute care. Lastly, *Phase III* consists of using BFR-RE to provide robust increases in muscle mass and strength while transitioning COVID-19 survivors to traditional high-intensity exercise without BFR.

3.7 Considerations and Limitations of Hypotheses

There are two important considerations and limitations to our hypotheses. First is the safety of implementing BFR.[214] Several authors [215-217] have commented on the potential for adverse cardiovascular responses to exercise with BFR in populations with cardiovascular disease (i.e., hypertension, heart failure, peripheral artery disease) who possess altered exercise pressor reflex function. The pathophysiology of COVID-19 resembles that of cardiovascular and inflammatory disease and those individuals developing severe COVID-19 illness are commonly older in age and display multiple pre-existing comorbidities.

Furthermore, some evidence indicates heightened sympathetic nerve activity [218] and an augmented exercise pressor responses [219] in COVID-19 survivors. Therefore, concerns surrounding acute cardiovascular responses to exercise with BFR should be extended to those individuals infected with or recovering from COVID-19. Perhaps the largest concern in this population is that of thrombotic complications given the high prevalence of hemostatic abnormalities. Nascimento and colleagues [214] suggested that the decision to implement exercise with BFR in COVID-19 patients should consider each patient's unique profile, including their disease severity, inflammatory markers, coagulation indices, and pharmacological interventions. Importantly, several aspects related to BFR prescription such as cuff pressure,[220-223] cuff width,[224] continuous versus intermittent pressure application,[221] and amount of exercising musculature [45] impact the acute cardiovascular and perceptual responses to exercise with BFR. Thus, appropriate exercise prescription is critical for minimizing potential risks. Additional evidence supporting BFR prescriptions for populations at higher risk of adverse events is warranted.

A second consideration is the capacity of medical professionals to implement BFR safely and effectively in clinical settings. Adequate understanding of BFR methodology and awareness of potential side effects and adverse outcomes is critical in making an informed decision about whether BFR is appropriate. Furthermore, access to proper technologies (i.e., cuffs and equipment for determining appropriate pressures) and knowledge of BFR exercise prescription plays a critical role in minimizing patient risk. Despite its growing use in rehabilitation, implementation of BFR does present some challenges for practitioners.[83] Given the therapeutic potential of BFR to improve patient outcomes, efforts must be made to ensure that clinicians possess knowledge of current best practices, have access to appropriate technologies for implementing BFR, and are aware of potential contraindications and risks associated with engaging in exercise with BFR.

3.8 Summary

We hypothesize that the use of BFR may be an effective strategy to rehabilitate physical function in COVID-19 survivors. The application of BFR-P and BFR-NMES during acute infection have the potential to mitigate muscle and strength loss occurring with severe COVID-19 illness and immobilization. During post-acute and outpatient rehabilitation, the combination of BFR with voluntary exercise (BFR-AE and BFR-RE) presents an alternative to traditional higher intensity exercise to restore muscle mass, muscle strength, and aerobic capacity. Additionally, the various applications of BFR may offer a systemic therapy to combat widespread organ dysfunction. Our progressive model of BFR application throughout the phases of acute infection and rehabilitation offers a viable approach to address the long-term consequences of COVID-19. We hope that our work encourages discussion and consideration among researchers and clinicians about the therapeutic potential of BFR to improve outcomes not only in COVID-19 survivors but in similar pathologies and cases of acute critical illness.

4 Development of a Prediction Equation to Estimate Lower-Limb Arterial Occlusion Pressure with a Thigh Sphygmomanometer

4.1 Abstract

During exercise with blood flow restriction (BFR), cuff pressures should be based on arterial occlusion pressure (AOP). Prediction equations using anthropometric, hemodynamic, and sociodemographic variables have been used to estimate AOP. Most of these equations have been designed for use with expensive cuff systems and implementation is limited to practitioners. The purpose of this study was to develop and validate an equation to predict AOP in the lower-limb when applying an 18cm wide thigh sphygmomanometer. Healthy adults (n=143) underwent measures of thigh circumference (TC), skinfold thickness (ST), estimated mid-thigh muscle cross-sectional area (CSA), and brachial and femoral systolic (SBP) and diastolic (DBP) blood pressure. Lower-limb AOP was assessed in a seated position (via Doppler ultrasound) using an 18cm wide thigh sphygmomanometer. For Part 1, theoretical models of hierarchical linear regression were used to determine predictors of AOP. For Part 2, the best set of predictors were used to construct a prediction equation to estimate AOP. Performance of the equation was evaluated in the development sample and internally validated using bootstrap resampling. Theoretical models containing measures of either TC or thigh composition (muscle CSA and ST) paired with brachial blood pressures explained the most variability in AOP (54%) with brachial SBP accounting for the majority of explained variability. A prediction equation including TC, brachial SBP and DBP, age, and sex showed good predictability (R^2=0.54, RMSE=7.14mmHg) and excellent calibration in the development data. The mean difference between observed and predicted values was 0.0mmHg, 95% CI [-1.54, 1.54] and Bland-Altman Limits of Agreement were ±18.2mmHg, 95% CI [±15.6, ±20.9]. Internal validation revealed small differences between apparent and optimism adjusted performance measures, suggesting

good generalizability. In conclusion, our prediction equation provides a valid way to estimate lower-limb AOP and offers a low-cost approach to implementing exercise with BFR.

4.2 Introduction

Exercise with blood flow restriction (BFR) is an effective training option to improve muscular size and strength [38,77,225] and aerobic capacity.[43,226] It is recommended that cuff pressures during BFR be selected based on arterial occlusion pressure (AOP) [65] which is the pressure required to occlude arterial blood flow to a limb. Currently, there are several methods for determining AOP which include the use of handheld Doppler,[227] pulse oximetry,[228,229] and specialized cuffs with built in pressure sensors.[230] However, clinicians, coaches, and athletes may not have access to this equipment. To estimate AOP without the need for direct measurement, several authors [227,231-234] have utilized anthropometric, hemodynamic, and sociodemographic variables to develop prediction equations.

These prediction equations provide a practical way to implement exercise with BFR, however, there are some important considerations. First, reporting of performance measures (i.e., calibration, agreement between predicted and measured values) are limited thus making it difficult to determine the ability of equations to provide accurate estimates of AOP. Second, equations have not been validated which is considered an essential step to developing useful prediction equations.[235,236] Third, equations have been developed to predict AOP in a supine position. Several reports [233,237,238] indicate that body position influences AOP and therefore estimates derived from these equations may not translate to exercising body positions. Lastly, most existing prediction equations were developed for use with expensive research grade pneumatic cuff systems (i.e., Hokanson System, KAASTU Master Cuff inflator). Thus, implementation of these prediction equations is not without limitations for practitioners.

In a ground breaking study, Cirilo-Sousa and colleagues [231] developed a prediction equation for use with a 18 cm wide thigh sphygmomanometer which represents a relatively inexpensive cuff (~$30 USD) that can be used for performing BFR in the lower-body.[239,240] These authors included the predictor variables of thigh circumference, brachial systolic blood pressure, age, and sex which were identified as significant predictors that collectively explained 40% of the variability in AOP. Consistent with other reports,[227,232,233,241] thigh circumference was identified as the main predictor explaining the largest amount of variability (26%). To date, this is the only study investigating predictors of AOP with an 18 cm wide cuff. In related work, Loenneke and colleagues [227] reported that thigh composition (i.e., muscle and fat cross-sectional area) and ankle blood pressure were also predictors of lower-limb AOP when using 5 and 13.5 cm wide cuffs. Furthermore, ankle blood pressure appeared to be a better predictor than brachial blood pressure, indicating that localized blood pressures closer to the site of cuff application may have a greater influence on AOP. Evidence [241] indicates that predictors of AOP depend on cuff width. It is unknown whether thigh composition and lower-limb blood pressures also predict AOP with wider cuffs. Determining the extent to which these variables predict AOP with an 18 cm wide cuff could help to further identify the best variables for prediction equation development.

The purpose of this study was to develop and validate an equation to predict AOP in the lower-limb when applying an 18 cm wide thigh sphygmomanometer in the seated position. For Part 1 of this study, we identified which hemodynamic (brachial or femoral blood pressures), anthropometric (thigh circumference or thigh composition), and sociodemographic (age and sex) variables predict AOP. Based on previous reports,[227,231] we hypothesized that thigh circumference and femoral systolic blood pressure would be the strongest predictors of AOP. For Part 2 of this study, we selected the best set of predictors from Part 1, developed a prediction equation, and internally validated the model to assess its generalizability.

4.3 Methods

4.3.1 Participants

Healthy adults between the ages of 18 and 39 years were recruited to participate in this study. Sex differences are an important biological variable to consider for research designs and physiological investigations.[242] Efforts were made to recruit equal numbers of males and females. It is important to point out that data collection occurred during the COVID-19 pandemic and in-between case surges. To include a larger number of females, menstrual cycle was not controlled for. Participants were excluded from the study if they had a BMI > 35, SBP > 140mmHg, DBP > 90mmHg, used nicotine products, had any known cardiometabolic, dermatological, or neurological disorders, a recent lower-body injury or surgery, or any implanted devices. Participants were informed of the purpose of the study, the risks involved, and gave informed written consent. This study was approved by the Institutional Review Board at Michigan Technological University.

4.3.2 Study Design and Overview

Participants visited the laboratory for one testing session. They were asked to avoid caffeine consumption and strenuous exercise for at least 8 hours prior to the visit and to refrain from eating at least 2 hours prior. Upon arrival, height and body mass were measured. Next, anthropometric measures including thigh circumference (TC) and skinfold thickness (ST) of the anterior thigh were assessed and used to estimate mid-thigh muscle cross-sectional area (CSA). Following 10 min of seated rest, brachial and femoral systolic blood pressure (SBP) and diastolic blood pressure (DBP) were be measured. Finally, lower-limb AOP was determined in the seated position using an 18 cm wide thigh sphygmomanometer. For Part 1, hierarchical linear regression was used to determine variables that constitute predictors of AOP in the lower limb. Theoretical models were constructed using the predictor variables of TC, brachial SBP and DBP, femoral SBP and DBP, muscle CSA, ST, age, and sex. The best model determined in Part 1 was selected and used in Part 2 to develop and

internally validate a prediction equation to estimate AOP. An overview of the study design is displayed in Figure 4.1.

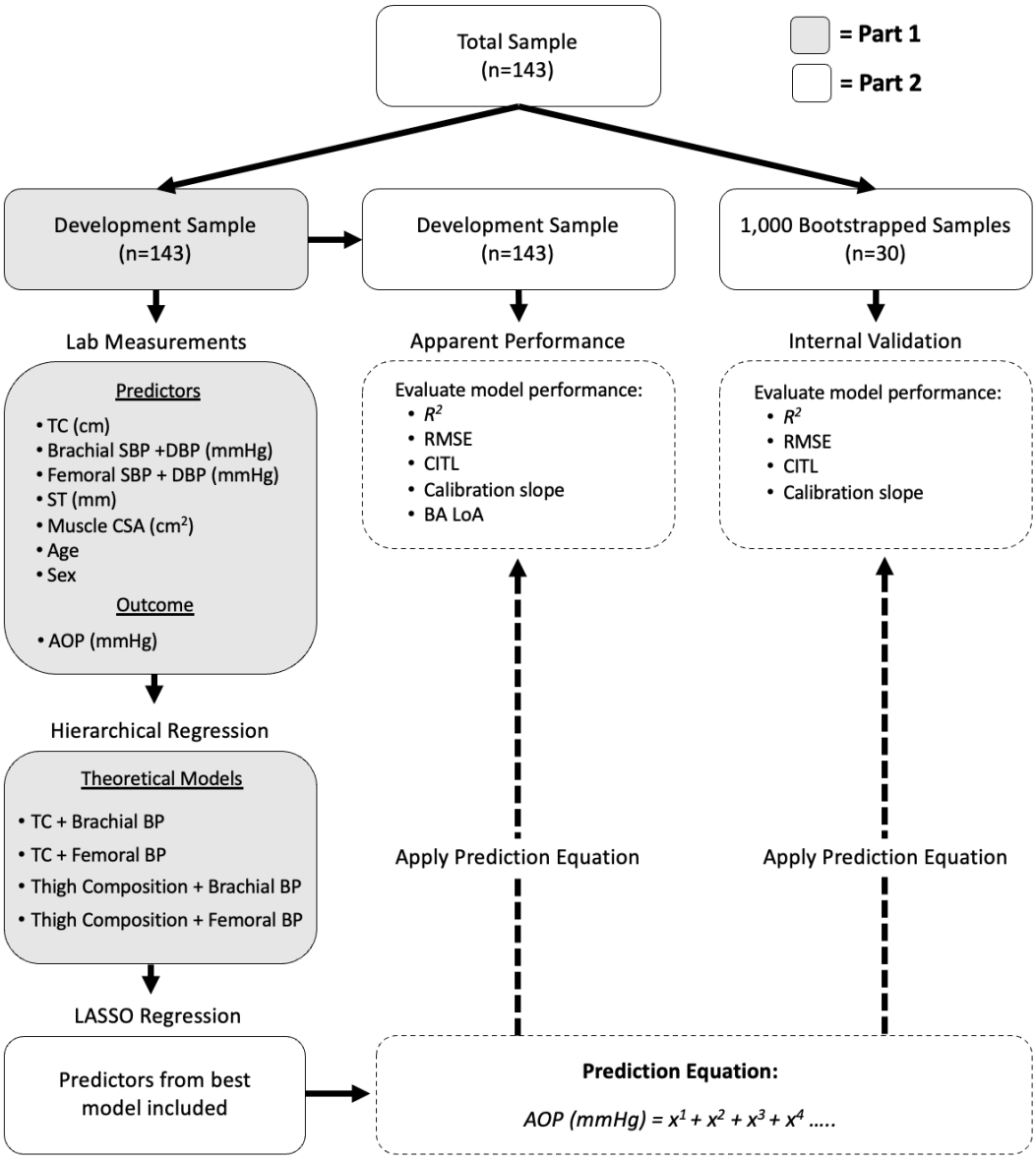

Figure 4.1 Overview of study design.

4.3.3 Anthropometric Measures

All anthropometric measures were obtained on the right leg of each participant. Thigh circumference was measured at 33% of the distance from the inguinal crease to the proximal patella using a standard tape measure. This measurement location was selected to represent the site at which the cuff was placed during AOP measurement. Measures were taken in duplicate, and the average value was used for analysis. Skinfold thickness of the anterior thigh was assessed using a spring-loaded caliper (Lange Skinfold Caliper, Beta Technologies, Santa Cruz, CA, USA) according to Internal Society for the Advancement of Kinanthropometry guidelines.[243] Lastly, muscle CSA was estimated at the mid-thigh using the procedures and formula developed by Housh and colleagues.[244] Based on preliminary data, reliability of circumference (ICC = 0.97) and skinfold measures (ICC = 0.99) were excellent, which is consistent with previously reported data.[245,246]

4.3.4 Blood Pressure

After resting quietly in a seated position for 10 min, brachial and femoral SBP and DBP were obtained in the right arm and leg using an appropriately sized automatic blood pressure cuff (Welch-Allyn, Model 4200B-E1, Skaneateles Falls, NY, USA). All blood pressure measures were obtained with the participant in a seated position. Brachial blood pressures were assessed first, followed by femoral blood pressures. Femoral blood pressures were measured by placing a thigh blood pressure cuff (Welch-Allyn, Thigh 13, Skaneateles Falls, NY, USA) at the most proximal portion of the thigh. A minimum of two measurements were taken at each site with a 1 min rest between measures. If SBP or DBP varied by more than 5 mmHg, measurements were repeated until values were within 5 mmHg of each other. The two sequential values within 5 mmHg were averaged and used for analysis.

4.3.5 Arterial Occlusion Pressure

An 18 cm wide thigh sphygmomanometer (Thigh Size Aneroid Sphygmomanometer, Elite Medical Instruments, Fullerton, CA, USA) was placed on the proximal portion of the thigh with the center of the bladder positioned at 33% of the distance from the inguinal crease to the proximal patella. The participant was placed in a seated position with the knee flexed to 90 degrees and pulse was detected at the posterior tibial artery using Doppler ultrasound (GE Logiq e BT12, GE Health Care, Chicago, IL, USA). To determine AOP, the sphygmomanometer was first inflated to 75 mmHg and the pressure was slowly increased until blood velocity in the posterior tibial artery reached zero based on the absence of the Doppler spectrum. The minimum pressure required to eliminate Doppler spectrum was recorded as the AOP. A minimum of two measures were obtained with a 2 min break between measures. If values varied by more than 5 mmHg, measurements were repeated until values were within 5 mmHg. The two consecutive values within 5 mmHg were averaged and used for analysis. Based on preliminary data, measurement of AOP using this method was reliable (ICC = 0.95) and is consistent with previous reliability data reported from our laboratory.[239,240,247]

4.3.6 Statistical Analysis

4.3.6.1 Part 1: Determining Predictors of AOP

Data from all participants was used to construct models of hierarchical linear regression to determine variables that constitute predictors of AOP in the lower limb. Given a power of 0.8 (ß = 0.20) and a two-tailed significance level (α) of 0.05, we determined that 90 participants would provide an adequate sample to detect a medium effect size (f^2) of 0.15 with six predictor variables. Theoretical models were constructed using various combinations of the predictor variables TC, brachial SBP and DBP, femoral SBP and DBP, muscle CSA, ST, age, and sex.

Pearson's correlation (r) was used to test the bivariate relationship between AOP and each of the continuous predictor variables. Four theoretical models were constructed. Separate models were constructed and analyzed to avoid collinearity between variables capturing similar physiological constructs. Model 1 was based on measures of TC and brachial blood pressures and included the predictors TC, brachial SBP, brachial DBP, age, and sex. Model 2 was based on measures of TC and femoral blood pressures, including the predictors TC, femoral SBP, femoral DBP, age, and sex. Model 3 was based on measures of thigh composition and brachial blood pressures, including the predictors muscle CSA, ST, brachial SBP, brachial DBP, age, and sex. Model 4 was based on measures of thigh composition and femoral blood pressures, including the predictors muscle CSA, ST, femoral SBP, femoral DBP, age, and sex. Predictor variables were entered into each respective hierarchical regression model in blocks consisting of one variable at a time. Variables were added in order from strongest to weakest bivariate correlation with AOP. Pearson's correlations (r), coefficient of determination (R^2), standard error of the estimate (SEE), mean squared error (MSE), and the change in *F* value were determined for each block as variables were added into the model. Assumptions of linear models were checked with a visual inspection of normality and residual plots. Multi-collinearity between predictor variables was assessed using variance inflation factor (VIF) and Pearson's correlations. Multi-collinearity was defined as a VIF ≥ 5 and/or Pearson's correlations of 0.80 or greater.[248]

4.3.6.2 Part 2: Developing and Validating Prediction Equation

Data from all participants were used to develop an equation to predict AOP. The minimum sample size for developing the prediction equation was determined using criteria described by Riley and colleagues [249] for prediction models with continuous outcome variables. Based on preliminary data (n = 88) utilizing a model with five predictor variables, an adjusted R^2 of 0.40, and a mean AOP of 154 mmHg and standard deviation of 13 mmHg, a sample of 150

participants was determined to minimize model optimism and provide precise estimates of model parameters.

We followed the transparent reporting of a multivariable model for individual prognosis or diagnosis (TRIPOD) guidance for development and reporting of multivariable prediction models.[236] The prediction equation was developed using candidate predictors from the best model resulting from Part 1 of the study. The best model was determined based on two criteria: 1) Bayesian Information Criterion (BIC) [250] and 2) the practicality of assessing the including predictor variables in the field (i.e., rehabilitation and sport training settings). Least absolute shrinkage and selection operator (LASSO) regression was carried out including each of the significant predictor variables identified from the best model selected from Part 1. LASSO is a penalization method for regression models that performs coefficient shrinkage and variable selection.[251] This approach was selected for its ability to reduce model overfitting. The optimal penalization parameter (λ) was selected using automated 30-fold cross-validation to determine the λ that minimizes mean-squared error in the model. Variables with coefficients that were reduced to zero after regularization were removed from the model. Performance of the resulting model was evaluated in the development dataset by assessing model R^2 (the proportion of variance in AOP explained by the model), model root-mean squared error (RMSE, the average difference between the predicted and observed values), calibration slope (slope from a model regressing observed on predicted AOP values; ideal value is 1), and calibration-in-the large (CITL, the intercept term from a model regressing observed on predicted AOP values; ideal value is 0). The degree of agreement between observed and predicted AOP values was assessed using techniques described by Bland and Altman.[252] The 95% limits of agreement were determined by calculating two standard deviations of the mean difference between observed and predicted values and 95% confidence intervals (CI) were constructed around the limits of agreement.[253] To statistically test the equivalence of mean observed and predicted AOP values we utilized a two one-sided paired t-test (90%

confidence interval, or 5% for each lower and upper limit) described by Lakens.[254] The equivalence region was selected as ± 10% of the mean AOP determined via Doppler ultrasound. This equivalence region was selected arbitrarily as a 10% error in AOP likely has little practical importance. The test was carried out using the TOST package available on R from the CRAN repository.[255]

Finally, internal validation was completed using bootstrap resampling methods in which 1,000 samples (n = 30) were randomly selected from the development dataset with replacement. The prediction equation developed from the full dataset was applied to each of the random samples and used to predict AOP. The variable selection process was not included in internal validation as this was performed via LASSO regression. The performance of the model across validation samples was assessed by evaluating model R^2, RMSE, calibration slope, and CITL. All data analysis was completed using R (R: A Language and Environment for Statistical Computing, 2020, R Foundation for Statistical Computing, Vienna, Austria).

4.4 Results

4.4.1 Part 1: Determining Predictors of AOP

One hundred and forty-three adults participated in this investigation. Demographic, anthropometric, and hemodynamic characteristics are presented in Table 4.1. Each of the continuous predictor variables except for ST and age were positively correlated with AOP (all $p < 0.001$). Pearson's correlations for each predictor variable with AOP are reported in Table 4.2. Model 1, which was based on TC and brachial blood pressures, consisted of five blocks whereby the predictor variables of brachial SBP, thigh circumference, brachial DBP, age, and sex were added in blocks 1-5, respectfully (Figure 4.2; A). Results of the hierarchical regression analysis for Model 1 are presented in Table 4.3. Block 4

explained the most variability in AOP (54%), with brachial SBP (ß = 0.449, Part = 0.671), TC (ß = 0.389, Part = 1.080), and age (ß = 0.134, Part = 0.416) constituting significant predictors. Standardized β coefficients indicated that brachial SBP explained the most variance in each block. Model 2, which was based on TC and femoral blood pressures, consisted of five blocks whereby the predictor variables of femoral SBP, thigh circumference, femoral DBP, age, and sex were added in blocks 1-5, respectfully (Figure 4.2; B). Results of the regression analysis for Model 2 are reported in Table 4.4. Block 2 explained the most variability in AOP (51%), with femoral SBP (ß = 0.465, Part = 0.658) and TC (ß = 0.416, Part = 1.158) constituting significant predictors. Model 3, based on thigh composition and brachial blood pressures, consisted of six blocks and variables were added to blocks 1-6 in the order of brachial SBP, brachial DBP, muscle CSA, age, ST, and sex (Figure 4.3; C). Results for Model 3 are reported in Table 4.5. Block 5 explained the most variability in AOP (54%), with brachial SBP (ß = 0.390, Part = 0.582), brachial DBP (ß = 0.137, Part = 0.273), muscle CSA (ß = 0.584, Part = 0.235), age (ß = 0.132, Part = 0.407), and ST (ß = 0.450, Part = 0.448) constituting significant predictors. Lastly, model 4, based on thigh composition and femoral blood pressures, consisted of six blocks and variables were added to blocks 1-6 in the order of brachial SBP, brachial DBP, muscle CSA, age, ST, and sex (Figure 4.2; D). The results for Model 4 are presented in Table 4.6. Block 5 explained the most variability in AOP (51%), with femoral SBP (ß = 0.359, Part = 0.508), muscle CSA (ß = 0.658, Part = 0.265), and ST (ß = 0.465, Part = 0.463) constituting significant predictors.

Table 4.1 Participant characteristics (Male: n=84, Female: n=59).

Variable	Mean ± SD	Minimum	Maximum
Age (years)	23 ± 4	18	39
Height (m)	1.7 ± 0.1	1.5	2.0
Body mass (kg)	75.0 ± 12.6	48.0	114.0
BMI (kg/m^2)	24.7 ± 3.2	17.9	34.4
TC (cm)	60.7 ± 5.0	50.0	78.8
Muscle CSA (cm^2)	148.4 ± 34.3	59.8	228.5
ST (mm)	24.8 ± 13.8	4.0	64.5
Brachial SBP (mmHg)	121 ± 9	97	139
Brachial DBP (mmHg)	74 ± 7	57	89
Femoral SBP (mmHg)	140 ± 10	112	165
Femoral DBP (mmHg)	83 ± 7	60	103
AOP (mmHg)	151 ± 14	111	190

AOP= Arterial Occlusion Pressure, DBP = Diastolic Blood pressure, Muscle CSA = Muscle Cross-Sectional Area, SBP = Systolic Blood Pressure, ST = Skinfold Thickness, TC= Thigh Circumference

Table 4.2 Pearson's correlation coefficients between predictor variables and AOP.

Predictor Variable	r	*p*-value
Brachial SBP	0.62	< 0.001
Femoral SBP	0.59	< 0.001
TC	0.56	< 0.001
Brachial DBP	0.44	< 0.001
Femoral DBP	0.38	< 0.001
Muscle CSA	0.36	< 0.001
Age	0.15	0.08
ST	0.01	0.89

DBP = Diastolic Blood pressure, Muscle CSA = Muscle Cross-Sectional Area, SBP = Systolic Blood Pressure, ST = Skinfold Thickness, TC= Thigh Circumference

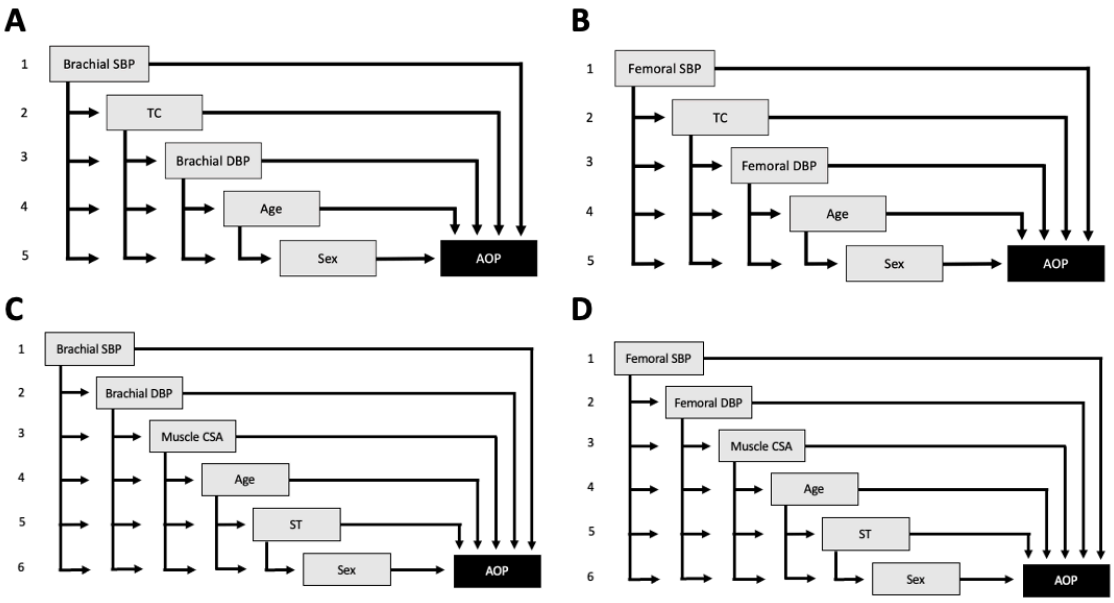

Figure 4.2 Theoretical hierarchical linear regression models based on; A. Thigh circumference and brachial blood pressures, B. Thigh circumference and femoral blood pressures, C. Thigh composition and brachial blood pressures, and D. Thigh composition and femoral blood pressures. SBP = Systolic blood pressure, DBP = Diastolic blood pressure, TC = Thigh circumference, Muscle CSA = Muscle Cross-sectional Area, ST = Skinfold thickness, AOP = Arterial Occlusion Pressure

Table 4.3 Results of hierarchical regression model based on TC and brachial blood pressures.

Model 1: Block 1					
	Stand. ß	*p* value	Part		
Brachial SBP	0.615	< 0.001	0.919		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.615	0.379	117.28	10.91	< 0.001
Model 1: Block 2					
	Stand. ß	*p* value	Part		
Brachial SBP	0.481	< 0.001	0.718		
TC	0.398	< 0.001	1.108		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.721	0.519	90.77	9.63	< 0.001
Model 1: Block 3					
	Stand. ß	*p* value	Part		
Brachial SBP	0.434	< 0.001	0.648		
TC	0.393	< 0.001	1.093		
Brachial DBP	0.083	0.257	0.165		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.724	0.524	89.93	9.62	0.257
Model 1: Block 4					
	Stand. ß	*p* value	Part		
Brachial SBP	0.449	< 0.001	0.671		
TC	0.389	< 0.001	1.080		
Brachial DBP	0.062	0.395	0.122		
Age	0.134	0.022	0.416		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.736	0.541	86.58	9.47	0.022
Model 1: Block 5					
	Stand. ß	*p* value	Part		
Brachial SBP	0.409	< 0.001	0.611		
TC	0.388	< 0.001	1.080		
Brachial DBP	0.097	0.231	0.193		

Age	0.126	0.034	0.391		
Sex	0.066	0.331	1.843		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.738	0.545	88.81	9.47	0.331

Table 4.4 Results of hierarchical regression model based on TC and femoral blood pressures

Model 2: Block 1					
	Stand. ß	*p* value	Part		
Femoral SBP	0.594	< 0.001	0.841		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.594	0.353	122.12	11.13	< 0.001
Model 2: Block 2					
	Stand. ß	*p* value	Part		
Femoral SBP	0.465	< 0.001	0.658		
TC	0.416	< 0.001	1.158		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.714	0.510	92.56	9.72	< 0.001
Model 2: Block 3					
	Stand. ß	*p* value	Part		
Femoral SBP	0.452	< 0.001	0.640		
TC	0.418	< 0.001	1.162		
Femoral DBP	0.019	0.817	0.036		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.714	0.510	92.53	9.76	0.817
Model 2: Block 4					
	Stand. ß	*p* value	Part		
Femoral SBP	0.449	< 0.001	0.636		
TC	0.418	< 0.001	1.164		
Femoral DBP	0.014	0.869	0.026		
Age	0.025	0.687	0.078		
	R	R^2	MSE	SEE	Sig. *F* Change

	0.714	0.510	92.42	9.79	0.687
Model 2: Block 5					
	Stand. ß	*p* value	Part		
Femoral SBP	0.407	< 0.001	0.576		
TC	0.419	< 0.001	1.167		
Femoral DBP	0.050	0.554	0.096		
Age	0.019	0.763	0.058		
Sex	0.100	0.117	2.76		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.721	0.519	90.78	9.73	0.117

Table 4.5 Results of hierarchical regression model based on thigh composition and brachial blood pressures.

Model 3: Block 1					
	Stand. ß	*p* value	Part		
Brachial SBP	0.615	< 0.001	0.919		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.615	0.379	117.28	10.91	< 0.001
Model 3: Block 2					
	Stand. ß	*p* value	Part		
Brachial SBP	0.547	< 0.001	0.816		
Brachial DBP	0.117	0.155	0.233		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.623	0.388	115.59	10.87	0.155
Model 3: Block 3					
	Stand. ß	*p* value	Part		
Brachial SBP	0.361	< 0.001	0.539		
Brachial DBP	0.269	< 0.01	0.536		
Muscle CSA	0.279	< 0.001	0.112		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.664	0.441	105.46	10.42	< 0.001

Model 3: Block 4					
	Stand. ß	*p* value	Part		
Brachial SBP	0.383	< 0.001	0.572		
Brachial DBP	0.242	< 0.01	0.481		
Muscle CSA	0.267	< 0.001	0.107		
Age	0.128	0.046	0.396		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.676	0.457	102.44	10.30	0.046
Model 3: Block 5					
	Stand. ß	*p* value	Part		
Brachial SBP	0.390	< 0.001	0.582		
Brachial DBP	0.137	0.109	0.273		
Muscle CSA	0.584	< 0.001	0.235		
Age	0.132	0.027	0.407		
ST	0.450	< 0.001	0.448		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.733	0.537	87.45	9.55	< 0.001
Model 3: Block 6					
	Stand. ß	*p* value	Part		
Brachial SBP	0.399	< 0.001	0.596		
Brachial DBP	0.133	0.125	0.264		
Muscle CSA	0.612	< 0.001	0.246		
Age	0.136	0.023	0.421		
ST	0.431	< 0.001	0.429		
Sex	-0.060	0.536	-1.678		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.734	0.538	87.20	9.58	0.536

Table 4.6 Results of hierarchical regression model based on thigh composition and femoral blood pressures.

Model 4: Block 1			
	Stand. ß	*p* value	Part
Femoral SBP	0.594	< 0.001	0.841

	R	R^2	MSE	SEE	Sig. F Change
	0.594	0.353	122.12	11.13	< 0.001
Model 4: Block 2					
	Stand. ß	p value	Part		
Femoral SBP	0.617	< 0.001	0.874		
Femoral DBP	-0.034	0.714	-0.064		
	R	R^2	MSE	SEE	Sig. F Change
	0.595	0.354	122.01	11.16	0.714
Model 4: Block 3					
	Stand. ß	p value	Part		
Femoral SBP	0.431	< 0.001	0.611		
Femoral DBP	0.148	0.134	0.281		
Muscle CSA	0.299	< 0.001	0.120		
	R	R^2	MSE	SEE	Sig. F Change
	0.649	0.421	109.27	10.60	< 0.001
Model 4: Block 4					
	Stand. ß	p value	Part		
Femoral SBP	0.431	< 0.001	0.610		
Femoral DBP	0.147	0.144	0.279		
Muscle CSA	0.299	< 0.001	0.120		
Age	0.006	0.934	0.017		
	R	R^2	MSE	SEE	Sig. F Change
	0.649	0.421	112.70	10.79	0.934
Model 4: Block 5					
	Stand. ß	p value	Part		
Femoral SBP	0.359	< 0.001	0.508		
Femoral DBP	0.131	0.159	0.248		
Muscle CSA	0.658	< 0.001	0.265		
Age	0.020	0.750	0.062		
ST	0.465	< 0.001	0.463		
	R	R^2	MSE	SEE	Sig. F Change
	0.714	0.510	92.53	9.83	< 0.001
Model 4: Block 6					

	Stand. ß	*p* value	Part		
Femoral SBP	0.358	< 0.001	0.506		
Femoral DBP	0.142	0.131	0.269		
Muscle CSA	0.703	< 0.001	0.283		
Age	0.022	0.721	0.069		
ST	0.436	< 0.001	0.434		
Sex	-0.084	0.402	-2.345		
	R	R^2	MSE	SEE	Sig. *F* Change
	0.716	0.512	92.05	9.84	0.402

4.4.2 Part 2: Developing and Validating Prediction Equation

4.4.2.1 Prediction Equation Development

The best model from Part 1 was determined to be Model 1 based on TC and brachial blood pressures which included TC, brachial SBP, and age as significant predictors of AOP. This model yielded the lowest BIC (Model 1 = 1,077, Model 2 = 1,085, Model 3 = 1,084, Model 4 = 1,092) and contained predictor variables that could be most easily assessed in rehabilitation and sports training settings. Accordingly, significant predictors from this model were selected as candidates for prediction equation development and were included in LASSO regression. The optimal value to use for λ was determined to be 0.042 (Figure 4.3). The coefficients for each predictor variable remained non-zero after regularization and thus all predictor variables were retained in the final model. The representative formula for the resulting equation was:

$$AOP\ (mmHg) = -12.179 + 1.084\ (Thigh\ Circumference) + 0.720\ (SBP) + 0.426\ (age)$$

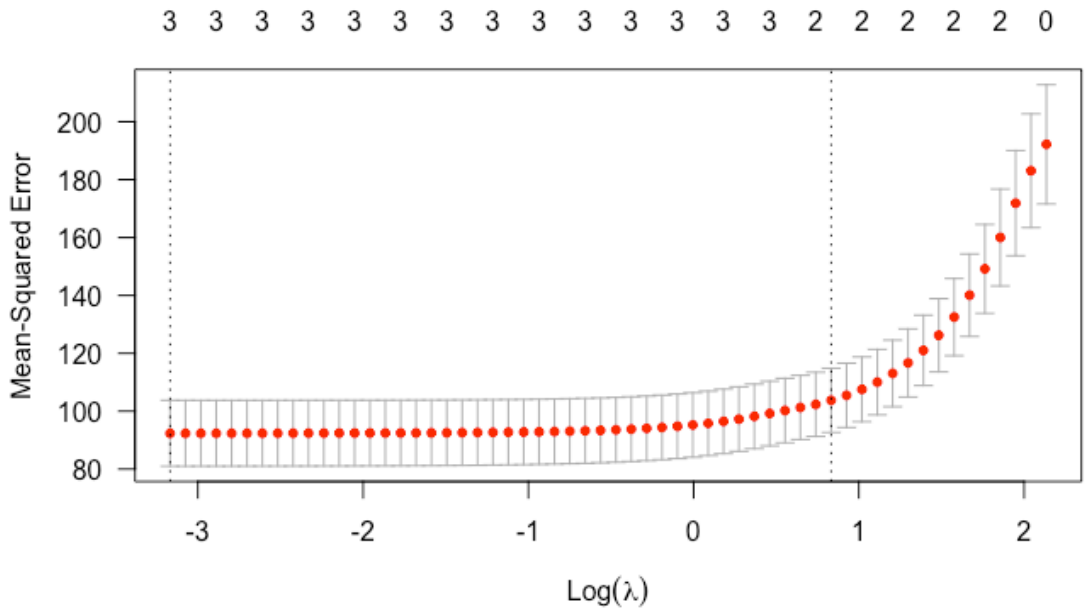

Figure 4.3 Model mean squared error (MSE) versus the log(λ) of 30-fold cross-validation. Left dotted line indicates the log(λ) with minimum cross-validation error. Right dotted line indicates the log(λ) with minimum cross-validation error plus one standard error. Numbers on the top of plot correspond to the number of non-zero regression coefficients included in the model.

4.4.2.2 Apparent Performance in Development Data

The equation explained 54% of the variability in AOP with an RMSE of 7.18 mmHg. The CITL and calibration slope were -0.88 and 1.01, respectfully (Figure 4.4). A Bland-Altman plot displaying the limits of agreement between measured and predicted AOP values is presented in Figure 4.5. The estimated mean difference between values was 0.0 mmHg, 95% CI [-1.41, 1.41]. The upper and lower 95% limits of agreement were 16.66 mmHg, 95% CI [15.07, 18.25] and -16.66 mmHg, 95% CI [-21.03, -18.25]. The model displayed proportional bias as the slope of the regression of the differences of observed and predicted values by the mean of values was different from 0 (0.36, 95% CI [0.23, 0.49], $p < 0.001$). Observed and predicted AOP values were equivalent, $t(152) = -11.132$, $p < 0.001$, given an equivalence region -8.51 to +8.51 mmHg. The 90% confidence

interval for the mean difference between observed and predicted AOP values was -1.27 and +1.27 mmHg, which was well within the selected equivalence region.

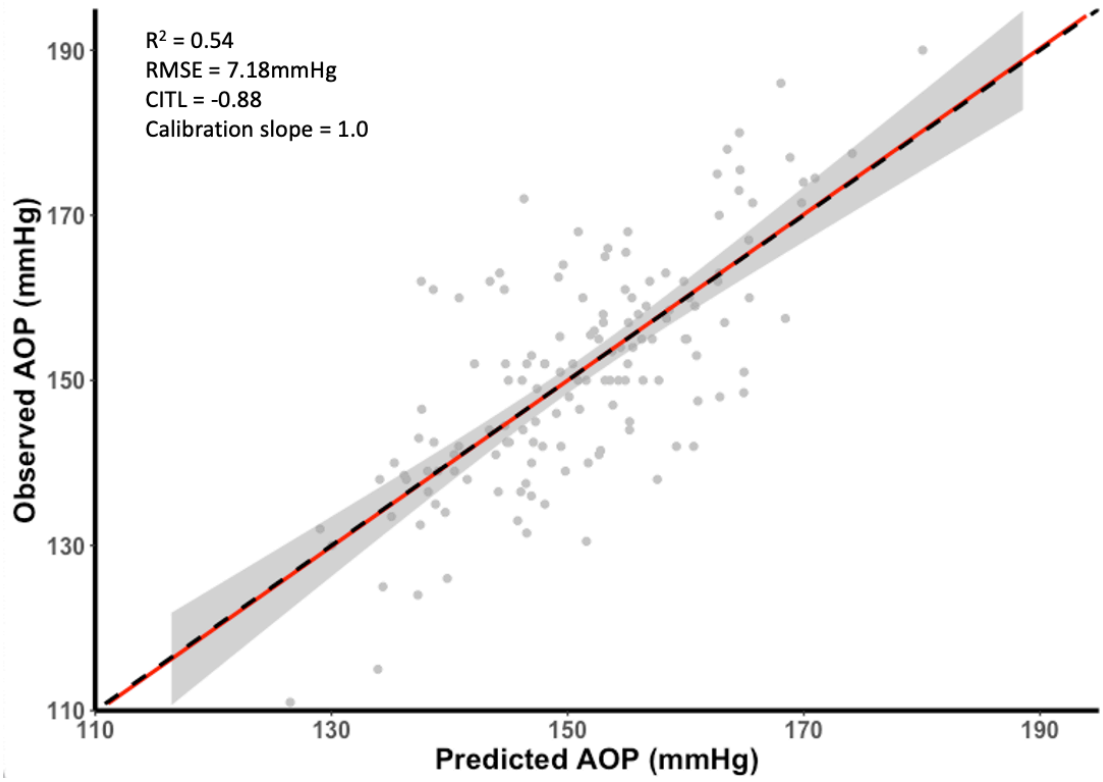

Figure 4.4 Calibration plot of observed versus predicted AOP values in the development dataset. Black dashed line represents the ideal trendline (b = 0, slope = 1). Red solid line represents the line of best fit between observed and predicted values and grey shaded region is the 95% CI.

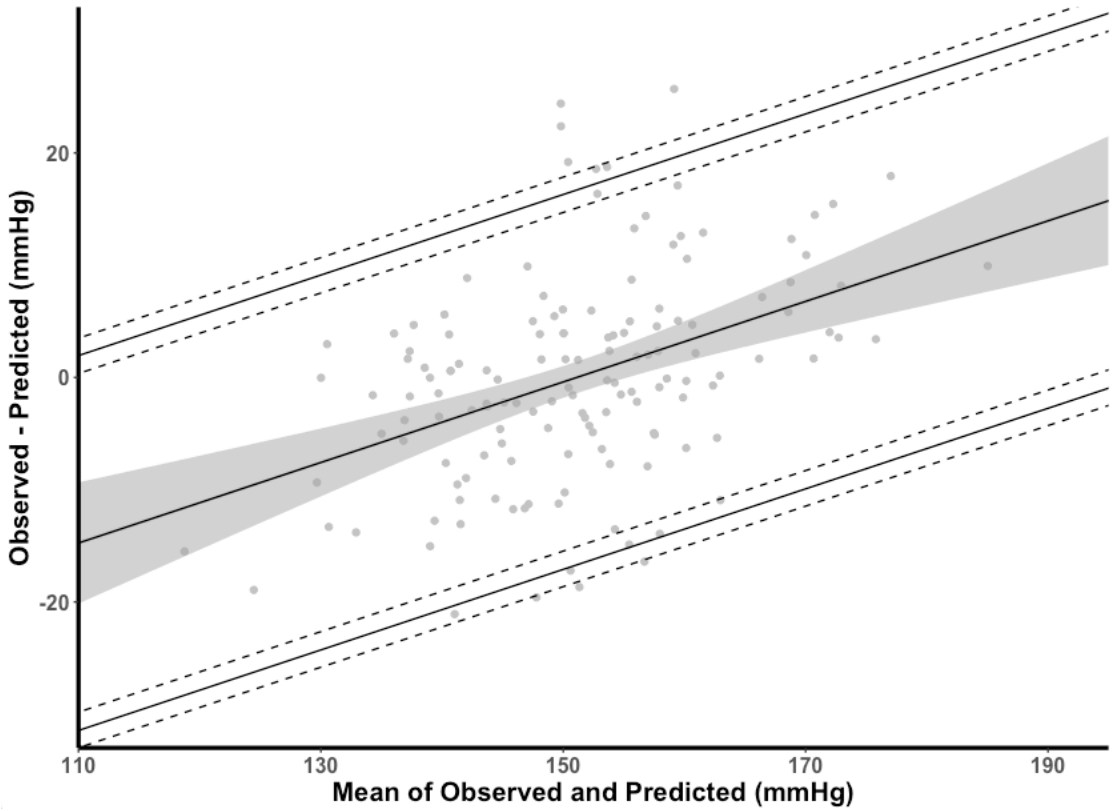

Figure 4.5 Regression based Bland-Altman plot displaying the bias and limits of agreement between observed and predicted AOP values in the development dataset. Middle black lines is a regression fit of the difference of values on the mean. Top and bottom black line represent the upper and lower limits of agreement (95% interval) across values. Shaded region represents 95% CIs around the bias. Black dashed lines represent 95% CIs around the limits of agreement.

4.4.2.3 Internal Validation

Distributions for each of the performance measures across internal validation samples are shown in Figure 4.5 (A-D). The mean model R^2 was 0.53 ± 0.13, 95% CI [0.52, 0.53], RMSE was 7.01 ± 5.86 mmHg, 95% CI [6.64, 7.37], CITL was 0.11 ± 25.81, 95% CI [-1.49, 1.72], and calibration slope was 0.99 ± 0.16, 95% CI [0.98, 1.00]. Accordingly, there were small differences between the apparent and optimism adjusted performance measures (R^2 = -0.01, RMSE = 0.17mmHg, CITL = -0.99, calibration slope = -0.02) indicating minimal overfitting.

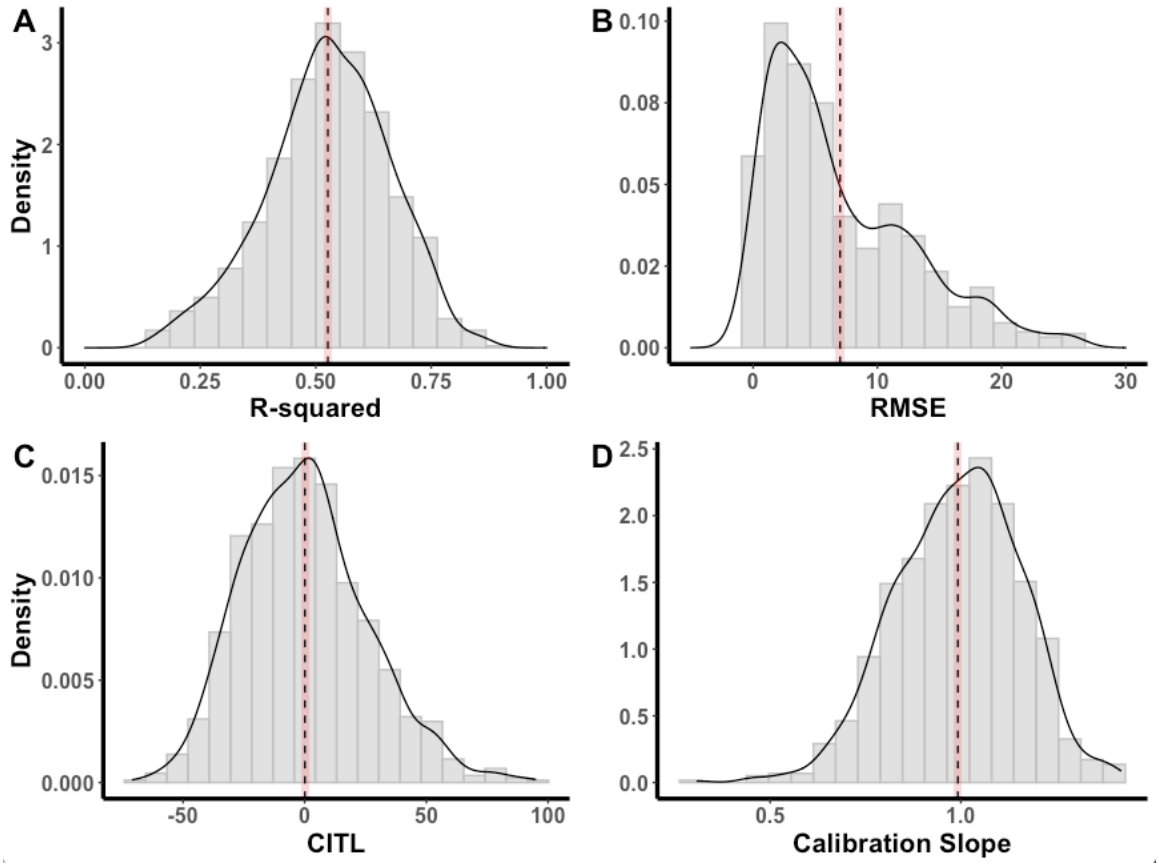

Figure 4.6 Distribution of performance measures across internal validation samples. **A.** Model R^2, **B.** Root mean squared error (RMSE), **C.** Calibration-in-the large (CITL), **D.** Calibration slope. Note that black dashed lines represent distribution means and red shaded regions represent 95% CIs.

4.5 Discussion

The purpose of this study was to develop and internally validate an equation to predict AOP in the lower-limb when using an 18 cm wide thigh sphygmomanometer in a seated position. Our main findings include: 1) models based on thigh circumference or thigh composition combined with brachial blood pressures explained the most variability in AOP, 2) brachial SBP represented the single strongest predictor of AOP, and 3) a prediction equation including TC, brachial SBP, and age provides a cost-effective approach to implementing lower-body BFR exercise without specialized equipment.

4.5.1 Part 1: Predictors of AOP

When considering different combinations of hemodynamic, anthropometric, and sociodemographic variables, our models explained 51-54% of the variability in AOP which are within the range of values (30-70%) previously reported [227,231-233] when utilizing similar sets of predictors. Our results indicated that thigh circumference predicts AOP equally as well as measures of thigh composition which is consistent with data reported by Loenneke and colleagues.[227] It is important to point out that these authors utilized narrower cuffs (5 and 13.5 cm wide) and thigh composition was assessed using computed tomography. Accordingly, our results suggest that more practical field-based measures of thigh composition including skinfold thickness and muscle CSA estimation are also associated with lower-limb AOP and are equally good predictors as thigh circumference when using a wider cuff.

Our results indicated that models including brachial blood pressures explained slightly more variability (3-4%) than models including femoral blood pressures which was unanticipated. For both femoral and brachial blood pressures, SBP but not DBP was associated with AOP. Furthermore, our data indicated that brachial SBP was the strongest predictor of AOP. Brachial SBP alone explained 38% of the variability in AOP when entered first into regression models and possessed the highest standardized β coefficients among other variables. These results differ from previous data [227,231-233] that have largely identified TC as the main predictor of lower body AOP. Note that, most studies investigating predictors of AOP have utilized narrow cuffs (5 and 13.5 cm wide) compared to the 18 cm wide cuff that was applied in our study. Earlier work from Crenshaw and colleagues [241] indicated that the influence of TC on lower-limb AOP decreases as cuff width increases. Specifically, these authors reported that Pearson correlations between thigh circumference and AOP for 4.5, 8, 12, and 18 cm wide cuffs were 0.89, 0.82, 0.77, and 0.44, respectfully. In our study we observed a similar bivariate correlation ($r = 0.56$) between thigh circumference and AOP when applying an 18 cm wide cuff. Wider cuffs transmit pressures more

efficiently into underlying soft tissues [241] which likely explains the reduced influence of TC on AOP when using wider cuffs. As the influence of TC deceases, it is possible that greater influence is shifted to hemodynamic variables in determining the amount of external pressure that is required to occlude arterial blood flow. Accordingly, this may in part explain why TC presented as a relatively weak predictor of lower-limb AOP in our data compared to previous reports [227,232,233,241] with narrower cuffs.

To the best of our knowledge only one study has investigated predictors of lower-limb AOP when utilizing an 18 cm wide cuff. Cirilo-Sousa and colleagues [231] identified TC, brachial SBP, age, and sex as significant predictors that explained 40% of the variability in AOP when using an 18 cm wide thigh sphygmomanometer. The greatest predictor was TC which alone explained 25% of the variability in AOP. In our analysis, a similar model including TC, brachial SBP and DBP, age, and sex, explained greater amounts of variability (55%) and only TC, brachial SBP, and age constituted significant predictors. Differences between studies may be due to the body position in which AOP was assessed. In our study we assessed AOP in a seated position whereas Cirilo-Sousa and colleagues assessed AOP in a supine position. Evidence [233] indicates that lower-limb AOP increases by ~20% when going from a supine to seated position, which is likely due to increases in localized blood pressure at the site of cuff application. Malhotra and colleagues [256] reported that measures of lower-limb SBP and DBP were 65 and 62 mmHg higher in a standing position when compared to a supine position. Thus, when assessing AOP in a seated position, blood pressure likely has a greater influence on the amount of external cuff pressure that is required to occlude arterial blood flow through the limb. These effects may become most apparent when using wider cuffs as the influence of TC is simultaneously reduced. Collectively, the combination of assessing AOP in a seated position along with the use of a wide cuff likely explain our findings that SBP and not TC was the greatest predictor of AOP. These results suggest that the influence of

anthropometric and hemodynamic variables on AOP may be dependent upon the body position that AOP is measured in as well as the width of cuff used.

We also examined the relationship between AOP and sociodemographic variables in which age but not sex served as a significant predictor. Although age statistically improved model performance when included, it was a relatively weak predictor that only helped to explain an additional ~2% of variability after first including anthropometric and blood pressure measures. Sex was entered last into each of our theoretical models and did not explain any additional variability. These findings differ from previous reports that have identified sex as a predictor of AOP in the lower- [231] and upper-body.[234] Our results suggest that sociodemographic variables have little influence on AOP after first accounting for limb size, limb composition, and blood pressure. It is important to note that our models, and other models [227,231-233] including similar anthropometric, hemodynamic, and sociodemographic variables, only account for 30-70% of the variability in AOP, leaving a large portion of variability unexplained. It is currently unknown what additional factors influence AOP. We speculate that anatomical characteristics of the conduit arteries at the site of cuff application have a large effect. For example, an artery's position within the limb relative to external pressure (i.e., artery depth and/or relation to bones and muscles) and intrinsic properties of the artery itself (i.e., artery diameter and/or structural composition) will likely influence the pressure within a given cuff that is required to mechanically compress and occlude the artery. The potential influence of age and sex on AOP may be mediated through their relationship with these factors. However, directly assessing the influence of such variables on AOP offers little practical utility for the purposes of implementing exercise with BFR. Therefore, practical approaches to estimating AOP and setting cuff pressures that use anthropometric, hemodynamic, and sociodemographic variables may have inherent limits.

4.5.2 Part 2: Development and Validation of Prediction Equation

In the development dataset an equation including TC, brachial SBP and age showed good predictability (R^2 = 0.54, RMSE = 7.18mmHg) and was well calibrated (CITL = -0.88, slope = 1.0). We analyzed group and individual level agreement between predicted and measured AOP values using Limits of Agreement proposed by Bland and Altman.[252] This method has been widely utilized [257] and provides a robust examination of agreement between two continuous measures. At the group level, agreement between predicted and measured AOP values was excellent. The mean difference between values was 0 mmHg indicating no systematic bias of under or overprediction. On the individual level, Limits of Agreement indicated that estimates of AOP were within ± 16.7 mmHg of direct measurements. Presence of proportional bias indicated under estimation of high AOP measures and over estimation of low AOP measures. Lastly, internal validation of the model was performed using bootstrap resampling, which is a preferred approach for validation of prediction models.[258] Results demonstrated minimal model overfitting, excellent calibration, and provided evidence of good generalizability.

Our prediction equation is intended to provide estimates of AOP that can be used to select appropriate pressures to utilize during exercise with BFR. Evidence indicates that pressures between 40 and 80% of AOP are effective in promoting muscular adaptations.[65] This represents a wide range of pressures that can be utilized. However, some acute and chronic responses to exercise with BFR are pressure dependent and may require more precise selection of pressure within this range. For example, higher pressures appear to promote greater vascular adaptations [259] whereas lower pressures attenuate acute cardiovascular and perceptual [220,223,260] responses such as blood pressure, pain, and discomfort during BFR exercise. Thus, the ability of our prediction equation to provide precise selection of pressure could provide distinct advantages. Setting pressure to 40% of AOP estimates derived from the prediction equation resulted in pressures that were equivalent to 40 (SD 3%) of actual AOP

measurements with 95% of pressures falling between 35% (-1.96 SD) and 45% (+1.96 SD). Likewise, setting pressure to 80% of AOP estimates resulted in pressures equivalent to 80 (SD 5%) of actual AOP measures with 95% of pressures falling between 70% (-1.96 SD) and 90% (+1.96 SD). Accordingly, potential error in AOP estimates derived from the prediction equation may result in exercising pressures outside of the effective range when selected at the upper and lower limits of recommendations. Although potential deviations outside of the effective range are small, a conservative approach to utilizing the prediction equation would be to select pressures between 45 and 70% of the estimated AOP. This accommodates for potential error in AOP estimation and ensures that selected exercising pressures fall within 40 and 80% of true AOP measures.

We are the first group to demonstrate that our equation to predict AOP is well calibrated and provides estimates that have an acceptable level of agreement with values measured via the gold standard method using Doppler ultrasound. Furthermore, AOP estimates derived from the prediction equation are more closely related to exercising body positions and can be used to select precise cuff pressures to utilize during exercise with BFR. Importantly, our prediction equation is the first internally validated method of estimating AOP. We have demonstrated that our equation displays a small amount of optimism and performance appears to be generalizable to new data. Several reviews [261-263] evaluating published clinical prediction models have indicated poor methodology and insufficient reporting. Accordingly, there have been several initiatives to improve prediction modeling research.[235,236,264] We hope that our work serves as an example to improve the methodological quality and reporting of predictive models in sport and exercise.

4.6 Limitations

There are some noteworthy limitations in our study. First, the prediction equation is specific to an 18 cm wide thigh sphygmomanometer. This represents a commonly utilized cuff for performing exercise with BFR, however, the equation

is not generalizable to other cuff widths. Second, measurement of AOP and predictor variables were not blinded to investigators. Third, in order to include more females in this analysis, menstrual cycle was not controlled for and may influence the relationship of variables to AOP. Fourth, we did not perform external validation of our developed prediction equation. Establishing true generalizability of our model requires application in independent data. Finally, the prediction equation was developed using a sample of young healthy adults. Additional work is needed to determine how the equation will perform when applied to different populations.

4.7 Conclusion

We conclude that our prediction equation utilizing TC, brachial SBP and DBP, age, and sex provides a valid way to estimate lower-body AOP when utilizing an 18 cm wide thigh sphygmomanometer in a seated position. Importantly, this equation provides a low-cost approach to implementing exercise with BFR which will help to make this training modality more accessible to clinicians, coaches, and athletes.

5 Development and Usability Testing of a Web-Based Application for the Clinical Implementation of Blood Flow Restriction

5.1 Abstract

Exercise with blood flow restriction (BFR) is emerging as effective alternative to traditional exercise for a variety of clinical populations and is currently used in rehabilitation settings. However, a lack of standardized methods for implementing exercise with BFR present a major barrier to its use by practitioners. The primary purpose of this study was to describe the development of a web-based application designed to serve as a decision support tool for practitioners to implement exercise with BFR. A secondary purpose was to perform preliminary usability testing of the web-based application in physical therapists. A web-based application was developed to guide practitioners through the steps of medically screening potential BFR candidates, selecting appropriate equipment for performing BFR, and determining safe and effective exercising cuff pressures. Usability of the application was evaluated in five licensed physical therapists using a mixed methods approach. User-based evaluations were conducted in which participants used the web-based application to implement exercise with BFR in several hypothetical patients. Afterwards, perceived usability of the application was evaluated using the System Usability Scale (SUS) and semi-structured interviews were conducted and responses analyzed using thematic analysis. All task scenarios resulted in successful implementation of exercise with BFR and the time to completion was 2.3±1.2 min. There was a total of 11 incidents during the completion of task scenarios which consisted of minor navigation problems (4), data input problems (2), and difficulty interpreting recommendations (5). Composite SUS scores were 94±5 and ranked highly compared to industry standards. During interview responses, participants reported that the web-based application was efficient to use, improved their confidence when implementing exercise with BFR, and would make practitioners

more likely to utilize exercise with BFR in clinical practice. These results suggest that our web-based application provides an effective and efficient tool for addressing barriers faced by physical therapists to the use of exercise with BFR. Accordingly, this tool will help to increase the accessibility of this modality in clinical settings and improve the safety and effectiveness its implementation. Several areas for improving the usability of the application were identified and will be addressed in the ongoing design process.

5.2 Introduction

Exercise with blood flow restriction (BFR) offers an effective approach for increasing muscle size and strength,[38-41] aerobic capacity,[42,43] and physical function [44] in healthy adults. Emerging evidence indicates that this modality may be an effective exercise option in a broad range of clinical populations including those living with hypertension,[66] cardiovascular disease,[67-72] diabetes,[73,74] renal dysfunction,[75,76] and most notably in those with musculoskeletal conditions.[77-80] Accordingly, exercise with BFR is now endorsed by the American Physical Therapy Association [81] and used in rehabilitation.[82] Despite its growing use, implementation of exercise with BFR remains challenging for practitioners [83] for several reasons. First, most interventions have been focused on healthy individuals and applied in controlled laboratory settings. Second, methods used to implement exercise with BFR vary widely [84] and include the use of different types of equipment (i.e., pneumatic cuffs, elastic wraps), a wide range of applied cuff pressures (e.g., 100-240 mmHg), and a variety of procedures for determining cuff pressure (i.e., arbitrarily selected, based on systolic blood pressure, based on limb circumference, perceived tightness). Finally, evidence [82] suggests that BFR use in clinical settings may be lagging behind current evidence-based recommendations. Thus, the current gap between research and clinical practice poses a major obstacle to implementation of BFR in real world settings.

Recently, Rolnick and colleagues [265] identified several perceived barriers

that practitioners face when implementing exercise with BFR. These barriers include conducting systematic medical screening of potential candidates to stratify risk of adverse events, the selection of appropriate training equipment for performing BFR, and determining cuff pressures to utilize during exercise. Importantly, these barriers were identified by individuals with prior experience implementing exercise with BFR and it is unclear what additional challenges that practitioners with minimal to no training or experience may face. Identifying and overcoming barriers faced by practitioners is important to enhancing access to BFR and ensuring that safe and effective practices are utilized. Recommendations for performing BFR have been previously described.[266,267] However, to the best of our knowledge there are no standardized methods published and no comprehensive guides available for practitioners to follow. An evidence-based decision support tool that walks practitioners through the process of medically screening candidates for BFR inclusion, selecting appropriate training equipment, and setting proper restriction pressures could help to enhance evidence-based practice, safety, and accessibility of exercise with BFR in clinical settings.

With the emerging use of smart devices such as mobile phones, tablets, and laptop computers in health care, there has been increasing development and use of medical software applications.[268,269] Some evidence [270] indicates that mobile and web-based applications increase productivity, enhance access to point-of-care tools, and improve clinical decision making and patient outcomes. Several mobile and web-based applications [271-273] have been developed to assist physical therapists in clinical decision making. Furthermore, Alsobhi and colleagues [274] reported that physical therapists' attitudes regarding the use of applications in clinical practice are positive, with the majority agreeing that they can be used as an assistive technology, used to enhance education, and can facilitate patient care. Accordingly, a web-based application presents a viable way to provide rehabilitation professionals with a decision support tool to aid in the implementation of exercise with BFR.

The primary purpose of this study was to describe the development of a web-based application to aid in the implementation of exercise with BFR. A secondary purpose was to conduct preliminary usability testing of the web-based application in physical therapists with no prior experience using exercise with BFR. Usability refers to the effectiveness, efficiency, and satisfaction with which a system can be utilized to complete a task in an intended group of users.[275] Evaluating usability is an important step in the user centered design process of interactive technological systems.[276] Importantly, an iterative process of usability testing performed early and frequently can provide continuous feedback throughout the design process.[277] Accordingly, our goal was to perform a preliminary phase of usability testing to identify major issues in the initial design of our web-based application.

5.3 Methods

5.3.1 Study Overview

A web-based application was developed to aid in evidence-based implementation of exercise with BFR. We utilized a mixed methods approach to evaluate the usability of the developed web-based application in physical therapists. Participants attended one virtual meeting held on the Zoom platform (Zoom Cloud Meetings, version 5.12.9, San Jose, CA, USA). First, they were introduced to the web-based application and given a brief description of its purpose. Next, a user-based evaluation was conducted in which participants were given several scenarios and were asked to use the web-based application to complete a series of tasks. Following the user-based evaluation, participants ratings of perceived usability of the web-based application were evaluated using the System Usability Scale. Lastly, semi-structured interviews were conducted consisting of a series of open-ended questions to elicit additional feedback. Interviews were qualitatively analyzed to identify themes across participant responses to each question.

5.3.2 Application Development

A web-based application was created using a commercially available website builder (Squarespace, New York City, New York, USA). Several interactive web applications were constructed using Shiny (Shiny: Web Application Framework for R, R package version 1.7.4.9002). These applications were published to the internet using shinyapps.io (Posit Software) and were embedded into pages of the website. Collectively, the web-based application was developed to guide practitioners through three primary steps of implementing exercise with BFR that have been previously identified as barriers. Specifically, steps included *Step 1: Medical Screening*, *Step 2*: *Selecting Equipment,* and *Step 3: Determining Cuff Pressure*. Below is an overview of the purpose and evidence-based rationale used to develop the functions and procedures included in each step.

Step 1: Medical Screening. The relative safety of performing exercise with BFR is an important concern.[216,278-280] Several potential contraindications and risk factors have been identified that may increase risk for adverse events. Accordingly, reviewing a candidate's lifestyle and medical history is important in stratifying risk and excluding those individuals in which risk may be heightened. The purpose of this step was to help practitioners conduct medical screening of potential candidates and stratify the risk of adverse events. Several authors [214,265,280,281] have developed tools to stratify risk and screen individuals for BFR inclusion. Existing screening tools were collected and used to develop an interactive medical screening application using Shiny.

Step 2: Selecting Equipment. Three main types of equipment have been used to implement exercise with BFR. These include automated pneumatic cuff systems,[230,282] manual pneumatic cuffs,[227] and elastic wraps.[283] The type of equipment utilized can impact the physiological and perceptual responses to exercise with BFR and may play a role in modulating risk of adverse events. Specifically, pneumatic cuff systems (i.e., automated and manual) allow for more

precise and standardized selection of external pressure applied to limbs compared to elastic wraps.[284] Furthermore, some automated pneumatic cuff systems supply constant applied pressures (i.e., autoregulated) during exercise which attenuates perceptual and hemodynamic responses [285] and reduces incidence of adverse events.[282] Accordingly, the purpose of this step was to recommend appropriate equipment for implementing exercise with BFR based on results of the medical screening conducted in *Step 1*. The user would then be free to select from recommended equipment types based on accessibility. Given that practitioners may not have knowledge of different BFR equipment types, we aimed to provide resources that would help to describe the equipment and direct practitioners to commercially available products.

Step 3: Determining Cuff Pressure. The amount of external pressure applied to the limb during exercise with BFR is an important methodological consideration for safety and effectiveness. When utilizing pneumatic cuff systems, it is recommended [65,286] that pressures during exercise with BFR be selected based on arterial occlusion pressure (AOP) which is the minimum amount of pressure required to occlude arterial blood flow to the limb. Thus, for use of pneumatic cuff systems, the web-based application was designed to 1) help users determine AOP, and 2) recommend exercising pressures based on that value.

Several methods for determining AOP are available. Automated pneumatic cuff systems have built in sensors for determining AOP,[230] whereas manual pneumatic cuffs require direct measurement of AOP using pulse oximetry,[228,229] handheld, or ultrasound Doppler.[227] For practitioners that may not have access to this equipment, an alternative approach is estimating AOP based on anthropometric, hemodynamic, and sociodemographic variables. Our laboratory and several authors [227,231-234] have developed prediction equations to estimate AOP for a variety of manual pneumatic cuffs of different width. The web-based application was designed to guide users through each of the different methods of determining and/or estimating AOP based on equipment availability. To aid in

AOP estimation, we developed an interactive application using Shiny that integrates prediction equations for 5, 11, 13, and 18 cm wide cuffs. Equations from Loenneke and colleagues [232] were used for estimating upper and lower-body AOP with a 5cm wide cuff. Unpublished prediction equations developed by our laboratory were used for estimating lower-body AOP for 11, 13, and 18 cm wide cuffs.

Evidence [65] indicates that pressures between 40 and 80% of AOP are effective in promoting muscular adaptations during exercise with BFR. However, lower pressures within this range attenuate acute cardiovascular and perceptual responses [220,223,260] such as blood pressure, pain, and discomfort during exercise with BFR and represent safer options for those with increased risk of adverse events. Thus, the web-based application was designed to provide specific pressure recommendations relative to AOP that are based on the results of medical screening obtained in *Step 1*. We developed an interactive application using Shiny that provides exercising cuff pressure recommendations based on AOP values input by the user.

Determining exercising pressure relative to AOP is not possible when utilizing elastic wraps. Several approaches [287] have been suggested for applying an appropriate amount of external pressure when utilizing this type of equipment to implement exercise with BFR. Limb circumference has been identified as the primary determinant of AOP when utilizing pneumatic cuffs.[227,231,232] Therefore, authors [287] have suggested that when utilizing elastic wraps for BFR, approaches to quantifying tightness of the wraps that are based on the circumference of the limb offer the most standardized method. Accordingly, the web-based application aimed to provide instructions on how to utilize these approaches for users choosing to implement exercise with BFR using elastic wraps.

5.3.3 Participants

Five licensed Physical Therapists (30±4 years, male = 2, female = 3) were recruited to participate in the study. A list of known physical therapists was

created and participants from this list were recruited through email and/or phone calls. Participants had 5±5 years of experience working in outpatient rehabilitation settings. Four participants were Doctors of Physical Therapy (DPT) currently working at facilities located in the Upper Peninsula of Michigan and one participant was a physiotherapist with a Masters in Sports Physiotherapy practicing in Europe. Participants had heard of BFR previously, however, none had any prior experience implementing exercise with BFR in clinical practice. Usability trials [288-290] have demonstrated that a sample of five participants can identify 80% of usability issues and that further participants become less likely to identify new issues. Accordingly, we utilized a convenience sample of five participants for our initial round of usability testing. Participants were informed of the purpose of the study and gave verbal consent. This study was approved by the Institutional Review Board at Michigan Technological University.

5.3.4 Usability Testing

*User-based Evaluation***.** Participants were given three scenarios, each consisting of a hypothetical patient, a reason for physical therapy treatment, and a specific goal for using BFR (Table 5.1). For each scenario participants were asked to use the web-based application to complete three tasks; 1) determine whether it was safe for the patient to engage in exercise with BFR, 2) select equipment for performing BFR based on what they were most likely to have access to, and 3) determine how much pressure to apply with the selected equipment during exercise. Patient scenarios were given to participants in a randomized order. Prior to beginning the task scenarios, participants were asked to share their computer screen and display the application webpage. While working through the assigned tasks, participants were instructed to use the “think aloud” [291] method by verbally walking through their thought process. The time taken to complete all three tasks, the number of incidents encountered, and type of incidents were recorded during each scenario. To explore which types of equipment participants had access to for implementing BFR, the type of equipment selected during task 2 and the method of determining cuff pressure during task 3 were recorded for each scenario. Each

scenario was categorized as “Successful” or “Unsuccessful” based on whether an appropriate pressure was selected for the hypothetical patient in task 3.

Table 5.1 Scenarios given to each participant during user-based evaluation.

	Scenario 1	**Scenario 2**	**Scenario 3**
Patient	62-year old Female	30-year old Male	50-year old Male
Cause for Treatment	Osteoarthritis	Patellofemoral pain	Post ACL reconstruction
Goal of BFR	Increase lower-body strength	Maintain strength lower-body strength	Regain lower-body strength
Characteristics	BMI: 31 BP: 135/90 mmHg	BMI: 24 BP: 125/82 mmHg TC: 60 cm	BMI: 20 BP: 118/78 mmHg TC: 52 cm
Health History	Diabetes Varicose veins in legs	NA	Surgery in last 4-weeks

System Usability Scale. Perceived usability of the application was evaluated using the System Usability Scale (SUS).[292] An SUS questionnaire was administered to participants using Google Forms. The SUS is a 10-item scale that examines the perceived usability of a technological tool. Responses are assessed on a Likert scale ranging from 1 (Strongly Disagree) to 5 (Strongly Agree). Responses on each item can be evaluated individually to determine specific usability issues and/or used to generate a composite SUS score between 0 and 100, with higher scores indicating higher perceptions of usability.[293] The SUS has been widely utilized which allows for relative comparison of SUS scores based on normative data. Importantly, the SUS is a valid [294-296] tool when assessing the usability of mobile applications and websites.

Semi-Structured Interviews. Participants were asked to respond to a set of 5 open-ended questions (Table 5.2). Questions were designed to collect feedback pertaining to the usability of the web-based application. Interviews lasted between 10 and 30 min (17±6 min). Audio recordings of interviews were transcribed for analysis.

Table 5.2 Semi-structured interview questions.

	Questions
1.	Is a there a specific reason why you have not utilized exercise with blood flow restriction in your clinical practice?
2.	What are some perceived barriers to implementing exercise with blood flow restriction in your clinical practice?
3.	What aspects of this web-based application did you find helpful in implementing exercise with blood flow restriction?
4.	How could this web-based application be improved to help you implement BFR more confidently?
5.	If this application was available, how do you think that it would change the use of blood flow restriction in clinical practice?

5.3.5 Data Analysis

Descriptive statistics were used to analyze time to task completion and the number of incidents while completing each task scenario. The type of incidents was qualitatively analyzed across all participants and placed into categories. For SUS responses, composite scores between 0 and 100 were calculated according to procedures described by Brooke.[292] Means and standard deviations were calculated for composite scores and for each individual response item. Composite SUS scores were interpreted relative to industry percentiles using a curved graded scale formulated by Lewis and Sauro.[293] Individual item responses were

interpreted by comparison to item benchmarks [293] established for SUS scores of 68 and 80. These item benchmarks represent mean Likert scale responses for each individual item that correspond to SUS composite scores at the 50th (SUS score 68) and 90th (SUS score 80) percentile of industry standards. Transcripts of semi-structured interviews were qualitatively analyzed using inductive thematic analysis as described by Braun and Clarke.[297] Six phases of analysis were utilized including: 1) familiarization with the data, 2) generating initial codes, 3) searching for themes, 4) reviewing themes, and 5) defining and naming themes, and 6) generating a report. Initial familiarization with the data was performed by IJW and consisted of re-reading interview transcripts while extracting meaning and patterns. Initial codes were developed by IJW using an inductive approach. Lastly, themes and subthemes were developed by establishing possible relationships between codes. Saturation in thematic analysis was reached within our sample and was defined as the point when no new codes were identified in two consecutive interviews. Importantly, it is not rare to achieve saturation with a small sample size when samples are highly homogenous.[298]

5.4 Results

5.4.1 Application Development

A detailed overview of the application workflow is displayed in Figure 5.1. Below is a description of features and evidence-based recommendations provided within each step of the application.

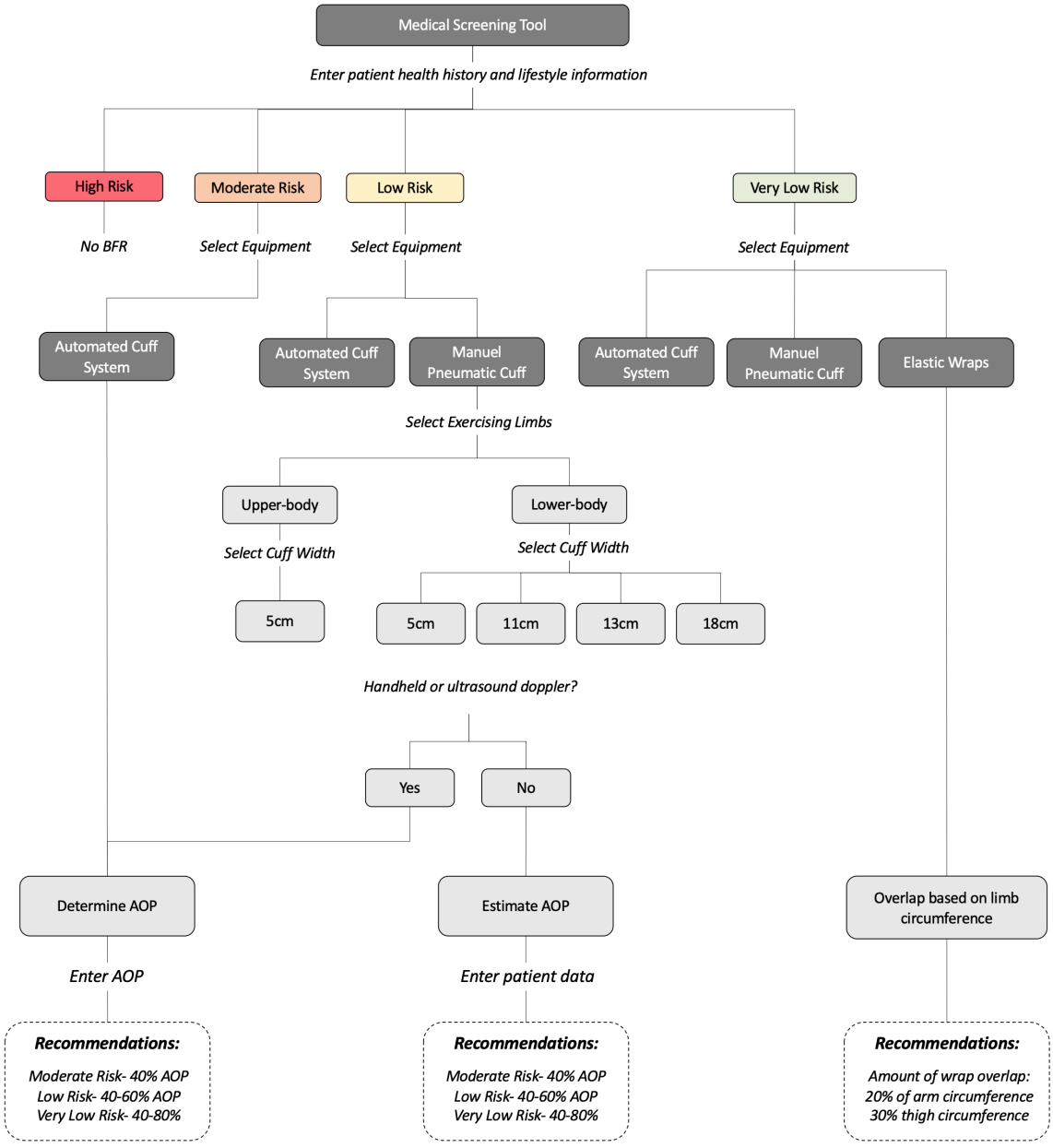

Figure 5.1 Workflow of web-based application.

Step1: Medical Screening. We utilized screening tools previously suggested by Kacin and colleagues [280] and Nakajima and colleagues [281] to develop a modified risk stratification tool. Although not comprehensive, these screening tools were selected for their simplicity and ease of completion. Kacin and colleagues [280] separated risk factors into 'absolute' and 'relative', in which those with absolute risk factors are automatically excluded from exercise with BFR and those with relative risk factors are prompted to seek medical advice. Nakajima and colleagues [281] proposed a point-based risk scoring system previously utilized by surgeons to assess risk of pulmonary embolism and deep-vein thrombosis. Risk factors are assigned points based on the level of relative risk that they incur, and points associated with each risk factor are additive. Those individuals accumulating 5 or more risk points are excluded from performing exercise with BFR. We integrated the two screening tools together by using the risk point system described by Nakajima and colleagues [281] while including additional absolute and relative risks described by Kacin and colleagues.[280] Absolute risks were assigned 5 points and relative risks were assigned 4 points. The modified medical screening tool was integrating into an interactive Shiny application and embedded on a medical screening page within the web-based application (Figure 5.2). The user enters a patient's medical history and lifestyle information into the input field of the application and is provided with a risk classification. The accumulation of ≥5 points classify individuals as "High Risk" and the application suggests that individuals be excluded from BFR. An accumulation of 4 risk points is classified as "Moderate Risk" and users are prompted to seek medical clearance from a primary care provider before engaging in exercise with BFR. An accumulation of ≤3 risk points (3 = "Low", ≤2 = "Very Low") suggests that exercise with BFR is not an absolute contraindication and it that can be performed. Therefore, users selecting a risk classification of "Low" or "Very Low" are prompted to move on to *Step 2*.

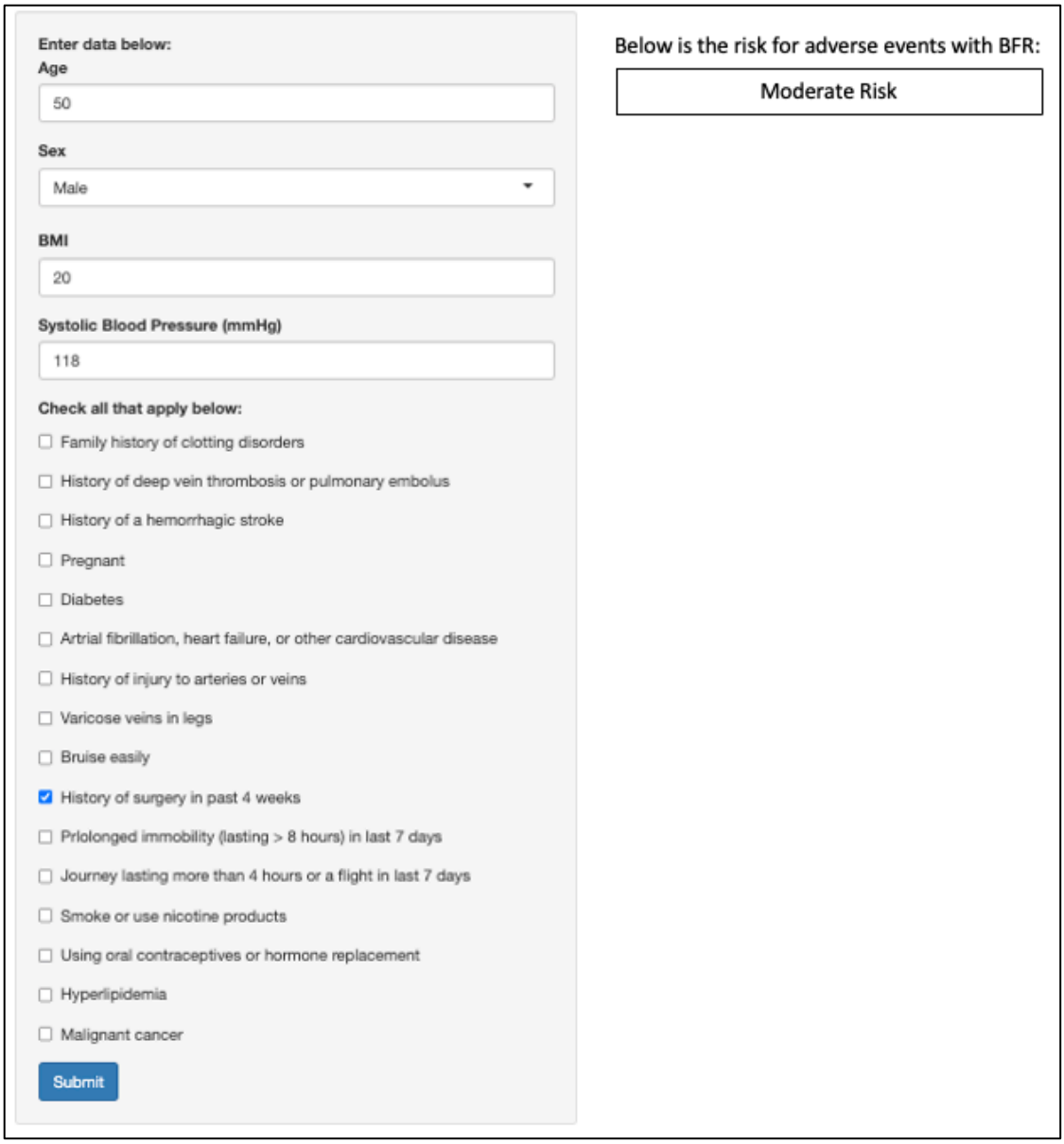

Figure 5.2 Screenshot of Shiny application for performing medical screening.

Step 2: Selecting Technologies. Recommended equipment for performing exercise with BFR was provided to users based on the risk stratification resulting in *Step 1*. For patients with a "Moderate Risk", the application provides users with the option to utilize automated cuff systems only. For patients with "Low Risk" the option of choosing either an automated cuff system or a manual pneumatic cuff was provided. Lastly, for patients with a "Very Low Risk", users were given the option to choose from an automated cuff system, a manual cuff system, or elastic

wraps. Selection of an automated cuff system or elastic wraps brought the user to the next step (*Step 3*). Selection of manual pneumatic cuffs prompted the user to select whether BFR will be performed in the lower- or upper-body. The user is then given the option to select from manual cuff widths commonly used for performing exercise with BFR in the selected limb (Upper-body: 5cm wide, Lower-body: 5cm, 11cm, 13cm, or 18cm). After selecting a specific cuff width, the user is brought to the *Step 3*. Screen shots of *Step 2* are provided in Figure 5.3. For each type of equipment recommended to users, a description of the equipment and links to commercially available products were provided.

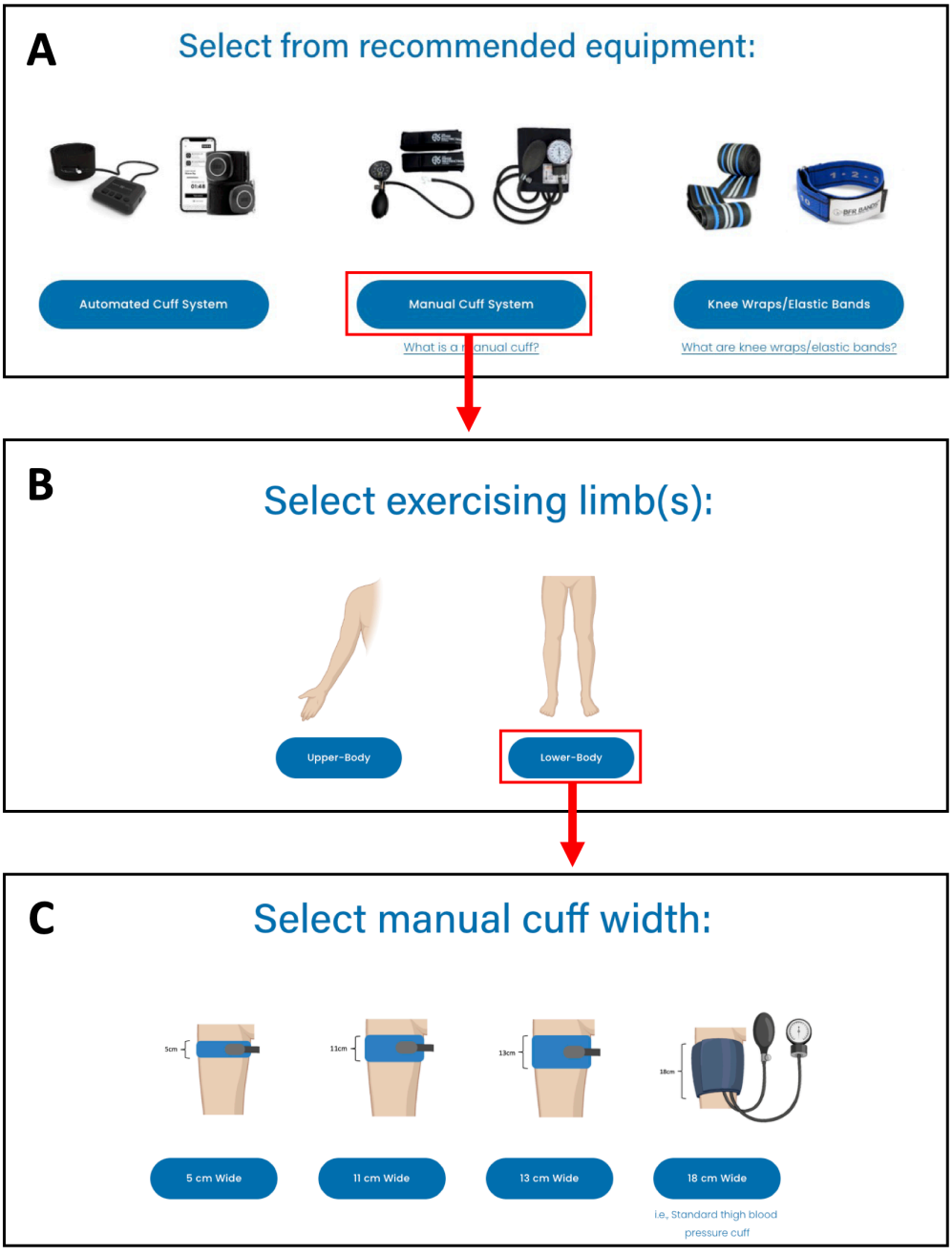

Figure 5.3 Screenshots from web-based application of *Step 2: Selecting Equipment* for performing exercise with BFR. Example shows the selection of a manual pneumatic cuff. **A.** User selects from recommended equipment types, **B.** User selects the limbs where BFR exercise will be performed, **C.** User selects the cuff width that will be used.

Step 3: Selecting Restriction Pressure. Users that selected to utilize pneumatic cuff systems (i.e., automated and manual) were prompted to determine AOP. When manual cuff systems are selected, the user is asked if they have access to equipment for assessing AOP directly (i.e., handheld or ultrasound Doppler). If they select “Yes”, they are brought to a page with instructions on how to measure AOP and provided links to video demonstrations for measuring AOP in both the upper- and lower-body. If they select “No”, they are brought to a webpage that helps them to estimate AOP using the Shiny application with integrated prediction equations (Figure 5.4). Within the application, the user selects the width of the manual cuff to be utilized and is provided with fields to input relevant predictor variables required (i.e., age, sex, limb circumference, systolic and diastolic blood pressure) for each respective prediction equation. Output from the application includes an estimated AOP for the selected cuff width.

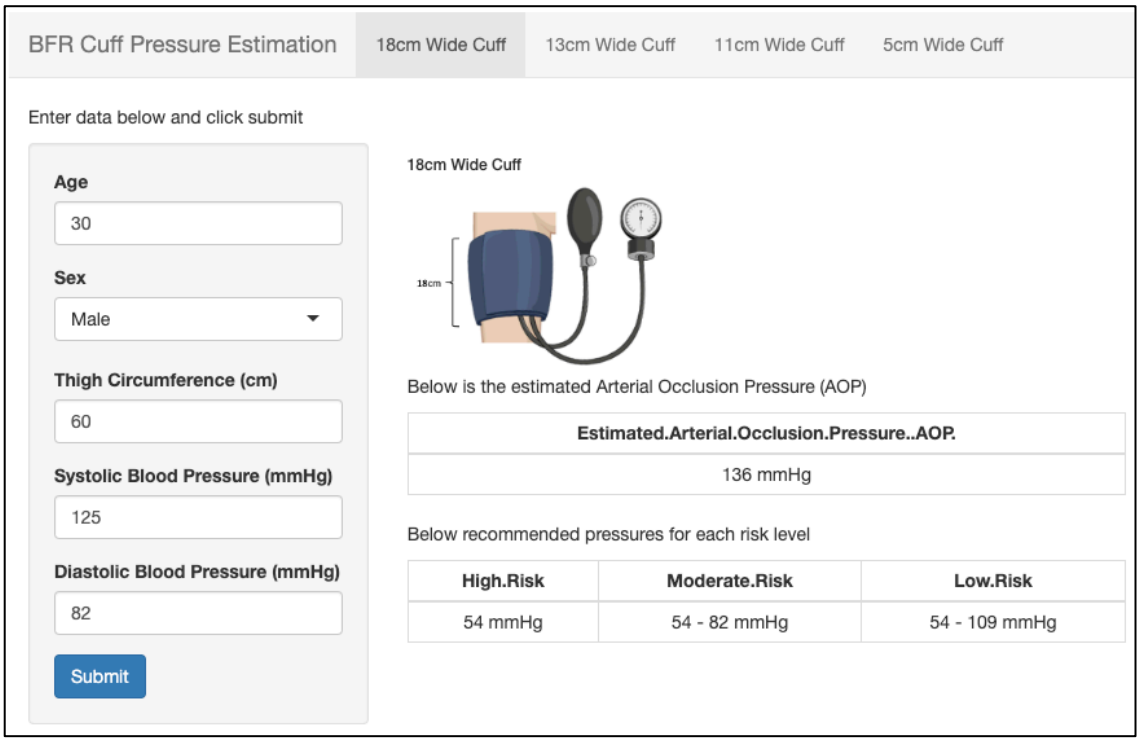

Figure 5.4 Screenshot of Shiny application for estimating AOP. User selects the width of cuff (top), enters relevant predictor variables (left), and is provided with cuff pressure recommendations based on the estimated AOP (right).

After AOP is either measured directly or estimated, pressures to utilize during exercise are provided relative to that value. Specific exercising pressure recommendations were given based on a patient's risk stratification obtained in *Step 1*. Pressures equivalent to 40% AOP are recommended for those with "Moderate Risk", 40-60% AOP for those with "Low Risk", and 40-80% AOP for those with "Very Low Risk". For those using automated cuffs or measuring AOP directly, users are prompted to use a Shiny application to enter the AOP value. The application then provides output of specific pressure recommendations based on the risk stratification levels stated above (Figure 5.5). For those choosing to estimate AOP, pressure recommendations are provided within the Shiny application based on the estimated AOP value.

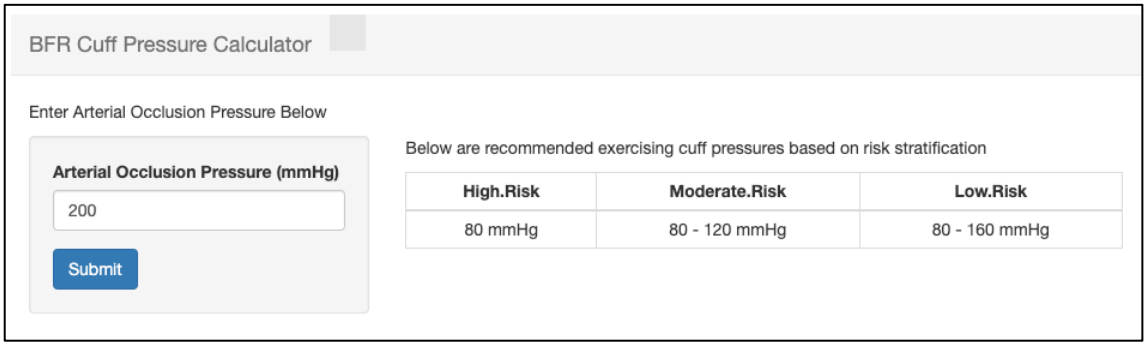

Figure 5.5 Screenshot of Shiny application that provides recommended exercising cuff pressures during BFR based on AOP. The user provides an AOP value (left) and is provided with recommended pressures to utilize based on the risk stratification level obtained during medical screening (right).

The option to utilize elastic wraps for performing exercise with BFR is only provided to those individuals with a "Very Low" risk classification obtained during medical screening. As the amount of pressure (i.e., mmHg) cannot be quantified for this type of equipment, the selection of elastic wraps provides the user with instructions on how tightly to apply the wraps during exercise. Specifically, users are provided with step-by-step directions for applying wraps based on the amount of overlap in the wrap relative to limb circumference as described by Aniceto and colleagues [287] and Abe and colleagues.[299] Instructions are provided for applying

the specific type of elastic wrap utilized by these authors (Harbinger Red-Line, Fairfield, CA, USA; 7.6 cm width). For the upper limbs, users are instructed to measure the circumference of the upper arm and to apply the wrap so that it is stretched to a length corresponding to 10% of the resting arm circumference during each revolution around the limb. For the lower limbs, users are instructed to measure the circumference of the thigh and apply the wrap so that is it is stretched to a length corresponding to 30% of the resting thigh circumference during each revolution around the limb.

5.4.2 Usability Testing

User-based Evaluation. The time to completion for task scenarios was 2.3±1.2 min and the number of incidents was 1±1. In the order that scenarios were given to participants, time to task completion was 3.3±1.4 min for the first scenario, 1.8±1.2 min for the second scenario, and 1.8±0.6 min for the third scenario. There was a total of 11 incidents among all participants during the completion of task scenarios. Incidents were categorized as navigation problems (4), data input problems (2), and difficulty interpreting recommendations (5). A summary of the type of incidents occurring during each task are presented in Table 5.3. When prompted to select equipment for implementing BFR, participants selected a manual thigh blood pressure cuff 80% of the time, knee wraps/elastic bands 10% of the time, and automated cuff systems 10% of the time. All participants selecting to use a manual thigh blood pressure cuff indicated that they did not have access to equipment for measuring AOP and utilized the application to estimate AOP. All task scenarios were completed “Successfully” and resulted in participants properly screening and determining an appropriate cuff pressure to utilize during exercise with BFR with all patient scenarios.

Table 5.3 Type and frequency of incidents occurring during user-based evaluations.

	Navigation	**Data Input**	**Interpreting Recommendation**
Step 1: Medical Screening	• Difficulty locating output from medical screening (2) • Unsure how to proceed to next step (2)	• Forgot to hit "Submit" button	NA
Step 2: Selecting Equipment	NA	NA	• Thought that width of cuff referred to limb circumference
Step 3: Determining Cuff Pressure	NA	• Entered units within input field and was given "error"	• Confusion about AOP value in output (2) • Difficulty remembering stratification level from medical screening • Problems interpreting elastic wrap directions

*Perceived Usability***.** Composite SUS scores were 94±5, which corresponded to an "A+" on the curved graded scale and ranked within the 96-100th percentile range of industry SUS standards. Composite and individual item SUS responses are presented in Table 5.4. All individual item responses were above benchmarks for an SUS composite score of 80.

Table 5.4 System Usability Scale (SUS) responses and normative data.

	Item Number										
Participant	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**Composite**
1	5	1	5	1	5	1	5	1	5	1	100
2	4	1	5	1	5	2	5	1	4	1	92.5
3	5	1	4	1	4	1	5	2	5	1	92.5
4	5	1	5	1	4	1	5	1	5	1	97.5
5	4	1	4	1	4	1	5	2	4	1	87.5
Mean±SD	4.6±0.6	1±0	4.6±0.6	1±0	4.4±0.6	1.2±0.5	5±0	1.4±0.6	4.6±0.6	1±0	94±5 (A+)
Benchmark	≥3.4	≤2.4	≥3.7	≤1.9	≥3.6	≤2.2	≥3.7	≤2.3	≥3.7	≤2.1	68 (C)
Benchmark	≥3.8	≤1.9	≥4.2	≤1.5	≥4.0	≤1.8	≥4.2	≤1.7	≥4.3	≤1.6	80 (A-)

Semi-Structured Interviews. Several themes and subthemes emerged from qualitative analysis of participants semi-structured interview responses. Below are themes and subthemes from participants responses to each question.

Question 1: Is there a specific reason why you have not utilized blood flow restriction in your clinical practice?

Two themes emerged as to why participants had not utilized exercise with BFR in their clinical practice including 1) Lack of consideration, and 2) Limited knowledge. Three out of five participants indicated that exercise with BFR was simply not a method that they often considered when treating patients. Furthermore, whether they had considered BFR or not, all participants reported that a lack of knowledge about BFR was a reason why they hadn't utilized it. Additionally, four participants commented that their lack of consideration and/or knowledge was due to limited exposure to exercise with BFR. Two participants stated that they hadn't seen BFR used in the clinic by colleagues, one participant commented on limited exposure during their schooling, and another commented on limited exposure in the media.

Theme 1: Lack of Consideration

> *"I haven't seen blood flow restriction used in the clinic so it's not something that just comes to mind as a treatment"*
>
> *"I think the biggest barrier to blood flow restriction, and I mean this tactfully, but I think its ignorance. Most physical therapists don't know about it, or they've heard about it, but they're not too familiar with it"*
>
> *"I don't feel like it has caught on. You don't see it on social media. You don't see it in your feeds. So to me, it's more of a 'I'm not seeing it' and if it is literally not in front of me, I forget about it"*

Theme 2: Limited Knowledge

> *"For me, knowledge is definitely the reason why I haven't used it. It's something that's on my radar. But I haven't really delved into trying to implement it or looked more into it"*
>
> *"It was only one seminar put on for students during school and I am not comfortable in it yet"*

“You don't have other clinicians utilizing it. So it's hard as an experienced therapist to be like, ‘Yeah, let me just go and grab this thing and reference someone else’”

“It's probably my lack of knowledge and really diving into BFR that is the main barrier to me using it with patients”

“I would have to look a lot into how I would use it correctly, not only ‘when’ and ‘why’, but ‘how’ to do correctly. ‘How’ would be a big question for me”

Question 2: What are some perceived barriers to implementing exercise with blood flow restriction in your clinical practice?

Three themes emerged as barriers to using exercise with BFR and included 1) Limited knowledge, 2) Limited access to resources, and 3) Patient and professional concerns. All participants reported that a lack of knowledge pertaining to the implementation of BFR presented a barrier to using it. Furthermore, several subthemes were identified related to specific areas of limited knowledge. These included uncertainty surrounding contraindications and safety of performing BFR (5/5 participants), what equipment to utilize for performing BFR (4/5 participants), and determining pressures to apply during exercise (5/5 participants). All participants also reported that limited access to resources posed a barrier. Four out of five participants mentioned having limited access to equipment for performing BFR and two out five commented on having limited time to implement BFR. Lastly, four out of five participants mentioned that the risk of BFR causing adverse events in patients and/or threatening their professional status were barriers to its use.

Theme 1: Limited Knowledge

Subtheme: Contraindications and safety

"I have not used blood flow restriction in my clinical practice mainly because I don't know all of the precautions and contraindications”

“I would have to look into when it's not safe to use when it's safe to use. And what type of things that I need to know about the patient before I can really evaluate whether this is a good thing to use or not”

"I'm not so sure about the evidence around its use in more at risk populations that we would typically see in a standard orthopedic outpatient setting"

"It doesn't seem clear as to what the risks are. What are the well-known risks?"

Subtheme: Selecting Equipment

"I'm not aware of the equipment that should be used. I need to know how or what would be the best equipment to get"

"I'm not very familiar with more easily accessible and cheaper kinds of options that you would find in a standard clinic. And just in general what is out there"

Subtheme: Determining Pressures

"I have a mental image of how I would apply it on the body, but I don't know how I would quantify the pressure"

"Given my lack of knowledge in the area I just straight up wouldn't know the pressure to work with. Yeah, I don't think I would have too much without that. I wouldn't be able to use it"

Theme 2: Access to Resources

"I'm not sure if I'd have the time to be able to figure it out in the clinic"

"I'm not sure how much time it would take me to apply BFR if we have restricted time during a session. How much time would this take, you know, compared to having them do regular exercise?"

"Most of this equipment we don't have at the clinic. Except for the blood pressure cuff and some elastic bands"

"I have not used it. And the reason why, I guess is because I didn't have access to any equipment."

Theme 3: Patient and Professional Concerns

"The biggest barrier to using exercise with blood flow restriction to me is not knowing precautions and contraindications and fear of having something go wrong medically with a patient"

"You just have the fear of not knowing how someone's going to react to it"

“Other clinicians may perceive that there's a significant risk. The fact that safety isn’t clear last I read is concerning and you never want to find out in the clinic or even be associated with that”

“Safety is always a consideration. You know, I worked hard to get my license. I don't want to lose it just yet.”

Question 3: What aspects of this application did you find helpful in implementing exercise with blood flow restriction?

Two themes were identified pertaining aspects of the application that participants found helpful including 1) Ease of use/efficiency and 2) Content and features. All participants agreed that the web-based application was easy to use and time efficient. Participants also agreed that the content and features included within each step of the application addressed gaps in knowledge and were useful for implementing exercise with BFR. All participants specifically mentioned *Step 1: Medical screening* and *Step 2: Determining Restriction Pressure* being particularly helpful.

Theme 1: Ease of use/efficiency

“It's just super intuitive to use”

“Once you get a round or two of using it, it's very user friendly”

“It was fast and easy to complete the medical screening. All the contraindications or precautions are easily listed, so I could just quickly go through my past medical history screening with them. All the instructions are easily listed on there. It was just overall pretty easy to use and efficient time wise”

“It was really easy to utilize and gives you the knowledge and the appropriate measures as to what to utilize”

Theme 2: Content and Features

“I think the application addressed many of the concerns that I have with implementing blood flow restriction, especially the precautions and contradictions and selecting pressures that are safe. Also, how to take the measurements, for like circumference”

“It was super handy, knowing how much pressure to use based on someone's risk factors and their risk stratification of low, moderate, high risk. It does a great job of risk stratification and giving us a practical application of how much pressure to apply based on easy data to obtain from the patient. So I think that's actually super helpful”

“I found all of the steps in the application helpful. I feel a lot safer having or getting to plot their medical information and someone telling me its safe or not. So that's very helpful, very useful. And of course, also, since I don't know any pressures or how to really do this by myself already, Step 3 is also very helpful”

Question 4: How could this application be improved to help you implement blood flow restriction more confidently?

Three participants provided feedback on how the application could be improved. Two participants did not give any suggestions. Suggestions included 1) better integrating the results of the medical screening into the selection of pressures to use during exercise with BFR and 2) including more information about the benefits and drawbacks of selecting certain types of equipment for implementing BFR.

“I wish that the risk categories from the medical screening had pulled over to the end because, like I forgot, and if I hadn't appropriately remembered I could have picked the wrong pressure”

“Maybe including the benefits to choosing the different types of cuffs, you know, if you list the cost of cuffs versus the wraps, putting like the pros and cons, a little bit under each type of equipment to aid the clinical decision making”

Question 5: If this application was available, how do you think it would change the use of blood flow restriction in clinical practice?

Two themes emerged related to how the web-based application would change the use of exercise with BFR in clinical settings and included 1) Improved confidence with using BFR and 2) Increased accessibility of BFR. Three out of five participants reported that having the application would increase practitioners’ confidence of using exercise with BFR. All participants stated that the web-based application would make exercise with BFR more accessible to practitioners.

Specifically, they reported that the web-based application lowered the requite knowledge needed to implement exercise with BFR (3/5 participants), lowered costs associated with BFR use (1/5 participants), and would make implementing BFR more time efficient (1/5 participants). Furthermore, two participants commented that the web-based application would make practitioners more likely to utilize exercise with BFR.

Theme 1: Improved confidence

> *"Having this makes it easier to do and it's harder to mess up, you know you've got that back up with it"*
>
> *"I think that it would be a very helpful application. I think that people would be more confident with when and how to use BFR for sure"*
>
> *"It takes away some of that uncertainty, and not knowing exactly what to do, and gives you more of that 'No, I can do this. This is easy' feeling"*

Theme 2: Increased Convenience and Accessibility

> *"Having this application available would make blood flow restriction more accessible to physical therapists. If physical therapists were aware of BFR and it's potential utility I think they would be more likely to utilize it. The application itself is user friendly, the clinic wouldn't have to invest in thousands of dollars to be able to use it, and it presents relatively cheap options for performing BFR"*
>
> *"Having something like the app where somebody that's relatively novice can just sort of dive in and use it, I think, is really helpful"*
>
> *"I was able to run through it pretty quickly. I think that's something that would make the idea of using blood flow restriction in the clinic a lot easier without, you know, falling way behind on documentation or anything like that"*
>
> *"I think the application could be a very valuable tool. If there's a process put in place of stratifying risk based on their medical history, their surgical history, and all that, and it gives us pressure to use I think that'll be really helpful. I definitely see myself using this in the future. I think if more people came across this they'd be a lot more likely to use blood flow restriction, especially in the sports PT world"*
>
> *"It certainly lowers the barrier of entry. I think, you know, it's easy to utilize and gives you everything you need"*

5.5 Discussion

The primary purpose of this study was to describe the development of a web-based application to aid in the implementation of exercise with BFR. A secondary purpose was to conduct preliminary usability testing in physical therapists to identify issues and provide feedback for further development. Our main findings were that 1) the web-based application can serve as an evidence-based decision support tool for implementation of exercise with BFR, 2) physical therapists found the functionality and content of the web-based application helpful for implementing exercise with BFR, and 3) usability of the web-based application was high in physical therapists possessing no previous experience using exercise with BFR. Lastly, several areas for improvement were identified including the addition of more informational content about BFR equipment, improving integration of steps and functions, and making user recommendations easier to interpret.

To the best of our knowledge, we are the first group to report the development of a decision support tool for evidence-based implementation of exercise with BFR. We utilized a commercially available website builder and interactive Shiny applications to construct a preliminary web-based application. Functional steps included in the preliminary design were aimed at addressing barriers to the implementation of BFR that have been previously identified [265] in practitioners. In agreement with findings of Rolnick and colleagues,[265] participants in this study reported that limited knowledge about the contraindications and safety of performing BFR, how to choose equipment for performing BFR, and how to determine cuff pressure presented barriers to utilizing this modality. Limited access to resources, such as equipment and time, as well as concerns about adverse health events in patients were also reported as barriers. Our results suggest that the content and functions included within our web-based application were helpful in addressing each of these perceived barriers. Participants stated that having the web-based application would increase their confidence implementing exercise with BFR, lower the requite

knowledge required to use BFR, and would make practitioners more likely to utilize the modality in clinical practice. An interesting finding was that almost all participants selected to utilize a thigh blood pressure cuff to implement exercise with BFR during hypothetical task scenarios using the web-based application. Furthermore, all participants choosing to utilize this equipment indicated that they did not have access to handheld or ultrasound doppler for directly measuring AOP. Accordingly, all participants determined exercising cuff pressures for this device by estimating AOP. These data indicate that a major strength of our web-based application was providing more accessible options for implementing BFR that did not require specialized equipment. Feedback about how to improve the content of the application was minimal. One participant suggested including more information about the various BFR equipment types would be helpful in making a more informed clinical decision when choosing which equipment to utilize with patients.

Results indicated that our web-based application had a high degree of usability within our sample of physical therapists. Composite SUS scores ranked highly among industry standards and all individual item responses were above benchmarks for an SUS score of 80. Importantly, our results indicated that the web-based application was effective, efficient, and satisfactory to use. Effectiveness of a system referrers to how well a systems performance meets the task that it was designed for. During user-based evaluation there was a 100% success rate in which all participants successfully implemented exercise with BFR in each of the hypothetical scenarios that they were presented with. This included successful medical screening of patients for BFR inclusion, selecting appropriate equipment for performing BFR, and selecting an appropriate cuff pressure to utilize based on risk stratification. Efficiency referrers to how much time and effort are required to use a system to achieve a desired task. Using the web-based application, participants were able to complete all steps of implementing exercise with BFR in under 3 minutes. After becoming familiarized to the web-based application, time to completion decreased by almost half,

suggesting that participants were able to quickly learn the system interface. Additionally, participants described the web-based application as being “easy to utilize”, “user friendly”, “intuitive”, and/or “time efficient” in their interview responses. Lastly, satisfaction refers to how pleasant a system is to utilize and its ability to favor positive attitudes from a user. Interview responses largely suggested that participants experience using the web-based application was positive. Several participants stated that they would use this application if it was available.

No critical design problems in the web-based application were identified. Incidents occurring during user-based evaluations helped to identify minor issues related to navigation, data input, and interpreting recommendations provided by the application. Navigation problems largely occurred during the medical screening. Specifically, the layout of the medical screening Shiny application made it difficult for users to locate the risk stratification output. Additionally, after identifying the risk stratification level in the Shiny application, participants had difficulty navigating back to the top of the webpage to select the resulting risk level and move onto the next step. Collectively, feedback suggested that the results from medical screening were not well integrated into the other functions of the application. For example, when determining exercising cuff pressures, participants were given pressure recommendations for all risk stratification levels and some participants had difficulty remembering the assigned risk level provided during medical screening. One participant suggested that cuff pressure recommendations in *Step 3* be provided only for the patient previously screened. This reflects a limitation of our overall application development (i.e., using a website with embedded Shiny applications). Shiny applications do not directly interface with the website, making it challenging to integrate results into future steps. Lastly, several participants had difficulty interpreting the pressure to utilize based on the output from the AOP estimation Shiny application. Specifically, a patient’s AOP was listed in the output along with recommended exercising pressures and several participants were confused about what the AOP value

represented. Lastly, one participant selecting to utilize elastic bands had difficulty interpreting how to apply the wraps based on the patient's limb circumference. Accordingly, several recommendations to improve usability of the web-based application include 1) re-designing the layout of the medical screening Shiny application so that the risk stratification output is easier to locate, 2) better integrating the results of medical screening into the determination of cuff pressure, 3) defining AOP and indicating more clearly the recommended pressures to use during exercise, and 4) improve instructions for setting tightness with elastic wraps. Collectively, development of a more integrated web-based application may help to overcome many of the issues identified by users.

5.6 Limitations

There two noteworthy limitations to this study. First, participants were given a limited number of hypothetical task scenarios during user-based evaluation and thus did not experience all possible scenarios for implementing exercise with BFR within the web-based application. Additionally, almost all participants chose to utilize the same equipment and methods for determining cuff pressure. Therefore, feedback related to alternative content and functions within the application was limited. Second, use of the web-based application by practitioners was carried out virtually and with hypothetical scenarios where all patient information was easily provided. Thus, the generalizability of these results to use of the application in real world clinical practice are limited.

5.7 Conclusion

Our web-based application presents a promising tool to help physical therapists implement safe and effective exercise with BFR. Through the application we were able to provide evidence-based guidance for medically screening potential BFR candidates, selecting appropriate equipment to utilize for performing BFR, and determining appropriate cuff pressures. The main content and functions included within the application appeared to address many of the major barriers that physical therapists face to utilizing exercise with BFR as a

rehabilitation strategy. Additionally, the application was effective and efficient in helping physical therapists to make appropriate decisions related to the implementation of exercise with BFR. Several areas for improvement were identified which will help to enhance the usability of this application.

6 Summary

Over the past 70 years, accumulating evidence [58] has highlighted the important role of physical activity in the prevention and treatment of chronic disease. The beneficial effects of physical activity, however, remain underestimated by the medical community, policy makers, and public at large. Novel insights from the COVID-19 pandemic have helped to shed further light on the role that physical activity and exercise can play in public health and in the management of infectious disease. Specifically, physical activity can reduce risk for severe COVID-19 outcomes (i.e., hospitalization, admission to the intensive care unit, death) and may assist with recovery in those individuals who were previously infected with the virus and experience persistent symptoms (i.e., post COVID-19 condition). Accordingly, strategies to increase physical activity levels are paramount for keeping individuals and their communities healthy and safe during the COVID-19 pandemic and beyond. Furthermore, enhancing the accessibility of unconventional exercise modalities, such as exercise with BFR, can help to provide alternative ways to achieve the benefits of exercise for those that are unable to engage in more traditional approaches. Accordingly, the overarching goal of this research was to promote and facilitate the use of physical activity as a critical form of medicine during the COVID-19 pandemic and beyond. Below is a summary of key findings, limitations, and future implications for each study.

6.1 Study 1

For Study 1, I leveraged Exercise is Medicine® on Campus (EIM-OC) at Michigan Technological University to provide critical physical activity resources to Michigan's rural Upper Peninsula during the COVID-19 pandemic. This work not only provided a timely response to the pandemic in our local community but helped to highlight the potential utility of our framework to facilitate physical activity beyond the pandemic. Physical inactivity is likely to remain a major public health challenge for years to come. Identifying interventions to facilitate physical activity in rural communities is especially important given the unique barriers to

physical activity that these communities face. Results of our program implementation suggest that locally situated colleges and universities can play an important role in promoting and facilitating physical activity for their surrounding communities. Furthermore, guided virtual home-based workouts could provide a feasible option for rural residents with limited access to physical activity infrastructure. A limitation of this work was that we did not directly assess the effectiveness of our intervention to increase public awareness or improve physical activity levels. Evaluating the effectiveness of our program framework to impact health behaviors is an important next step.

6.2 Study 2

With Study 2, I provided a working hypothesis and theoretical framework for how BFR may be utilized to restore physical function in those individuals infected with COVID-19. Specifically, I presented the hypotheses that: 1) use of passive BFR modalities (BFR-P and BFR-NMES) can mitigate losses of muscle mass and muscle strength that occur during acute infection and 2) exercise with BFR (BFR-AE and BFR-RE) can serve as an effective alternative to traditional higher intensity exercise for regaining muscle mass, muscle strength, and aerobic capacity during convalescence. In addition to restoring physical function, I highlighted how the various applications of BFR may also serve as a targeted therapy to address the underlying pathophysiology of COVID-19 and provide benefits to numerous organ systems effected by the disease. Lastly, I proposed a theoretical framework with which BFR could be implemented throughout the progression from acute illness to outpatient rehabilitation with the goal to improve short and long-term outcomes in COVID-19 survivors. This work is both timely and impactful as it presents a novel therapeutic option with potential to combat the long-term effects of COVID-19. Additionally, this work will help to encourage discussion and consideration among researchers and clinicians not only about the potential utility of BFR in the treatment of COVID-19 but its application to similar pathologies and cases of acute critical illness. Limitations include potential safety concerns regarding the use of BFR in clinical populations, such as those

infected with COVID-19, and the ability of practitioners to implement BFR safely and effectively in clinical settings. Future efforts are needed to establish the safety of performing BFR in populations that may be at a heighten risk for adverse events and ensure that practitioners possess knowledge of current best practices for implementing BFR and have access to appropriate technologies.

6.3 Study 3

With Study 3, I investigated which sociodemographic, anthropometric, and hemodynamic variables predict lower-limb AOP when utilizing an 18cm wide thigh sphygmomanometer. Furthermore, I used these results to develop a prediction equation to estimate lower-limb AOP with this inexpensive cuff. Key findings were that models based on thigh circumference or thigh composition combined with brachial blood pressures explained the most variability in AOP (~55%) and that brachial SBP represented the single strongest predictor of AOP. Additionally, a prediction equation including thigh circumference, brachial SBP, brachial DBP, age, and sex provides a valid way to estimate AOP. This equation offers a low-cost approach to implementing exercise with BFR which will help to make this training modality more accessible to clinicians, coaches, and athletes. A noteworthy limitation of this work is that I did not perform external validation of the developed prediction equation. Establishing true generalizability of the model requires application in independent data. Finally, the prediction equation was developed using a sample of young healthy adults. Additional work is needed to determine how the equation will perform when applied to different populations.

6.4 Study 4

With Study 4, I developed a web-based application to aid practitioners in implementing exercise with BFR and performed preliminary usability testing of the application in physical therapists. With the web-based application I provided evidence-based guidance for medically screening potential BFR candidates, selecting appropriate equipment to utilize for performing BFR, and determining appropriate exercising cuff pressures. Results indicated that the main content

and functions included within the application addressed many of the major barriers that physical therapists face to utilizing exercise with BFR as a rehabilitation strategy. Furthermore, when utilizing the application to implement exercise with BFR in hypothetical patients, almost all participants chose to apply a thigh sphygmomanometer and determined exercising cuff pressures using the prediction equation developed in Study 3. These results suggest that cost-effective approaches to implementing exercise with BFR may have widespread use in clinical settings. Lastly, the web-based application was effective and efficient in helping physical therapists to make appropriate decisions related to the implementation of exercise with BFR. Importantly, this web-based application will help to improve access, safety, and effectiveness of exercise with BFR in clinical settings. Limitations of this work are that participants did not experience all possible scenarios for implementing exercise with BFR while using the application which limits feedback on its usability. Additionally, use of the web-based application by practitioners was carried out virtually and with hypothetical scenarios. Thus, the generalizability of these results to use of the application in real world clinical practice are limited. Future work will seek to address usability issues identified in this study, conduct more extensive testing in conditions more closely resembling true clinical use, and improve upon the design of the web-based application for future use.

6.5 Conclusion

Results of this diverse body of work demonstrate how physical activity and exercise could be leveraged to address 1) the immediate public health threat of COVID-19, 2) the long-term consequences of COVID-19, and 3) the ongoing physical inactivity pandemic. As society builds forward from the COVID-19 pandemic, physical activity and exercise will continue to represent an affordable, accessible, and highly robust form of medicine that combats not only chronic disease but infectious disease. Importantly, this work helps to facilitate the utilization of exercise with BFR which provides a feasible alternative to obtaining the benefits of exercise in those individuals for whom traditional approaches may

be challenging or contraindicated. By encouraging the consideration of BFR use and improving its accessibility, this research expands upon possible interventions with which physical activity and exercise and be leveraged to improve the health and wellness of society.

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A Study 1 Addendum

This addendum serves to elaborate and extend upon the rationale used to develop and implement the community-based physical activity program described in Study 1- Promoting Physical Activity in Rural Communities During COVID-19 with Exercise Is Medicine® On Campus. Although not explained in the published manuscript, implementation of our physical activity program was guided using a population-based framework to address social determinants of health in the Upper Peninsula of Michigan.

Social determinants of health consist of the personal, social, economic, and environmental factors that influence an individual's overall health status (SDOH; World Health Organization, 2020). These determinants vary across individuals, between populations, and are largely influenced by policymaking, social factors, health services, individual behavior, and biology or genetics. While physical activity itself can be regarded as a determinant of health, the behavior of engaging in physical activity has determinants of its own. Factors within the social and physical environment directly influence the opportunity to engage in physical activity and thus can make the behavior more or less likely. Importantly, factors influencing physical activity depend on the place, context, and composition of a population.

In the rural Upper Peninsula of Michigan, several unique social and environmental factors may contribute to physical activity behaviors. First, the built environment which provides infrastructure for engaging in physical activity is limited. This includes access to fitness centers, outpatient rehabilitation clinics, parks, and recreational facilities, as well as bicycle and pedestrian routes that promote active commuting. Additionally, many residents live long distances from existing infrastructure, increasing dependance upon transportation for physical activity engagement. Second, the natural environment poses several challenges. Specially, climate conditions during winter months limit access to outdoor physical activities, active commuting, and transportation for a large portion of the

calendar year. Third, there is limited access to healthcare professionals and credentialed fitness professionals that promote and provide physical activity programming. The majority of the Upper Peninsula's counties are categorized by the U.S. Health Resources and Services Administration as Medically Underserviced Areas. This reduces the capacity for residents to receive counseling and education about healthy living behaviors such as physical activity. Lastly, demographic and socioeconomic status pose barriers to physical activity for a large number of residents. According to the Upper Peninsula Community Health Needs Assessment (2021), 23% of residents are above the age of 65 years old, with some counties as high as 40%. Additionally, almost all Upper Peninsula counties have a percentage of households with an income less than $25,000 that is greater than the statewide average. Combined with a large population of older adults living on a fixed income, costs associated with physical activity pose another potential barrier.

The overall framework and implementation of our community-based physical activity program was designed to address specific barriers to physical activity identified in the Upper Peninsula of Michigan. Importantly, our program was implemented during the COVID-19 pandemic which placed further constraints on physical activity implementation. To circumvent these constraints and address unique barriers in the Upper Peninsula we chose to offer a virtual physical activity program that could be accessed from home. In the Upper Peninsula, 84% of households have computers and 73% of have internet (Upper Peninsula Community Health Needs Assessment, 2021), suggesting that most residents would be able to access a web-based program. For those individuals who did not have the necessary technology or ability to access our program online we also aired our program on local television and offered a DVD option that could be ordered upon request. To address the potential barrier of cost, the virtual program was free of charge and was designed to deliver physical activity sessions that could be completed from home without the need for any specialized exercise equipment. A home-based virtual program also removed the

impact of climate and provided ways to stay active indoors during winter months. Lastly, physical activity sessions themselves were designed to accommodate for a wide variety of ages, fitness levels, mobility levels, and exercise preferences. Specifically, we provided exercise adaptations that cater to older individuals and/or those living with disabilities and encouraged community members to self-select an intensity that they felt most comfortable with. By offering a variety of different workout types, including aerobic exercise, resistance exercise, agility and balance movements, yoga, and stretching/standing breaks, community members were given the ability to choose between workouts that they most enjoyed.

Collectively, this addendum describes the theoretical rationale by which our physical activity program was mapped onto the unique environmental and social determinants of physical activity in the rural Upper Peninsula of Michigan during the COVID-19 pandemic. Accordingly, this work can be framed as more than public outreach and represents the development and implementation of a population-based framework.

B Wedig et al., 2020 BJSM

Infographic

Infographic. Stay physically active during COVID-19 with exercise as medicine

Isaac J Wedig,[1] Tristan A Duelge,[1] Steven J Elmer [1,2]

INTRODUCTION

There are over 35 000 000 reported cases of COVID-19 disease and 1 000 000 deaths across more than 200 countries worldwide.[1] With cases continuing to rise and a robust vaccine not yet available for safe and widespread delivery, lifestyle adaptations will be needed for the foreseeable future. As we try to contain the spread of the virus, adults are spending more time at home. Recent evidence[2] suggests that physical activity levels have decreased by ~30% and sitting time has increased by ~30%. This is a major concern as physical inactivity and sedentary behaviour are risk factors[3] for cardiovascular disease, obesity, cancer, diabetes, hypertension, bone and joint disease, depression and premature death.

To date, more than 130 authors from across the world have provided COVID-19-related commentary on these concerns. Many experts[4] have emphasised the importance of increasing healthy living behaviours and others[5] have indicated that we are now simultaneously fighting not one but two pandemics (ie, COVID-19, physical inactivity). Physical inactivity alone results in over 3 million deaths per year[5] and a global burden of US$50 billion.[6] Immediate action is required to facilitate physical activity during the COVID-19 pandemic because it is an effective form of medicine[3] to promote good health, prevent disease and bolster immune function. Accordingly, widespread messaging to keep adults physically active is of paramount importance.

Several organisations including the WHO, American Heart Association and American College of Sports Medicine have offered initial suggestions and resources for engaging in physical activity during the COVID-19 pandemic. Expanding on these resources, our infographic aims to present a comprehensive illustration for promoting daily physical activity to the lay audience during the COVID-19 pandemic (figure 1). As illustrated, adults are spending more time at home, moving less and sitting more. Physical activity provides numerous health benefits, some of which may even help directly combat the effects of COVID-19. For substantial health benefits, adults should engage in 150–300 min of moderate-to-vigorous intensity physical activity each week and limit the time spent sitting. The recommended levels of physical activity are safely attainable even at home. Using a combination of both formal and informal activities, 150 min can be reached during the week with frequent sessions of physical activity spread throughout the day. Sedentary behaviour can be further reduced by breaking up prolonged sitting with short active breaks. In summary, this infographic offers as an evidence-based tool for public health officials, clinicians, educators and policymakers to communicate the importance of engaging in physical activity during the COVID-19 pandemic.

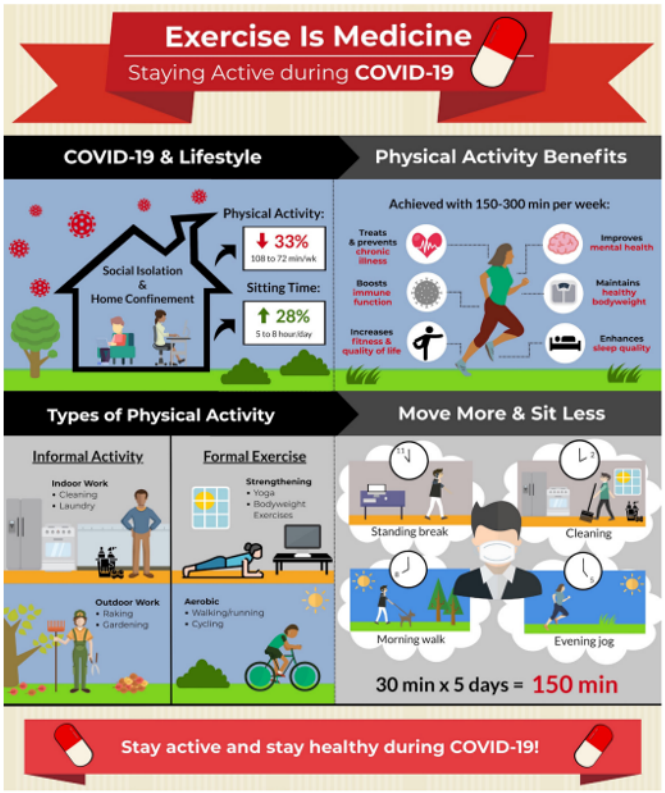

Figure 1 Infographic.

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Correction notice This article has been corrected since it published Online First. The figure has been replaced and the acknowledgement statement added.

Acknowledgements Exercise is Medicine is a registered trademark of the American College of Sports Medicine.

Contributors All authors (IJW, TAD and SJE) conceptualised the overall idea for the infographic manuscript. IJW developed the infographic and TAD contributed. All authors approved the final version of the infographic image. IJW and SJE drafted the

manuscript and TAD provided critical feedback. All authors approved the final version of the manuscript.

Funding This research was supported by an award from the Midwest Regional Chapter of the American College of Sports Medicine.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

To cite Wedig IJ, Duelge TA, Elmer SJ. *Br J Sports Med* 2021;**55**:346–347.

Accepted 12 October 2020
Published Online First 23 October 2020

Br J Sports Med 2021;**55**:346–347.
doi:10.1136/bjsports-2020-103282

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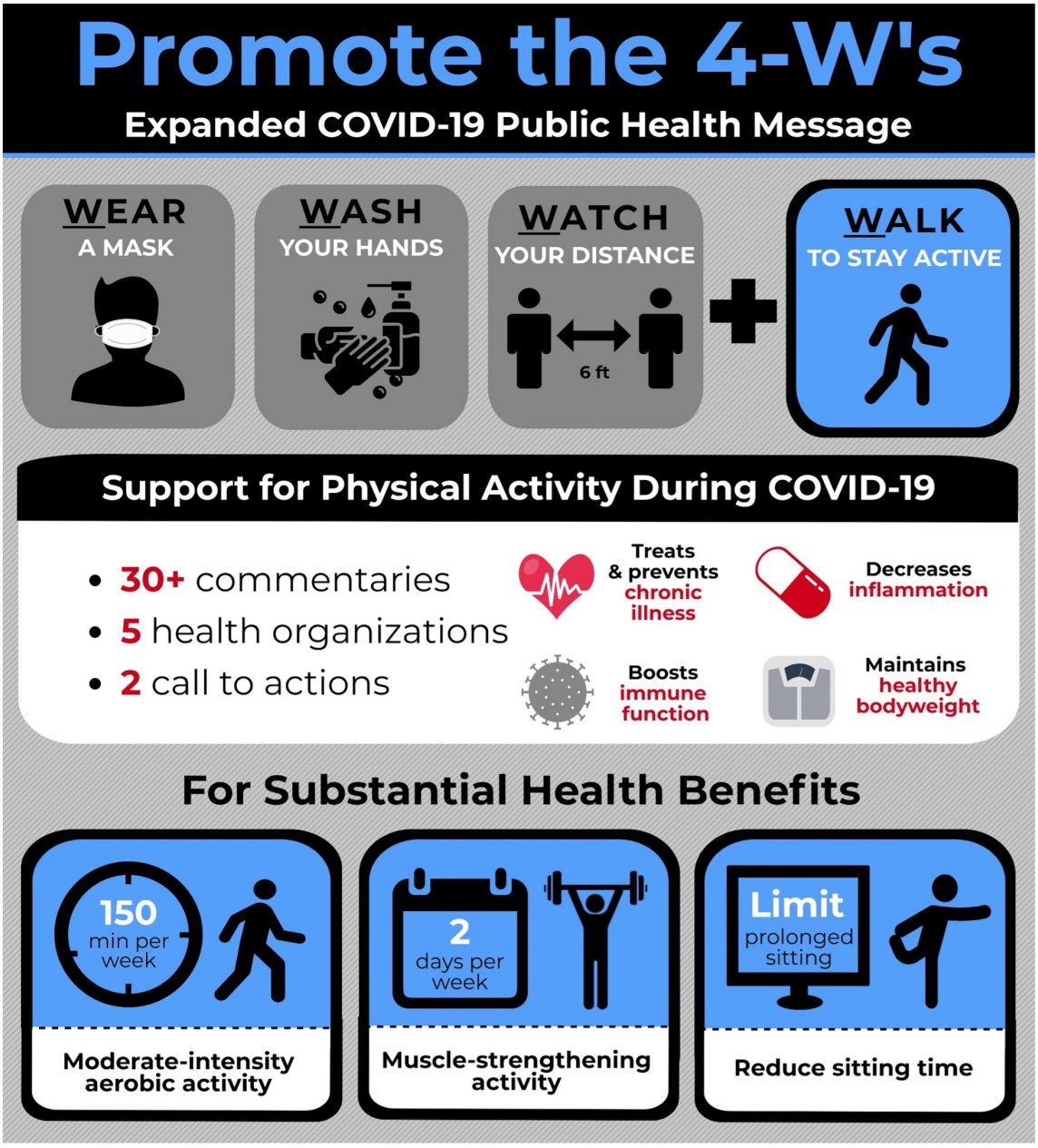
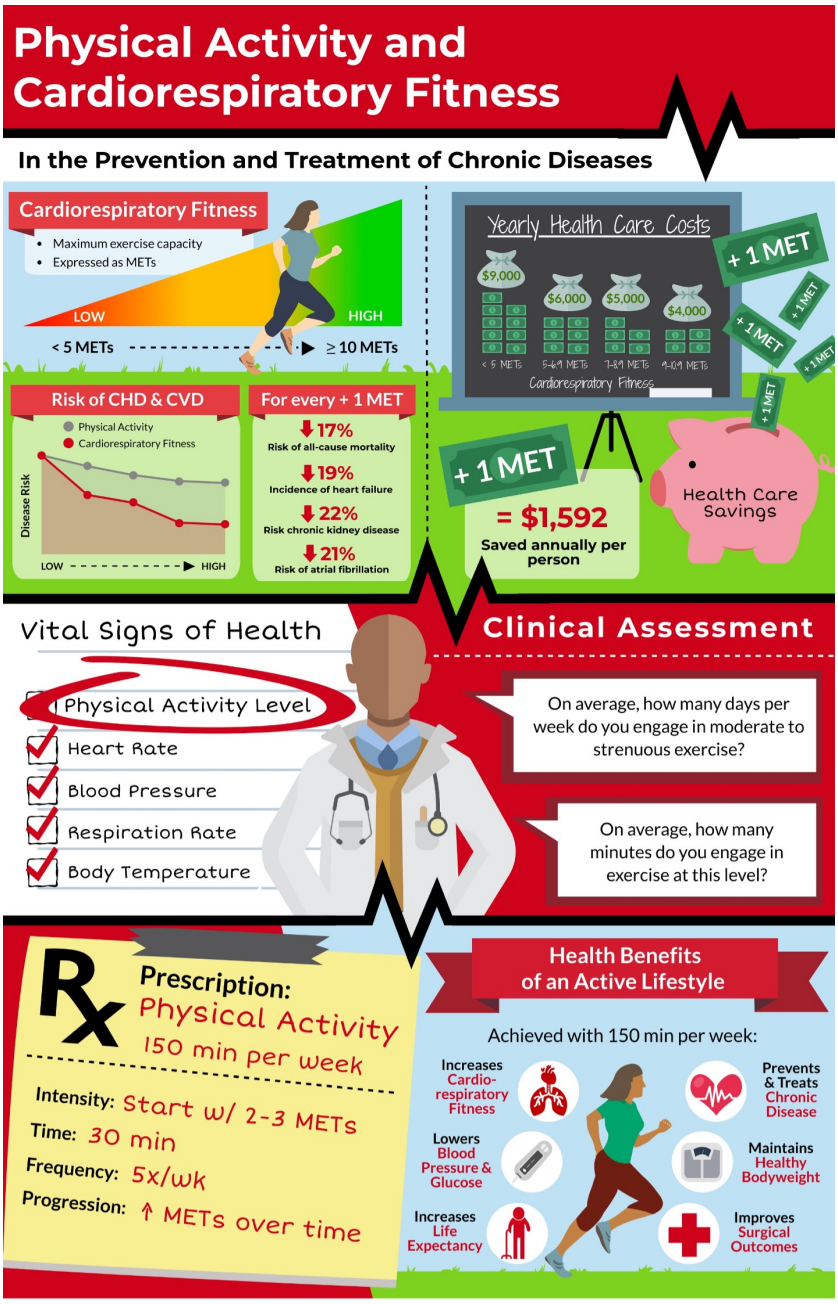
*Infographic also published in book titled *Home-based Cardiac Rehabilitation: Helping Patients Help Themselves* by Barry Franklin and Weimo Zhu

C Infographic. Promote the 4W's



*Infographic published in *Baylor University Medical Center Proceedings*

D Infographic. Physical Activity and Cardiorespiratory Fitness In the Prevention and Treatment of Chronic Disease



*Infographic published in *Mayo Clinic Proceedings* and *Kinesiology Review*

E Presentations & Awards

E.1 Presentations

TITLE	CONFERENCE	DATE	TYPE
Development and Validation Of a Prediction Equation for Practical Implementation of Blood Flow Restriction Exercise	National ACSM Meeting	5/31/2023	Oral
Predictors of Arterial Occlusion Pressure in the Lower-Body Across Commonly Used Cuff Widths	American Physiology Summit	4/23/2023	Poster
Role of Physical Activity During the COVID-19 Pandemic: Lessons Learned and Future Considerations	Midwest ACSM Meeting	10/20/2022	Oral
A Prediction Equation for Blood Flow Restriction Exercise That Accounts for Cuff Width*	Michigan Physiological Society Annual Meeting	6/17/2022	Oral
A Prediction Equation for Blood Flow Restriction Exercise That Accounts for Cuff Width	National ACSM Meeting	6/4/2022	Poster
A Practical Application of Blood Flow Restriction Exercise	Experimental Biology	4/3/2022	Poster
Blood Flow Restriction Exercise: Moving Evidence into Practice	Midwest ACSM Meeting	9/5/2021	Oral
Exercise is Medicine On Campus at Michigan Tech: Promoting Physical Activity during the COVID-19 Pandemic*	Michigan Physiological Society Annual Meeting	6/24/2021	Oral
Collaborative Group Testing Implemented Online using Zoom*	Experimental Biology	4/3/2021	Poster

Arm Cranking with Blood Flow Restriction: A Potential Exercise for use in Space?	Michigan Space Grant Consortium Fall Conference	10/17/2020	Oral
Exercise Is Medicine: Staying Active during the COVID-19 Pandemic	Michigan Physiological Society Annual Meeting	6/27/2020	Oral

*Indicates award winning presentations

E.2 Awards

Outstanding Scholarship Award (February 22, 2023)
Presented by Michigan Technological University Graduate School

1st Place Oral Presentation- Graduate Research Colloquium (March 27, 2022) Presented by Michigan Technological University Graduate Student Government

***Top Presenter- Michigan Physiological Society Annual Meeting** (July 1, 2021) Presented by Michigan Physiological Society

***Research Recognition Award- Teaching of Physiology Section** (April 13, 2021) Presented by American Physiological Society

***3rd Place Oral Presentation- Graduate Research Colloquium** (April 3, 2021) Presented by Michigan Technological University Graduate Student Government

Outstanding Graduate Student Teaching Award (May 19, 2020)
Presented by Michigan Technological University Graduate School

F IRB Documents

F.1 Study 3

Practical Application of Blood Flow Restriction Exercise

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BACKGROUND/SCIENTIFIC RATIONALE

Exercise with blood flow restriction (BFR) is emerging as an effective training option to increase muscle size and strength, in healthy, clinical, and athletic populations. This modality involves exercising with a pressurized cuff applied to the upper portion of a limb, which serves to partially limit blood flow going to the working muscles (arterial) and returning to the heart (venous) (9). The advantages that BFR exercise has over traditional training are: 1) increases in muscle size and strength are elicited using at low training loads (4), 2) these adaptations occur faster with blood flow restriction, and 3) increases in muscle size and strength can be stimulated using both resistance (i.e., lifting light weights) and aerobic (i.e., walking) exercise (10). Accordingly, BFR offers an alternative option for improving muscle size and strength in populations such as the elderly, those with orthopedic limitations, and various diseased states, to whom higher intensity exercise may be difficult or contraindicated. Recently, BFR was endorsed by the American Physical Therapy Association and is now being used in clinical settings. Additionally, BFR is used in professional and collegiate athletics. However, the need for specialized equipment in order to perform BFR presents a major barrier to its accessibility (8).

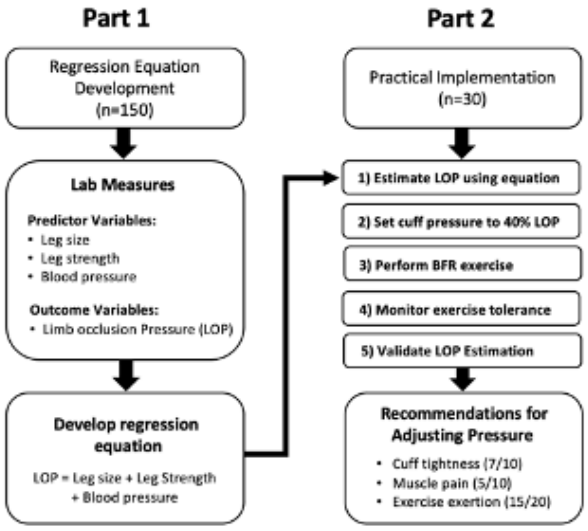
In order to standardize cuff pressures during BFR exercise, current guidelines (see reference 7, Tables 1-3 of that paper) recommend that pressures be selected based upon limb occlusion pressure or the amount of pressure required to occlude arterial blood flow to a limb. This pressure depends not only on unique characteristics of the individual, such as limb size and blood pressure, but also on the type of cuff being used (i.e., cuff width, shape, material) (5). Thus, when prescribing BFR exercise, limb occlusion pressure should be assessed on an individual basis using the same cuff that will be applied during exercise. Once limb occlusion pressure is obtained, exercise is performed at a percentage of that pressure (e.g., 40-80% of limb occlusion pressure) in order to minimize the risk of adverse events (e.g., venous thromboembolism) while maximizing the training stimulus. While several devices for measuring limb occlusion pressure and implementing BFR have been made commercially available, high costs (e.g., $1,000-$30,000) limit their use. Developing more cost-effective alternatives could help to make this training modality more widely available to clinicians, coaches, and athletes.

Previously, our laboratory group has implemented lower body BFR exercise training using an 18 cm wide thigh blood pressure cuff applied to the upper thigh (2,3). This inexpensive pneumatic cuff (e.g., $20 from Amazon) offers a practical way to implement BFR that allows for the selection of individualized cuff pressures. However, prescribing the appropriate pressure to use during exercise still requires expensive equipment such as Doppler Ultrasound in order to obtain limb occlusion pressure measurements. Designing a model that could predict limb occlusion pressure without the need for direct measurement could further reduce cost and provide a convenient method for practitioners to utilize this therapy. Loenneke and colleagues (5) have shown that a

significant amount of variance in limb occlusion pressure can be explained by two factors: 1) limb size and 2) brachial systolic blood pressure. This suggests that these easily obtained measures could serve as useful predictors in estimating limb occlusion pressure and prescribing safe and effective exercising cuff pressures. It is important to note that these authors used an expensive research grade BFR cuff which limits its application for practitioners who do not have access to such equipment. Therefore, an important next step is to replicate this study by using a BFR cuff that is more appropriate for use by actual practitioners.

OBJECTIVES/AIMS

The purpose of this project is to establish a practical method for implementing BFR. For Part 1, we will create a regression equation using leg size, leg strength, and blood pressure to estimate limb occlusion pressure when applying a standard $20 thigh blood pressure cuff. For Part 2, we will develop a protocol to implement BFR using this thigh blood pressure cuff. Specifically, we will 1) use the equation from Part 1 to initially estimate the limb occlusion pressure, 2) set the BFR cuff pressure using evidence-based guidelines, 3) perform several initial BFR exercise sessions, 4) monitor BFR exercise tolerance, and 5) validate the estimated limb occlusion pressure. Collectively, Part 1 and Part 2 will help us develop a step by step guide for implementing BFR using low-cost equipment. Importantly, this practical guide will make BFR accessible to clinicians, coaches, and athletes, expanding their toolkit and enhancing rehabilitation and sport training.



STUDY DESIGN

I. *Target Population and Inclusion/Exclusion Criteria*

Part 1

Participants will be excluded from the proposed study if they:

- Are not between the ages of 18-44

- Have a BMI ≥ 30
- Use products that contain tobacco
- Have diabetes
- Have any cardiopulmonary disorders, including but not limited to hypertension
- Have had a recent lower-body injury or surgery
- Have had a history of ACL injury or surgery
- Any implanted devices such as but not limited to a pacemaker or pain pump
- Any skin or dermatological disorders
- Any neurological disorders
- Unable to refrain from vigorous exercise during the study period (i.e., no additional exercises performed at a pace where only a few words are sustainable)

Part 2
Participants will be excluded from the proposed study if they:

- Are not between the ages of 18-44
- Have a BMI ≥ 30
- Use products that contain tobacco
- Have diabetes
- Have any cardiopulmonary disorders, including but not limited to hypertension
- Have had a recent lower-body injury or surgery
- Have had a history of ACL injury or surgery
- Any implanted devices such as but not limited to a pacemaker or pain pump
- Any skin or dermatological disorders
- Any neurological disorders
- Unable to refrain from vigorous exercise during the study period (i.e., no additional exercises performed at a pace where only a few words are sustainable)
- Blood flow restriction screening score ≥ 5 points

II. *Participant Enrollment*

We intend to recruit 150 participants for Part 1 of the study and 30 participants for Part 2. Thus, a total of 180 participants will be recruited.

III. *Recruitment and Screening Procedures*

Participants will be recruited from the Houghton/Hancock area by word of mouth, email (Appendix A), and flyer (Appendix B). Participants will be informed as to the nature of the study and associated risks (described below). To confirm that the participants meet the inclusion/exclusion criteria, all participants will: 1) fill out an information sheet (Appendix C), 2) answer a series of questions associated with the blood flow restriction screening tool (Appendix D), and 3) complete the PAR-Q (Appendix E) prior to coming to the laboratory for an initial orientation meeting and officially consenting to participate in the study. Additionally, participants will be asked if they have any specific lower-body injuries that would influence their exercise performance and will be excluded if they do have such an injury.

IV. *Informed Consent Process and Documentation*

During the orientation session, the participant will meet privately with the principle investigator's office in the Exercise Physiology Laboratory. Written informed consent will be received from the participant during their orientation visit, prior to beginning any of the study protocols. Participants will be informed as to the nature of the study and associated risks (described below). Following this explanation, individuals will be informed that participation is completely voluntary and that

they are free to participate or not as they choose. They will also be informed that they are free to withdraw at any time during the study. The principal investigators will take all the time necessary to explain these procedures. Individuals will also be given adequate time to read the consent form and ask questions prior to giving written consent. In short, it will be clearly explained to each individual that participation is voluntary and confidentiality will be maintained throughout the study. Upon receiving written consent, the participant will be enrolled in the study. If the participant does not consent or is found to be ineligible to enroll in the study, then their information will be destroyed.

V. *Data Collection Procedures*

All participants in Part 1 of the study will be asked to attend one visit to the Exercise Physiology Laboratory that will last approximately 2 hours. Listed below for Part 1 are the laboratory measures that will be assessed during this visit. Participants will be asked to avoid caffeine on the day of this visit and refrain from eating at least 2-hours prior (note that these are not exclusion criteria). The participants in Part 2 of the study will be asked to attend eight total laboratory visits. Two of these visits will consist of collecting the same laboratory measures outlined in Part 1. Additionally, they will be asked to complete six BFR exercise sessions, 3 visits/week for 2 weeks, each lasting 30 minutes. The exercise protocol that will be completed during these visits is listed below for Part 2. Note that, participants will be required to refrain from vigorous exercise (i.e., an exercise intensity where only a few words are sustainable) during the study period (i.e., for Part 1 - one day; for Part 2 - 10-14 days).

Part 1 - Regression Equation Development

Laboratory Measures

For Part 1 of the study, participants will report to the laboratory where leg size, leg strength, blood pressure, and limb occlusion pressure will be measured. Collectively, leg size, leg strength, and blood pressure will serve as predictor variables and limb occlusion pressure will serve as the outcome variable for the regression equation.

Predictor Variables

- *Leg Size:* The circumference of the participants right thigh will be measured at four different locations including,1) the proximal border of the patella, 2) the gluteal furrow, 3) 50% of the distance from the inguinal crease to the proximal border of the patella, and 4) 33% of the distance from the inguinal crease to the proximal border of the patella. Additionally, the following leg lengths will be measured, 1) floor to the proximal border of the patella, 2) floor to 50% of the distance from the inguinal crease to the proximal border of the patella, and 3) floor to gluteal furrow. Anatomical locations of these measurements will be marked with a non-toxic and skin safe washable marker and measurements will be taken using a tap measure. Skinfold thickness of the anterior thigh will be measured according to American College of Sports Medicine (ACSM) guidelines. All measurements will be kept for analysis and used to calculate a lean thigh volume (i.e., leg size) for each participant.

  A B-mode ultrasound (GE Logiq e BT12, GE Health Care, Chicago, IL, USA) will be used to measure the size of the participants rectus femoris and vastus lateralis muscles. The participant will be positioned supine with their knee flexed to 10 degrees. A 12 MHz scanning head will be placed on the anterior thigh without depressing the skin. The scanning probe will be placed on the anterior thigh at 66% of the distance from the anterior superior iliac spine to the proximal patella. Muscle thickness for each muscle will be measured as the distance between the superficial and deep aponeurosis at the widest distance. The ultrasound probe will be wiped clean of any residual ultrasound gel and then

disinfected with Protex disinfecting wipes as recommended by the manufacturer. Protex disinfectant wipes are a one-step disinfectant that effectively kills a wide range of bacteria, viruses, and fungi (http://www.parkerlabs.com/protex-ultra.asp). The investigators will also practice proper hand hygiene before and after each examination.

- *Leg Strength*: Each participant will be set-up on Biodex dynamometer (Biodex 4, Biodex Medical Systems, NY, USA) machine. They will be comfortably seated in the upright position in the machine's chair with their legs comfortably dangling. Their right leg will be secured to the footrest of the device. Participants will be asked to perform three brief (5 seconds) maximal strength efforts attempting to straighten their knee with their leg strapped to a padded device which will measure their strength. Shoulder and abdominal straps will be used to secure participants to the chair. Prior to the leg strength procedure, the participant will complete a 5 min general warm-up (walking, leg swings, dynamic hamstring stretching, dynamic quadriceps stretching) along with 3 submaximal knee extension practice movements (at 50, 75, 90% of maximal effort, respectively). Additionally, the participant will complete a 5 min cool down (walking, leg swings, static hamstring stretching, static quadriceps stretching).

- *Blood Pressure:* After 10 minutes of resting quietly in a supine position, the participant's systolic and diastolic blood pressure will be measured in the right arm and right leg using an appropriately sized automatic blood pressure cuff (Omron, Model HEM-907XL). Blood pressure in both limbs will be measured in duplicate and values will be averaged for analysis.

Outcome Variable

- *Limb Occlusion Pressure:* Occlusion pressure will be assessed by placing an 18 cm wide nylon blood pressure cuff (Thigh Size Aneroid Sphygmomanometer, Elite Medical Instruments, Fullerton, CA, USA) around the most proximal portion of the right leg. The investigator will inflate the occlusion cuff starting at 100 mmHg and increase the pressure until no blood flow can be detected at the ankle (posterior tibial artery) using visual and auditory signals from a Doppler Ultrasound. The investigator will then slowly deflate the occlusion cuff until blood flow resumes. The cuff will be removed and disinfected using Protex disinfecting wipes between participants. The investigators will also practice proper hand hygiene before and after each examination.

Regression Equation

Of the measured predictor variables (leg size, leg strength, blood pressure) we will assess which combination help to explain the most variation in limb occlusion pressure. This combination of predictors will be integrated into a mathematical equation that will be used to estimate an individual's limb occlusion pressure based on their unique measurements. Referencing the literature (5), we anticipate that leg size and blood pressure will explain ~60% of the variability in limb occlusion pressure. Leg strength may help to explain some additional variability. Importantly, because all of the variation in limb occlusion pressure cannot be accounted for, the estimated limb occlusion pressure derived from the equation will only serve a starting point for BFR use. Part 2 below will build upon the equation by establishing practical recommendations for further adjusting cuff pressure after initial estimation.

Part 2 - Practical Implementation

Overview

For Part 2 of the study, a different group of participants will report to the laboratory. We will perform the same set of laboratory measures completed in Part 1 and use those measures to implement BFR exercise. The steps below outline the procedures for applying BFR exercise.

1) *Estimate LOP using equation:* During their first visit, participants leg size, leg strength, and blood pressure will be assessed using the same methods outlined in Part 1. Next, using the regression equation from Part 1, each participants leg size, leg strength, and blood pressure values will be used to estimate their limb occlusion pressure when applying an 18 cm thigh blood pressure cuff. Preliminary data from our laboratory (2,3) indicates that when using this type of cuff, limb occlusion pressure ranges from 160-214 mmHg. Based on this data, we will use a conservative upper end cut-off of 160 mmHg for all participants estimated limb occlusion pressure.

2) *Set cuff pressure to 40% LOP:* The cuff pressure will be set to 40% of the individual's estimated limb occlusion pressure. This pressure corresponds to the lower end of the recommended range for exercising cuff pressures, 40-80% of limb occlusion pressure (7). This is the initial cuff pressure that will used during the first BFR exercise session.

3) *Perform BFR exercise:* The participant will complete six BFR exercise sessions spread across a 2-week time frame. During each session, they will start with a 5 min warm-up (walking, leg swings, dynamic hamstring stretching, dynamic quadriceps stretching) and then perform 1 set of 30 repetitions of knee extension and bodyweight half-squats. Subsequently, they will perform three BFR exercises; 1) knee extension, 2) bodyweight half-squats, and 3) walking. Once the blood pressure cuff is applied to their upper thigh and the pressure is set, the participant will perform 3 sets of 30 repetitions of knee extension using an elastic band or light weight for resistance. Next, they will perform 3 sets of 30 repetitions of bodyweight half squats. Lastly, they will perform 3 intervals of walking for 2 minutes at a preferred walking speed. For each exercise, 1 minute of rest will be provided between sets and 2 minutes of rest between exercises. The exercise session will conclude with a 5 min cool down (walking, leg swings, hamstring stretching, quadriceps stretching).

4) *Monitor BFR exercise tolerance:* As stated above, participants will be asked to refrain from exercise during the study period (i.e., 10-14 days). Throughout the exercise sessions the participant will be asked to rate the perceived tightness of the cuff at rest (0-10; 0= no tightness/pressure, 10= intense tightness/pressure), pain in the working muscle during exercise (0-10; 0=no pain, 10= worst pain possible), and level of exertion during exercise (6-20; 6=no exertion at all, 20=maximal exertion). Cuff pressures will be adjusted appropriately throughout the session to keep the cuff at a perceived tightness of 7 out of 10 (moderate pressure with no pain at cuff location), pain within the working musculature within the 4-7 range, and exertion during exercise within 13-15. Note, that some discomfort and pain/fatigue in the muscle is expected during BFR exercise. Adjusting the cuff pressure by 5-10 mmHg can alter the discomfort level considerably. Therefore, during exercise we will make minor adjustments to the BFR cuff pressure if needed. Joint pain and muscle soreness will be assessed at the beginning of each exercise session to assess the participants cumulative tolerance to the BFR exercise sessions. If joint pain or muscle soreness is excessive (i.e., greater than a 5, 0-10 scale) then the exercise session will not be performed that day and an extra 1-2 days of rest will be provided. If joint pain or muscle soreness persist then the exercise sessions will be discontinued. Importantly, we have used a similar BFR exercise monitoring protocol with adults recovering from anterior cruciate ligament reconstruction and total knee arthroplasty and these participants

tolerated the BFR exercise progression very well. Thus, we are confident we can implement the proposed protocol with younger to middle-aged adults safely.

5) *Validate LOP Estimation*: After completing all the exercise sessions, each participant will be asked to attend one last visit to the laboratory. During this visit we will assess the participants limb occlusion pressure using the same procedures outlined in Part 1. This will help to validate the estimated cuff pressures that were used during the exercise sessions. Ideally, the estimated limb occlusion pressure and the actual limb occlusion pressure values will be very close. The visit should last no longer than 30 minutes.

Recommendations

Part 2 will help to offer a step-by-step guide for the practical implementation of BFR exercise using a blood pressure cuff. Specifically, the guide will help practitioners in setting and adjust exercising cuff pressures based on the participants perceptual measures of exercise tolerance. Importantly, this practical guide will make BFR more accessible to clinicians, coaches, and athletes, expanding their toolkit and enhancing quality of rehabilitation and sport training.

VI. *Study Timelines*

The time commitment for each participant in Part 1 of the study (orientation session, one laboratory visit) will be 2.5 hours. Participants in Part 2 of the study will be asked to attend the orientation session and eight laboratory visits, a total time commitment of approximately 5 hours over a two-week period. For Part 1 of the study we plan to collect data on 5-10 participants per week. Once 80% of our total participant sample has completed Part 1, we will begin Part 2 of the study.

VII. *Study Location*

Part 1 of the study will take place in the Exercise Physiology Lab (SDC 121B) and Human Biomechanics Lab (SDC 121A) located in the Student Development Complex. Anthropometric, muscle thickness, and arterial limb occlusion measures will be performed in the Exercise Physiology Lab. Isometric knee extension strength will be measured in the Human Biomechanics Lab. Part 2 of the study will take place in the Exercise Physiology Lab and Multipurpose Room of the SDC.

VIII. *Participant Compensation*

The participants in this study will not be compensated for their participation in this study.

IX. *Study Resources*

The Exercise Physiology Laboratory, Biomechanics Laboratory, and multipurpose room of the SDC are each equipped with a first aid kit and AED. Additionally, investigators are first aid/CPR/AED certified. Participants will be asked how they are feeling throughout exercise protocols. If they give any indication of abnormal stress or injury, the protocol will be stopped. In the event of any incident, we will call we will call 911 and then MTU EMS. Isaac Wedig is a doctoral student in the Department of Kinesiology and Integrative Physiology and a Certified Strength and Conditioning Specialist (CSCS) through the National Strength and Conditioning Association (NSCA). He will administer all laboratory assessments and exercise sessions. Dr. Elmer is an Associate Professor in the Department of Kinesiology and Integrative Physiology at Michigan Tech University. He has worked on collaborative projects with faculty from the Departments of Kinesiology, Physical Therapy, Medicine, Mechanical Engineering, and Bioengineering at the Michigan Tech University, University of Maine, and University of Utah. Dr. Elmer has trained Mr. Wedig and will also have direct contact with all participants. Note that, Dr. Elmer's laboratory has

administered BFR exercise with healthy adults and adults recovering ACL ligament and total knee join replacement surgeries. To date, this research has resulted in several peer-reviewed papers published in applied physiology, sports medicine, and physical therapy journals. In addition, his BFR team has included a local physical therapist, Lydia Lytle, DPT, PT.

EXPECTED RISKS/BENEFITS

I. *Potential Risks*

Part 1 – Regression Equation Development

Leg Size: Ultrasonography used to measure leg size and muscle thickness is used in both research and clinical settings with individuals with injury, chronic disease, and advanced age. Thus, there is minimal risk involved. Participants may experience some redness on their skin resulting from the preparation of the skin and the contact of the ultrasound head and gel. However, this is only temporary and should resolve quickly. The participant will be instructed to alert the researchers if at any time they are feeling discomfort and would like to discontinue their participation. To prevent cross contamination, these experimental procedures will not be performed on any participant with known or suspected infection in the body region to be tested, and the ultrasound probe will be cleaned after each use and disinfected after each participant has completed the experimental procedure (Protex disinfecting wipes). These measures have been previously approved by the Michigan Technological University Institutional Review Board (IRB #980620-4). Note that, to ensure that the participant is comfortable with the leg size procedure, the researcher will ask the participant for permission to identify key bony landmarks near the knee and hip (i.e., "Are you comfortable if I palpate the side of your knee and hip to identify key bony landmarks?") and also have a second researcher present in the laboratory.

Leg Strength: Muscle strength will be assessed using a static movement. Resistance exercise, in general, is recommended by the American College of Sports Medicine and National Strength and Conditioning Association as a safe and effective method to enhance musculoskeletal health. To minimize risk such as muscular strains, an appropriate warm-up and cool-down will always be utilized. Specifically, the warm-up will include a 5 min general warm-up (walking, leg swings, dynamic hamstring stretching, dynamic quadriceps stretching) along with 3 submaximal knee extension practice movements. The cool down will also be 5 min (walking, leg swings, static hamstring stretching, static quadriceps stretching). Muscle strength testing has been previously approved by the Michigan Technological University Institutional Review Board (IRB #980620-4).

Blood Pressure: This assessment does not have any major associated risks; however, the blood pressure cuff may be uncomfortable but only lasts a few seconds. The blood pressure cuff will be cleaned after each use and disinfected after each participant has completed the experimental procedure (Protex disinfecting wipes).

Limb Occlusion Pressure: Doppler Ultrasonography is used to asses blood flow research and in clinical settings with individuals with injury, chronic disease, and advanced age. Thus, there is minimal risk involved. Participants may experience some redness on their skin resulting from the preparation of the skin and the contact of the ultrasound head and gel. However, this is only temporary and should resolve quickly. The participant will be instructed to alert the researchers if at any time they are feeling discomfort and would like to discontinue their participation. An inflatable occlusion cuff will be inflated until blood flow is no longer detected, this procedure is similar to measuring blood pressure. This test does not have any associated risks; however, the cuff may be uncomfortable but only lasts a few seconds. To prevent cross contamination, these experimental procedures will not be performed on any participant with known or suspected

infection in the body region to be tested, and the ultrasound probe will be cleaned after each use and disinfected after each participant has completed the experimental procedure (Protex disinfecting wipes). The limb occlusion procedures described here have been previously approved by the Michigan Technological University Institutional Review Board (IRB #1024563-1).

Part 2 - Practical Implementation
Leg Size: The risks for this procedure are the same as those described in Part 1.

Leg Strength: The risks for this procedure are the same as those described in Part 1.

Blood Pressure: The risks for this procedure are the same as those described in Part 1.

Blood Flow Restriction Exercise: Blood flow restricted exercise has been widely used in Japan for decades and is now used in the United States. It also endorsed for use in clinical settings by the American Physical Therapy Association. This form of training involves lifting light weights (and sometimes only body weight) while partially occluding blow flow returning from the working muscles, has been successfully utilized with healthy active individuals, individuals recovering from ACL injury, and older adults (1). In a national Japanese survey of facilities using blood flow restricted exercise, in which over 13,000 individuals engaged, in training various modes of blood flow restricted exercise (walking, cycling, weight training), the most common side effects were bruising at the site of the tourniquet cuff (incidence=13.1%) and temporary numbness (1.3%). More serious side effects were rare and included: venous thrombosis (0.055%), cerebral infarction (0.008%), rhabdomyolysis (0.008%) and pulmonary embolism (0.008%) (6). Although these events are extremely rare, it should be noted that determining the relative safety of blood flow restriction requires a detailed study of several potential outcomes, and we acknowledge that unforeseen risks do exist. To minimize these risks even further we will limit the training to approximately 15 minutes and the pressure in the cuff will be released immediately upon completion of the exercise

As outlined in Appendix D, we have included an additional screen tool to offer a more robust assessment of risks specific to limb occlusion pressure measures/blood flow restriction exercise for all participants including both men and women (11). Based on this screening tool, points are assigned given risk factors such as age, sex, oral contraceptive use, history of deep vein thrombosis, ect. If a potential participant accumulates 5 or more risk assessment points, they will be excluded from participating in this study.

Further, our laboratory has consulted with Dr. Summer Cook, Associate Professor in the Department of Kinesiology at the University of New Hampshire and Dr. John McDaniel, Associate Professor in the School of Health Sciences at Kent State University, regarding the protocols and safety precautions for utilizing blood flow restricted exercise. Dr. Cook has received funding from the National Institutes of Health to use blood flow restricted exercise with frail elderly individuals. She also serves on her University's IRB review board. Dr. McDaniel has received funding from the VA Medical System and performed blood flow restriction with individuals living with spinal cord injury. Dr. Elmer has discussed the use of blood flow restricted exercise with Dr. Cook and Dr. McDaniel and will consult with them as necessary. Exercises with BFR have been previously approved by the Michigan Technological University Institutional Review Board (IRB #1024563-1, #980620-3, #1082133-2).

Limb Occlusion Pressure: The risks for this procedure are the same as those described in Part 1.

Laboratory Space and Environment: There are no known risks for conducting the research protocol in the laboratory environment.

II. *Benefits*

We cannot promise any direct benefit for taking part in this study. However, the results may help to make blood flow restriction exercise more accessible to clinicians and strength and conditioning coaches, potentially translating this useful modality into practice and improving rehabilitation and sport training.

III. *Privacy/Confidentiality of Participants*

Privacy of the participant will be kept throughout the study by: 1) conducting the orientation session in a private office, 2) ensuring that only Dr. Elmer and Mr. Wedig are present in the laboratory during data collection, and 3) keeping the laboratory door closed at all times. We will treat participants' identity with professional standards of confidentiality. The data from this study may be published, but the participants' identity will not be shown. Paper files with the participants' information and corresponding six-digit code will be stored separately from research data in a locked file cabinet in Dr. Elmer's office (Student Development Complex 121B). This master file will be shredded and destroyed by Dr. Elmer and Mr. Wedig. All participant research data will be kept on MTU servers and only accessible by Dr. Elmer and Mr. Wedig.

IV. *Unanticipated Problems/Adverse Events*

Any unanticipated problems or adverse events will be reported to the MTU-IRB and within 7 calendar days.

V. *Participant Complaints*

If there are participant complaints these will be discussed among the research team. The team will discuss how the complaint/potential issue could affect all of the participants in the study. If a change to the protocol is required an IRB amendment will be made accordingly.

STUDY DATA

I. *Data Management Procedures and Confidentiality*

The data from this study may be published, but the participants' identity will not be shown. All data will be maintained for three years after this study is completed. These files will then be shredded and destroyed. Further, electronic data records will be stored on an MTU password protected computer in the Exercise Physiology Laboratory. Only the Dr. Elmer and Mr. Wedig will have access to these files. The Michigan Technological University Institutional Review Board (IRB) will have the right to inspect both the research data collected and experimental records.

II. *Data Analysis/Statistical Considerations*

Part 1: Hierarchal linear regression will be used to determine which variables predict arterial occlusion pressure. Given a power of 0.8 (ß = 0.20) and a two-tailed significance level (α) of 0.05, 100 participants will provide an adequate sample to detect a medium effect size (f^2) of 0.15 with six predictor variables. The best predictors of AOP that are identified will then be used to develop a prediction equation using least absolute shrinkage and selection operator (LASSO) regression. Based on preliminary data (n=88) utilizing a model with three predictor variables, an adjusted R^2 of 0.40, and a mean and standard deviation of 154 and 13 mmHg in the outcome variable AOP, a sample of 100 participants will minimize model optimism and provide precise estimates of model parameters. Thus, 100 individuals will provide an adequate sample to both determine predictors of AOP and develop a prediction equation. In order to externally validate the prediction equation, its performance will be assessed in a sample of participants that were not included in model

development. Testing the model in a sample of 50 individuals will provide precise estimates of the model's external performance. Collectively, to both develop and validate the prediction equation we require 150 participants. The resulting equation will be used to estimate arterial occlusion pressure for part two of the study.

Part 2: Based on preliminary data collected in our laboratory (2,3), we estimate that 30 participants will be sufficient to developing the protocol for implementing BFR exercise with a blood pressure cuff.

III. *Participant Withdrawal*

Participation is voluntary. The research team will answer any of the participants' questions about the study. Any significant findings which develop during the study which in our opinion may affect the participants' desire to participate will be provided as soon as possible. The participants are free to withdraw their consent and stop participating at any time and for any reason. This includes the right to withdraw during the actual test. The research team also has the right to withdraw a participant from the study if they: 1) are not adhering to the exercise program (i.e., unable to complete 3 exercise sessions per week) and 2) if they experience excessive discomfort, pain, and/or soreness with blood flow restriction exercise. When a participant withdraws/is withdrawn from their information and data will be archived and potentially analyzed.

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Appendix A: Email Language
Dear Community Members:

Researchers at Michigan Tech University are seeking individuals to participate in a research study. The purpose of this study is to establish a practical method for implementing a new type of exercise called "exercise with blood flow restriction". The benefit of using exercise with blood flow restriction is that it provides a high-intensity workout for muscles but without overtaxing the joints and helps to strengthen muscles faster than traditional exercise. Results from this study could allow clinicians to prescribe better and safer exercise intensities for patients recovering from an injury. It could also benefit coaches who train competitive athletes. We seek individuals 18-44 years to participate in this study.

You will be excluded from this study if you:

- Are not between the ages of 18-44
- Have a BMI ≥ 30
- Use products that contain tobacco
- Have diabetes
- Have any cardiopulmonary disorders, including but not limited to hypertension
- Have had a recent lower-body injury or surgery
- Have had a history of ACL injury or surgery
- Any implanted devices such as but not limited to a pacemaker or pain pump
- Any skin or dermatological disorders
- Any neurological disorders
- Unable to refrain from vigorous exercise during the study period (i.e., no additional exercises performed at a pace where only a few words are sustainable)
- Blood flow restriction screening score ≥ 5 points

Volunteer participants will visit our laboratory in the Student Development Complex at Michigan Technological University. If you are interested in participating please contact Isaac Wedig by email or phone for more information.

Sincerely,

Isaac Wedig, MS
Doctoral Student
Department of Kinesiology and Integrative Physiology
Michigan Tech University
ijwedig@mtu.edu
(906) 458-2778

Steven Elmer, PhD
Assistant Professor
Department of Kinesiology and Integrative Physiology
Michigan Tech University
sjelmer@mtu.edu
(906) 487-2324

Appendix B: Flyer

Appendix C: General Health History

Name: Phone number:

Occupation: E-mail:

Age: Height: Weight: BMI: Sex: M F

Do you use products that contain tobacco?	Yes	No
Have you ever fainted during exercise?	Yes	No
Have you ever had a stroke or heart attack?	Yes	No
Do you have high blood pressure or any heart issues?	Yes	No
Do you have asthma or exercise-induced asthma?	Yes	No
Do you have diabetes?	Yes	No
Do you have any implanted devices?	Yes	No
Do you have any neurological disorders?	Yes	No

1. Are you currently taking any medications? If yes, please describe your medications?

2. Have you had any lower-body ankle, knee, or hip injuries (surgeries, broken bones, etc.)? If yes, please describe your injury and state when the injury occurred.

3. Have you previously had an injury to your ACL ligament? If yes, please describe your ACL injury and state when the injury occurred.

4. If you stated yes to #2 or 3 above, does your injury prevent you from performing lower body exercise (e.g., brisk walking, lifting weights)?

5. How often do you exercise (days/week, duration, type of exercise)?

6. Do you perform any specific lower-body exercise (lifting weights, running)?

Appendix D: Blood Flow Restriction Screening Tool

Nakajima et al., 2011

5	History of deep vein thrombosis; Hereditary thrombotic tendency; Antiphospholipid antibody syndrome
4	Pregnant women
3	Varicose veins in legs; Prolonged immobility (unable to perform 8 hours of thromboprophylaxis rehabilitation); Atrial fibrillation or heart failure
2	60 years old; BMI > 30; Hyperlipidemia; Malignancy; Using lower limb tourniquet; Oral contraceptives or andrenocortical steroids; Quadriplegia: High hemoglobin levels
1	40-58 years old; women; BMI 25-30

Excluded from BFR training if score ≥ 5, Scores are additive in each category

Appendix E: Physical Activity Readiness Questionnaire (2020 PAR-Q+)
See attached

CONSENT TO PARTICIPATE IN RESEARCH

Part 1: Practical Application of Blood Flow Restriction Exercise

Principal Investigator: Isaac Wedig MS, CSCS (Doctoral Student)
Co-investigator: Steven Elmer PhD (Professor)
Department of Kinesiology and Integrative Physiology
Michigan Technological University
Houghton, MI 49931
Phone: (906) 487-2324
Email: ijwedig@mtu.edu & sjelmer@mtu.edu

INTRODUCTION

You are invited to participate in a research study being conducted by Mr. Isaac Wedig, a PhD student in the Department of Kinesiology and Integrative Physiology at Michigan Technological University. This study is being conducted as part of his dissertation. Professor Steven Elmer, a faculty member in the department, will be assisting and overseeing the study. Your participation is entirely voluntary. Please read the information below and ask questions about anything you do not understand, before deciding whether or not to participate.

You will be excluded from the proposed study if:

- Are not between the ages of 18-44
- Have a BMI ≥ 30
- Use products that contain tobacco
- Have diabetes
- Have any cardiopulmonary disorders, including but not limited to hypertension
- Have had a recent lower-body injury or surgery
- Have had a history of ACL injury or surgery
- Any implanted devices such as but not limited to a pacemaker or pain pump
- Any skin or dermatological disorders
- Any neurological disorders
- Unable to refrain from exercise during the study
- Unable to refrain from vigorous exercise prior to performing the research protocol (i.e., no exercises performed at a pace where only a few words are sustainable the day before the study)

If you do not meet any of the exclusion criteria listed above, you are eligible to participate in the study. A total of 150 participants will be recruited. There will be two visits to the laboratory, one for orientation and one where all research study activities (or protocols) will be conducted. The total time commitment to participate in the study is approximately 2.5 hours.

PURPOSE OF THE STUDY

The purpose of this study is to establish a practical and inexpensive method for implementing a new type of exercise called "exercise with blood flow restriction". This type of exercise consists of walking and lifting light weights while wearing an inflatable leg cuff (similar to a tourniquet) to limit blood going to and from the working muscles. The benefit of using exercise with blood flow restriction is that it provides a high-intensity workout for muscles but without overtaxing the joints and helps to strengthen muscles faster than traditional exercise. This is becoming a sought-after alternative for prescribing exercise for populations with exercise restrictions, such as the elderly,

Initials:

those with knee joint injurious, and various diseased states to whom higher intensity exercise may be difficult or dangerous.

One challenge with using exercise with blood flow restriction is that it requires very expensive equipment (for example $1,000). For this study, we will first measure your leg size, leg strength, and blood pressure. We will also identify the pressure that briefly stops the blood from moving in your leg, which is needed for using exercise with blood flow restriction. These measurements will help us develop a mathematical equation for performing exercise with blood flow restriction using a simple inexpensive leg blood pressure cuff (for example $20 from Amazon).

PROCEDURES / RISKS / DISCOMFORTS

If you volunteer to participate in this study, you will be asked to do the following things:

Orientation Session: You will need to attend a required orientation session prior to participating in this research study. During this visit, the procedures and equipment will be explained to you, and you will be able to ask questions about what you will do. Following orientation and upon receiving your written consent to participate, you will be enrolled in the study. If you choose not to participate or are found not eligible, all data obtained from you will be destroyed.

Laboratory Visit: For this study we will ask you to complete one laboratory visit. We will ask that you avoid caffeine and exercise on the day of this visit and refrain from eating at least 2-hours prior. During your laboratory visit we will perform the following assessments:

- *Leg Size*: The circumference around your right thigh will be measured at four different locations. The location for each measurement site will be marked with a non-toxic skin-safe washable marker and measured using a tape measure. On the same leg we will also measure several different leg lengths. Lastly, we will take a skinfold measurement on the front of your thigh. Using their index finger and thumb, the investigator will pinch an area of skin on the front of your thigh and use a caliper to measure the thickness of the pinched skin. This procedure may be uncomfortable but it will only last a few seconds. There is no associated risk, however, you may experience temporary redness on your skin at the pinch site, which should resolve quickly.

  We will also directly measure the size of two muscles that make up your upper thigh. You will be positioned comfortably on an examination table, and a small round-shaped ultrasound probe will be placed on your skin over two different sites of your thigh. Ultrasound machines are used in clinical settings and there is minimal risk involved. You may experience some redness on your skin resulting from the contact of the ultrasound probe and gel. However, this is only temporary and should resolve quickly. There is a risk of an allergic reaction (itching, redness, small raised bumps, and/or burning, on and near the area of contact). Symptoms are generally short-lived (few days to few weeks) and you should seek immediate medical attention in case of a severe reaction.

- *Leg Strength:* Prior to completing the leg strength test, you will perform a 5 min warm-up consisting of walking, leg swings, and light stretching. After this, you will be seated on a specialized laboratory weight lifting machine similar to something that you might use in the gym. Your right leg will be strapped to the lever arm of the device. You will be asked to push as hard as you can against the arm, attempting to straighten your knee, similar to a seated knee extension exercise that you might do the gym. During the test, the machine will provide resistance and measure the strength of your quadriceps muscles. These tests will require several brief maximal effort muscle contractions (5 seconds). During the

strength tests you will likely experience only minimal discomfort. There is, however, a risk of muscle strains, or other soft tissue injuries. To minimize the risk of injury with this exercise, you will start with at least practice tests at a submaximal effort and be instructed on how to perform the exercise with the proper technique. For these tests you may experience fatigue in your lower body muscles similar to lifting weights. At the end of this test you will perform a 5 min cool down consisting of walking, leg swings, and light stretching.

- *Blood Pressure*: After laying down comfortably on an examination table for 10-minutes, we will measure your blood pressure in both your arm and your leg. First, an automated blood pressure cuff will be placed on your arm. We will take two measurements with a 1-minute break between measurements. Each measure should take about 15-20 seconds. After collecting blood pressures on your arm, we will repeat the same procedure but with the blood pressure cuff applied to your upper thigh.

- *Limb Occlusion Pressure:* An inflatable blood pressure cuff will be placed around your upper thigh. The researcher will inflate the cuff until blood flow is no longer detected using ultrasound. The researcher will then immediately release the pressure in the cuff. This procedure is similar to having blood pressure taken. It is important to note that the cuff placed around your limb may be uncomfortable, but it will only last a few seconds. To prevent cross contamination, these procedures will not be performed on any participant with a known or suspected infection in the body region to be tested, and the ultrasound machine and occlusion cuff will be cleaned after each use and disinfected after each participant has completed the experimental procedure using disinfecting wipes.

To further minimize the risks, only healthy individuals 18-44 years of age will be recruited for this study. Furthermore, all safety precautions will be followed and the laboratory is equipped with a first aid kit and AED. You will be asked how you are feeling throughout the protocols. If you give any indication of abnormal stress or injury, the protocol will be stopped. In the event of any incident, we will call 911 and then MTU EMS.

If you are taking medications, it is your responsibility to consult with your physician regarding your participation in this study. Do not volunteer for this study if you have been instructed to abstain from this study by a physician. Any problems you experience throughout this study should be discussed immediately with your physician.

INJURY RESULTING FROM RISKS OR DISCOMFORTS

In the event of physical and/or mental injury resulting from participation in this research project, Michigan Technological University does not provide any medical, hospitalization or other insurance for participants in this research study, nor will Michigan Technological University provide any medical treatment or compensation for any injury sustained as a result of participation in this research study, except as required by law.

POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY

We cannot promise any direct benefit for taking part in this study. However, the results may help to make blood flow restriction exercise more accessible to clinicians and strength and conditioning coaches, potentially translating this useful modality into practice and improving rehabilitation and sport training practices.

Initials:

COMPENSATION
There will be no compensation for your participation in this research.

CONFIDENTIALITY
Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or as required by law. The data from this study may be published, but your identity will not be shown. All electronic records containing your information will be stored on password protected computers located in the Exercise Physiology Laboratory and coded using an alphanumeric combination (e.g. AA001). Paper files with your information and corresponding alphanumeric code will be stored separately from all research data and in a locked file cabinet in Dr. Elmer's office (Student Development Complex 121B). Only Dr. Elmer and Mr. Wedig will have access to these data. Federal IRB regulations require the retention of records for three years after the completion of the final report. The Michigan Technological University Institutional Review Board (IRB) reserves the right to inspect both the research data collected and your experimental records. Finally, the de-identified data collected from you in this study could be used be used for future exercise physiology research studies or distributed to another investigator in Dr. Elmer's research laboratory for future research studies without additional informed consent from you.

PARTICIPATION AND WITHDRAWAL
You can choose whether or not to be in this study. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind or loss of benefits to which you are otherwise entitled. You may also refuse to answer any questions you do not want to answer. The investigator may withdraw you from this research if circumstances arise which warrant doing so. These circumstances include: injury leading to an inability to complete testing, adverse reactions to testing such as dizziness, confusion, increased chest pain, or shortness of breath. If you withdraw or are withdrawn by investigators, any data obtained will be archived and potentially analyzed.

IDENTIFICATION OF INVESTIGATORS
If you have any questions or concerns about this research, please contact:

- Isaac Wedig, MS, CSCS
  Michigan Technological University
  Phone: (906)-458-2778
  Email: ijwedig@mtu.edu

- Steven Elmer, PhD
  Michigan Technological University
  Phone: (906)-487-2324
  Email: sjemler@mtu.edu

Initials:

RIGHTS OF RESEARCH SUBJECTS
The Michigan Technological Institutional Review Board (MTU-IRB) has reviewed my request to conduct this project. If you have any concerns about your rights in this study, please contact the MTU-IRB at 906-487-2902 or email IRB@mtu.edu.

I understand the procedures described above. My questions have been answered to my satisfaction, and I confirm that I am age 18 years or older and I agree to participate in this study. I have been given a copy of this form.

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

CONSENT TO PARTICIPATE IN RESEARCH

Part 2: Practical Application of Blood Flow Restriction Exercise

Principal Investigator: Isaac Wedig MS, CSCS (Doctoral Student)
Co-investigator: Steven Elmer PhD (Professor)
Department of Kinesiology and Integrative Physiology
Michigan Technological University
Houghton, MI 49931
Phone: (906) 487-2324
Email: ijwedig@mtu.edu & sjelmer@mtu.edu

INTRODUCTION

You are invited to participate in a research study being conducted by Mr. Isaac Wedig, a PhD student in the Department of Kinesiology and Integrative Physiology at Michigan Technological University. This study is being conducted as part of his dissertation. Professor Steven Elmer, a faculty member in the department, will be assisting and overseeing the study. Your participation is entirely voluntary. Please read the information below and ask questions about anything you do not understand, before deciding whether or not to participate.

You will be excluded from the proposed study if:

- Are not between the ages of 18-44
- Have a BMI ≥ 30
- Use products that contain tobacco
- Have diabetes
- Have any cardiopulmonary disorders, including but not limited to hypertension
- Have had a recent lower-body injury or surgery
- Have had a history of ACL injury or surgery
- Any implanted devices such as but not limited to a pacemaker or pain pump
- Any skin or dermatological disorders
- Any neurological disorders
- Unable to refrain from vigorous exercise during the 2-week study period (i.e., no exercises performed at a pace where only a few words are sustainable)
- Blood flow restriction screening score ≥ 5 points

If you do not meet any of the exclusion criteria listed above, you are eligible to participate in the study. A total of 30 participants will be recruited. The total time commitment to participate in the study is ~5 hours spread across an orientation session and 8 laboratory visits.

Orientation session (0.5 hour)
Laboratory Visit 1 (1 hour)
Laboratory Visit 2-7 (30 minutes/visit x 6 visits = 3 hours)
Laboratory Visit 8 (0.5 hour)

PURPOSE OF THE STUDY

The purpose of this study is to establish a practical and inexpensive method for implementing a new type of exercise called "exercise with blood flow restriction". This type of exercise consists of walking and lifting light weights while wearing an inflatable leg cuff (similar to a tourniquet) to limit blood going to and from the working muscles. The benefit of using exercise with blood flow restriction is that it provides a high-intensity workout for muscles but without overtaxing the joints and helps to strengthen muscles faster than traditional exercise. This is becoming a sought-after

Initials: _____

alternative for prescribing exercise for populations with exercise restrictions, such as the elderly, those with knee joint injurious, and various diseased states to whom higher intensity exercise may be difficult or dangerous.

For this study, we will first measure your leg size, leg strength, and blood pressure. These measurements will help us prescribe exercise with blood flow restriction using a simple inexpensive leg blood pressure cuff (for example $20 from Amazon). With this equipment you will perform 6 sessions of exercise with blood flow restriction. At the very end of the study we will also identify the pressure that briefly stops the blood from moving in your leg, which is useful validation measure when using exercise with blood flow restriction.

PROCEDURES / RISKS / DISCOMFORTS

If you volunteer to participate in this study, you will be asked to do the following things:

Orientation: You will need to attend a required orientation session prior to participating in this research study. During this visit, the procedures and equipment will be explained to you, and you will be able to ask questions about what you will do. You will also be asked to fill out a physical activity readiness questionnaire (PAR-Q) to ensure that it is safe for you to engage in exercise and have no contraindications. Following orientation and upon receiving your written consent to participate, you will be enrolled in the study. If you choose not to participate or are found not eligible, all data obtained from you will be destroyed.

Laboratory Visit 1: For this study we will ask you to complete one laboratory visit before beginning exercise sessions. We will ask that you avoid caffeine and exercise on the day of this visit and refrain from eating at least 2-hours prior. During your laboratory visit we will perform the following assessments:

- *Leg Size*: The circumference around your right thigh will be measured at four different locations. The location for each measurement site will be marked with a non-toxic skin-safe washable marker and measured using a tape measure. On the same leg we will also measure several different leg lengths. Lastly, we will take a skinfold measurement on the front of your thigh. Using their index finger and thumb, the investigator will pinch an area of skin on the front of your thigh and use a caliper to measure the thickness of the pinched skin. This procedure may be uncomfortable but it will only last a few seconds. There is no associated risk, however, you may experience temporary redness on your skin at the pinch site, which should resolve quickly.

  We will also directly measure the size of two muscles that make up your quadriceps. You will be positioned comfortably on an examination table, and a small round-shaped ultrasound probe will be placed on your skin over two different sites of your thigh. Ultrasound machines are used in clinical settings and there is minimal risk involved. You may experience some redness on your skin resulting from the contact of the ultrasound probe and gel. However, this is only temporary and should resolve quickly. There is a risk of an allergic reaction (itching, redness, small raised bumps, and/or burning, on and near the area of contact). Symptoms are generally short-lived (few days to few weeks) and you should seek immediate medical attention in case of a severe reaction.

- *Leg Strength:* Prior to completing the leg strength test, you will perform a 5 min warm-up consisting of walking, leg swings, and light stretching. After this, you will be seated on a specialized laboratory weight lifting machine similar to something that you might use in the gym. Your right leg will be strapped to the lever arm of the device. You will be asked to

Initials: _____

push as hard as you can against the arm, attempting to straighten your knee, similar to a seated knee extension exercise that you might do the gym. During the test, the machine will provide resistance and measure the strength of your quadriceps muscles. These tests will require several brief maximal effort muscle contractions (5 seconds). During the strength tests you will likely experience only minimal discomfort. There is, however, a risk of muscle strains, or other soft tissue injuries. To minimize the risk of injury with this exercise, you will start with at least practice tests at a submaximal effort and be instructed on how to perform the exercise with the proper technique. For these tests you may experience fatigue in your lower body muscles similar to lifting weights. At the end of this test you will perform a 5 min cool down consisting of walking, leg swings, and light stretching.

- *Blood Pressure*: After laying down comfortably on an examination table for 10-minutes, we will measure your blood pressure in both your arm and your leg. First, an automated blood pressure cuff will be placed on your arm. We will take two measurements with a 1-minute break between measurements. Each measure should take about 15-20 seconds. After collecting blood pressures on your arm, we will repeat the same procedure but with the blood pressure cuff applied to your upper thigh.

Laboratory Visits 2-7 Exercise Sessions: After your first laboratory visit we will ask that you complete six exercise sessions (3x/week for 2 consecutive weeks). During this time (e.g., 10-14 days), we will ask that you to refrain from vigorous exercise (i.e., no exercises performed at a pace where only a few words are sustainable). Each session will last approximately 30 minutes. During each session you will first perform a 5 min warm-up consisting of walking, leg swings, and light stretches. Next you will complete three different exercises with blood flow restriction.

1. Knee extension - 3 sets of 30 repetitions using elastic bands or light weight for resistance
2. Mini squats - 3 sets of 30 repetitions using body weight for resistance
3. Walking - 3 intervals at a preferred walking speed lasting 2 minutes

You will be given a 1-minute break between each set and a 2-minutes break between each exercise. During the exercises, a blood pressure cuff will be applied to your upper thigh and inflated to approximately 40% of your limb occlusion pressure. The cuff will remain inflated for the entire duration of the session, including rest periods, until you complete all three of the exercises. Throughout the session we will frequently ask you to rate the tightness of the cuff on your leg, the level of pain that you are experiencing in your working muscle during the exercises, and the difficulty of the exercises. We will adjust the tightness of the cuff so that the pressure remains moderate and your pain and exercise difficulty is tolerable. The pressure in the cuff will be released immediately upon finishing the last exercise. After the exercises with blood flow restriction are completed, you will perform a 5 min cool down consisting of walking, leg swings, and light stretches.

At the beginning of each session we will assess your joint and muscle pain. If joint pain or muscle soreness is excessive (i.e., greater than a 5, 0-10 scale) then the exercise session will not be performed that day and an extra 1-2 days of rest will be provided. If joint pain or muscle soreness persist then the exercise sessions will be discontinued. Note that, when exercising with a blood pressure cuff you will experience substantial fatigue in your leg muscles similar to that when lifting heavy weights. You may even experience some burning, tingling, and discomfort during the rest periods, which is normal. The most common side effects for this exercise are bruising at the site of the blood pressure cuff and temporary numbness. More serious side effects include blood clots

Initials: _____

in the leg veins (0.055%), stroke (0.008%), extreme muscle damage (0.008%), and blood clots in the lungs (0.008%). It should be noted that determining the relative safety of blood flow restriction exercise requires a detailed study of several potential outcomes. We acknowledge that unforeseen risks do exist and there is currently a lack of research documenting all of the risks for performing this type of exercise. Your risk may be higher if you smoke, use oral contraceptives, or have long periods of immobility. The researchers will assess your risks for performing this type of exercise using a blood flow restriction screening tool that includes questions about your medical history. To minimize the risk of muscular strains or cardiovascular events, training will always include a warm-up and cool-down without blood pressure cuffs. We will also provide a cooling fan and water.

Laboratory Visit 8: We will ask you to attend one final laboratory visit after completing the six exercise sessions. We will ask that you avoid caffeine and exercise on the day of this visit and refrain from eating at least 2-hours prior. During your visit we will perform the following assessment:

- *Limb Occlusion Pressure:* An inflatable blood pressure cuff will be placed around your upper thigh. The researcher will inflate the cuff until blood flow is no longer detected using ultrasound. The researcher will then immediately release the pressure in the cuff. This procedure is similar to having blood pressure taken. It is important to note that the cuff placed around your limb may be uncomfortable, but it will only last a few seconds. To prevent cross contamination, these procedures will not be performed on any participant with a known or suspected infection in the body region to be tested, and the ultrasound machine and occlusion cuff will be cleaned after each use and disinfected after each participant has completed the experimental procedure using disinfecting wipes.

To further minimize the risks, only healthy individuals 18-44 years of age will be recruited for this study. Furthermore, all safety precautions will be followed and the laboratory is equipped with a first aid kit and AED. You will be asked how you are feeling throughout the protocols. If you give any indication of abnormal stress or injury, the protocol will be stopped. In the event of any incident, we will call 911 and then MTU EMS.

If you are taking medications, it is your responsibility to consult with your physician regarding your participation in this study. Do not volunteer for this study if you have been instructed to abstain from this study by a physician. Any problems you experience throughout this study should be discussed immediately with your physician.

INJURY RESULTING FROM RISKS OR DISCOMFORTS

In the event of physical and/or mental injury resulting from participation in this research project, Michigan Technological University does not provide any medical, hospitalization or other insurance for participants in this research study, nor will Michigan Technological University provide any medical treatment or compensation for any injury sustained as a result of participation in this research study, except as required by law.

POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY

We cannot promise any direct benefit for taking part in this study. However, the results may help to make blood flow restriction exercise more accessible to clinicians and strength and conditioning coaches, potentially translating this useful modality into practice and improving rehabilitation and sport training practices.

Initials: _____

COMPENSATION
There will be no compensation for your participation in this research.

CONFIDENTIALITY
Any information that is obtained in connection with this study and that can be identified with you will remain confidential and will be disclosed only with your permission or as required by law. The data from this study may be published, but your identity will not be shown. All electronic records containing your information will be stored on password protected computers located in the Exercise Physiology Laboratory and coded using an alphanumeric combination (e.g. AA001). Paper files with your information and corresponding alphanumeric code will be stored separately from all research data and in a locked file cabinet in Dr. Elmer's office (Student Development Complex 121B). Only Dr. Elmer and Mr. Wedig will have access to these data. Federal IRB regulations require the retention of records for three years after the completion of the final report. The Michigan Technological University Institutional Review Board (IRB) reserves the right to inspect both the research data collected and your experimental records. Finally, the de-identified data collected from you in this study could be used be used for future exercise physiology research studies or distributed to another investigator in Dr. Elmer's research laboratory for future research studies without additional informed consent from you.

PARTICIPATION AND WITHDRAWAL
You can choose whether or not to be in this study. If you volunteer to be in this study, you may withdraw at any time without consequences of any kind or loss of benefits to which you are otherwise entitled. You may also refuse to answer any questions you do not want to answer. The investigator may withdraw you from this research if circumstances arise which warrant doing so. These circumstances include: injury leading to an inability to complete testing, adverse reactions to testing such as dizziness, confusion, increased chest pain, or shortness of breath. If you withdraw or are withdrawn by investigators, any data obtained will be archived and potentially analyzed.

IDENTIFICATION OF INVESTIGATORS
If you have any questions or concerns about this research, please contact:

- Isaac Wedig, MS, CSCS
  Michigan Technological University
  Phone: (906)-458-2778
  Email: ijwedig@mtu.edu

- Steven Elmer, PhD
  Michigan Technological University
  Phone: (906)-487-2324
  Email: sjemler@mtu.edu

Initials: _____

RIGHTS OF RESEARCH SUBJECTS
The Michigan Technological Institutional Review Board (MTU-IRB) has reviewed my request to conduct this project. If you have any concerns about your rights in this study, please contact the MTU-IRB at 906-487-2902 or email IRB@mtu.edu.

I understand the procedures described above. My questions have been answered to my satisfaction, and I confirm that I am age 18 years or older and I agree to participate in this study. I have been given a copy of this form.

_____
Printed Name of Subject

_____ _____
Signature of Subject Date

Michigan Technological University

Research Integrity

DATE:	November 14, 2022
TO:	Steven Elmer
FROM:	Christina Lehmann, Director Human Research Protection Program
RE:	M2126, [1792437-6]
TITLE:	Practical Application of Blood Flow Restriction Exercise
SUBMISSION TYPE:	Amendment/Modification
REVIEW TYPE:	Expedited
MTU-IRB ACTION:	Approved
NEW STATUS:	**Active – Open to Enrollment**

The request for amendments/modifications, to the above-referenced study project, has been reviewed and APPROVED by a voting member of the MTU-IRB. **This project remains "no more than minimal risk".**

UPDATED MTU-IRB APPROVED DOCUMENTS

All associated documents (advertisements and informed consents) were re-stamped with the official MTU-IRB stamp. Researchers must use these updated official documents for recruitment and enrollment of participants. The updated documents are available for download in the "Reviews" section under "Board Documents" of this package on IRBNet. **Only copies of the re-stamped and updated documents may be used, all unused older copies need to be destroyed.**

AMENDMENTS/MODIFICATIONS

The new approval of this study project applies only to this project and only under the conditions and procedures described in the amendment/modification package. If/when changes become necessary but are not limited to: changes in protocol, personnel, study location, participant recruitment, etc., as set forth in this approval, a **Renewal, Change, or Closure Request** form must be submitted via IRBNet. **You must receive notification of approval PRIOR to implementing the change(s).**

REAPPROVAL (CONTINUING REVIEW) REQUIREMENTS

This study project was determined no more than minimal risk and reviewed/approved on or after January 21, 2019 via the expedited process and does not require yearly continuing reviews or reapproval. For minimal risk projects, a "Next Report Due" date will be activated in IRBNet when initially approved. If the project remains active two years after the initial approval date, you will be contacted by the HRPP office for a report of current research activity.

COMPLETION OF PROJECT

Upon the completion of this project, one final IRBNet package needs to be submitted. The completed **Renewal, Change, or Closure Request** form is the only required document to close the project. After submission of this final package and a status of "Closed – Project Complete" is granted by the MTU-IRB office, no more work associated with this project may be conducted. If future work is needed after closure of this project, a completely new project will need to be submitted to the MTU-IRB for review and approval.

Lakeshore Center | 1400 Townsend Drive, Houghton, MI 49931-1295
906-487-2902 | f. 906-487-1979 | **mtu.edu**

IRB COMPLIANCE REMINDERS

Please review the following and adhere to all requirements noted to ensure compliance with federal regulations and MTU-IRB policy:

- Informed consent is a process beginning with a description of the study and assurance of participant understanding followed by a signed consent form. Before beginning a more than minimal risk project involving human participants, the principal investigator must obtain a properly executed informed consent from each participant and/or the person legally responsible for the participant. ***It is the principle investigators ethical responsibility to ensure participants have thoroughly read the consent document, they understand the project, and are aware of any potential risks PRIOR to allowing them to sign a consent document.**

- Informed consent must continue throughout the study through a dialogue between the researcher and the research participant. Federal regulations require each participant receive a copy of the signed consent document.

- Again, the MTU-IRB approved consent document was uploaded to IRBNet with the official MTU-IRB stamped approval on it. Only copies of the most recent official MTU-IRB stamped informed consent are to be distributed to participants relating to this project. If any changes or modifications are needed regarding this form, the same approval process indicated under the AMENDMENTS/ MODIFCATIONS section of this memo must be followed.

- Individual identification of human participants in any publication is an invasion of privacy.

- The approved project is subject to periodic review by the MTU-IRB.

- All required research records must be securely retained in either paper or electronic format for a minimum of three years following the closure of the approved study. This includes signed consent documents from all participants.

- All Unanticipated Problems and/or Serious Adverse Events to participants or other parties affected by the research must be reported to the MTU-IRB office within two days of the event occurrence. Likewise, any instances of non-compliance or complaints regarding this study must be reported to the MTU-IRB in a timely manner. For guidance on reporting any of this information, please contact the HRPP office.

If you have any questions or need guidance on human subject research training, please contact human research protection personnel at 906-487-2902 or send an e-mail message to irb@mtu.edu.

F.2 Study 4

Michigan Tech

Office of Compliance, Integrity, and Safety
Phone: 906-487-2902 E-mail: IRB@mtu.edu
1400 Townsend Drive
Lakeshore Center, 3rd Floor
Houghton, MI 49931

Reset Form

Exemption Request and/or Limited Review

Federal regulations (45 CFR 46) permit the exemption of some types of research from IRB review.
Exemption does not mean that you do not need to submit a study for review; our office requests information about your study and will determine the level of review required for approval.
If you have any questions, feel free to contact our office.

Eligible for Exemption: There are several classifications of research which may involve human subjects but their classification falls outside of the IRB's policies and jurisdiction.

Determination that research is exempt or requires limited Institutional Review Board (IRB) review is made through the Office of Compliance, Integrity, and Safety. Exemption from review is only available to certain categories of research as define by federal regulation. If you have questions about whether your project might qualify for exemption, please contact our office.

Project Title	Usability of a Decision Support Tool for the Implementation of Exercise with Blood Flow Restriction		
Project Start Date	Jan 1, 2023	Project End Date	Dec 31, 2023
Principal Investigator	Erich Petushek	Department	Cognitive and Learning Sciences CLS
E-mail	ejpetush@mtu.edu	Phone	906-487-3204

I. Project Description

1. Purpose and goals of the research:
(text field will expand)

The purpose of this research is to usability test a decision support tool designed to aid physical therapists in implementing exercise with blood flow restriction. Exercise with blood flow restriction is endorsed by the American Physical Therapy Association and is part of a physical therapists professional scope of practice. However, despite its growing use in rehabilitation settings, implementation of blood flow restriction remains challenging for practitioners for several reasons. First, the majority of blood flow restriction interventions in the literature are applied to healthy individuals in a controlled laboratory setting with the use of specialized equipment. Second, there is a lack of consensus on standardized procedures when implementing this modality. Development of a user oriented decision support tool (i.e., decision tree/checklist) that provides a step-by-step guide to implementing blood flow restriction would help to overcome many of the barriers that practitioners face to utilizing this training modality. Accordingly, this would help to improve access, safety, and effectiveness of blood flow restriction in clinical settings. This study will specifically measure the usability of a decision support tool for use by physical therapists and collect feedback on its potential utility for implementing BFR in clinical settings.

2. Methods and procedures: Describe in detail what subjects will be asked to do, what information will be collected about them, and when or how often research procedures will be conducted. You may also upload an attachment describing the methods including a graph, table, timeline of events.

20 licensed physical therapists will be recruited to participate in the study. They will be invited to attend a Zoom meeting where they will be presented with the decision support tool, given a brief overview of its purpose, and asked to complete a hypothetical goal-oriented task using the tool as a guide. The task will consist of giving the participant a hypothetical patient and asking them to establish a protocol to implement blood flow restriction with that individual. Prior to beginning the task, they will be asked share their audio, turn off their video, and the meeting will be recorded. Participants will be instructed to think aloud and verbally walk through the task. Using the transcribed audio, the participant's time to task completion, the type and number of incidents, and comments will be assessed. After the task is completed, the participant will respond to 10 Likert scale survey questions about the efficiency, effectiveness, and satisfaction of the decision support tool. Lastly, they will be asked to participate in an oral interview by responding to several discussion questions prompted by the investigator that will pertain to the potential use of this tool in clinical practice. Again this audio will be recorded, transcribed, and analyzed to assess common themes among interviews.

3. Research Site:

Michigan Technological University

4A. Will you obtain identifiable private information about these individuals? ◉ Yes ○ No

Private Information includes information about behavior that occurs in a context in which an individual can reasonable expect that no observation or recording is taking place, or information provided for specific purposes which the individual can reasonably expect will not be made public (e.g. student record).

Identifiable means that the identity of the participant may be ascertained by the investigator or associated with the information (e.g. by name, code number, pattern of answers, etc.)

4B. Will data be collected and stored in a manner such that participants may be individually identified directly or indirectly? ◉ Yes ○ No

5. Does the study present more than minimal risk to the participants? ○ Yes ◉ No

Minimal risk means that the risks of harm or discomfort anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during performance of routine physical or psychological examinations or tests. Note that the concept of risk goes beyond physical risk and includes psychological, emotional, or behavioral risk as well as risks to employability, economic well being, social standing, and risks of civil and criminal liability.

If Yes, you can not use this form, please submit a Protocol Document

6. Is this a graduate level research project? ◉ Yes ○ No

II. Exemption Categories

Check the category or categories which apply and respond to the questions within that exemption section:

☐ **Category 1:** Research, conducted in established or commonly accepted educational settings that specificially involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

a) Describe the established or commonly accepted educational setting of the research:

b) Could the research adversely impact student achievement in anyway? ○ Yes ○ No

If Yes, the study does not qualify under this category

c) Could the research adversely impact the assessment of educators who provide instruction? ○ Yes ○ No

If Yes, the study does not qualify under this category

d) Does the research involve a comparison of a proven educational technique to a novel technique? ○ Yes ○ No

If Yes, the study does not qualify under this category

☐ **Category 2:** Research that only includes interactions involving education tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria are met:

☐ The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained either directly or through identifiers linked to the subjects (e.g., anonymous survey);

☐ Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, education advancement, or reputation;

a) Does the research involve minor participants? ○ Yes ○ No

b) If yes, does the research involve surveys? ○ Yes ○ No

If yes to b, exemption category 2 does not apply. Complete a Protocol Document and submit for expedited review.

☐ The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained either directly or through identifiers linked to the subjects, and disclosure has risks, **then an IRB limited review will be conducted to ensure privacy and confidentiality of subjects.** This category may NOT be applied to research with children.

a) Does the research involve an intervention? ○ Yes ○ No

Intervention is defined as, "manipulations of the subject or the subject's environment that are performed for research purposes."

If yes, exemption category 2 does not apply

☒ **Category 3:** Research involving benign behavioral *intervention** in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:

A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

B) Any disclosure of the human subject's response outside the research would not reasonable place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

C) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subject, **and an IRB limited review will be conducted to ensure privacy and confidentially of subjects.**

***benign behavioral interventions** are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the intervention offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subject play an online game, having them solve puzzles under various noise condition, or having them decide how to allocate a nominal amount of cash received between themselves and someone else.

a) Describe the benign behavioral intervention:

The participants will be asked to use a decision support tool in order to develop a protocol for implementing blood flow restriction exercise with a hypothetical patient. They will then be asked to respond to a 10 question online survey administered via Google Forms asking about the effectiveness, efficiency, and satisfaction of using the tool (System Usability Score Survey). Lastly, they will be asked to participate in an oral interview by responding to 5 discussion questions pertaining to their thoughts surrounding the utility of the tool in clinical practice.

If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research.

b) Does the research involve deception? ○ Yes ◉ No

c) If so, will subjects prospectively agree to be unaware of or misled regarding the nature of the research? ○ Yes ○ No

If Yes to B) but no to C), the research will not qualify under this category. You must complete and submit a Protocol Document, you cannot use this form.

Does the research involve minors? ○ Yes ◉ No

If yes, the research does not qualify under this category. You must complete and submit a Protocol Document, you cannot use this form.

☐ **Category 4:** Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable bio specimens. **Call our office for assistance.**

☐ **Category 5:** Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels or payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by federal employees, and studies under contracts or consulting arrangements, cooperative agrements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as section 1115 and 1115A of the Social Security Act, as amended.

NOTE: exemption under Category 5 is only permitted upon Federal Agency approval AND after being published on a federal website.

☐ **Category 6:** Taste & food quality evaluation and consumer acceptance studies: (a) if wholesome foods without additives are consumed; or (b) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Michigan Tech is not currently set up to use these two exemptions categories at this time. Call our office for assistance.

Category 7: Storage or maintenance for secondary research for which broad consent is required.
Category 8: Secondary research for which broad consent is required.

III. Participants, recruitment, and informed consent

1. Describe the proposed participants:

   The participants will be licensed and practicing physical therapists with or without previous experience in implementing exercise with blood flow restriction.

2. Recruitment: Describe recruitment procedures. Include how participants will be initially identified, approached, or contacted regarding the research and in what setting. *Please provide a copy of any recruitment materials, advertisements, flyers, text of e-mails, etc. which will be used.*

   The PI will make a list of potential physical therapists. The participants listed will be directly contacted and recruited through email and/or phone calls using the included recruitment script.

3. Describe procedures for informing participants about the research and how they will actively indicate their agreement to participate. *Please provide a copy of the oral script or information sheet which will be used.*

Participants will be proved with a brief consent information in the Zoom chat box. They will be allowed to ask any questions and be asked to respond either orally or in the chat box if they agree to participate in the research study.

4. Compensation/incentives: Will participants or others be offered incentives for their participation (e.g., gifts, payment, reimbursement, services, extra or course credit, or other incentives? ○ Yes ◉ No

If yes, please describe the amount, alternative ways to earn compensation (i.e., in cases of course/extra credit), and when compensation/incentives will be awarded. Please be sure to follow the guidance document, **Procedure for Compensation for Human Subject Participants (found on our website).**

5. Dual relationships: Does the investigator, co-investigators, or any member of the research team, or anyone assisting with the research have an authority relationship (e.g., instructor/student, employer or supervisor/employee, or other) with potential participants? ○ Yes ◉ No

If yes, describe the relationship, and indicate how the research will be conducted to avoid undue influence on participation

6. Will any aspect of the research be conducted in a classroom setting during class time? ○ Yes ◉ No

If yes, describe what those who choose not to participate will be doing, and provide justification for use of class time for research. *You may be asked to include the course syllabus.*

7. Will all participants, their parents/guardians and /or their legally authorized representative (as applicable) be fluent in English? ◉ Yes ○ No

If no, explain how informed consent will be obtained, and provide a copy of the translated documents(s) to be used.

8. If research will be conducted at an international site, indicate the investigator's familiarity with the culture and cultural norms, and how the research may affect an individual's standing in their community ☒ N/A

IV. Instruments

Be sure to upload the questionnaire(s), survey instrument(s), or list of interview or focus group questions to your irbnet.org submission package.

V. Privacy and Confidentiality

1. Privacy: Describe the conditions under which interaction with the subjects will occur (e.g., consent discussion occurs in a private room). Explain how these conditions adequately address the PRIVACY of subject:

Interactions between investigator(s) will occur via a password protected Zoom meeting held on an MTU Zoom account. Online survey responses will be gathered using Google Forms and will be administered on a secure password protected MTU Google account.

2. Personally identifiable information: Will the researchers obtain any personally identifiable information (PII) from or about participants (e.g. names, address, telephone numbers, etc.)?

(•) Yes ( ) No - (proceed to Question 3)

a) What direct identifiers will be obtained?

Name and audio recording will be obtained via the Zoom platform.

b) How long will the PII be maintained?

The PII will be maintained until the audio recordings are transcribed (within 7-days of collecting), then they will be deleted.

c) Why is it necessary to maintain direct identifiers?

Given the constraints of the Zoom platform (e.g., displays name when entering room, no way to distort audio recording), we will collect this information but delete it when the audio files are transcribed.

d) Describe the coding system that will be used to protect against disclosure of these identifiers.

Participants will be coded with numbers (e.g., "Participant 1"). Any verbalized PII will not be transcribed.

e) How long will the link between identifiers and code be maintained?

There will not be a link between identifiers and code.

f) Explain how the research will mitigate a risk of participant responses that could place them at risks such as criminal or civil liability, or be damaging to their financial standing, employability, insurability, reputation, or be stigmatizing (e.g. limiting access to identifiers, obtaining a Certificate of Confidentiality from NIH, etc.). *If a Certificate of Confidentiality is obtained, provide a copy to the IRB once available.*

We will delete the audio recording of the Zoom interview after the transcription and remove any identifiers.

3. Will any demographic information be collected which could lead to a deductive disclosure of participant(s) indentifies? If so, how will participant privacy be addressed?

No

4. In what format(s) will the data originate, be shared among team members/collaborators, and be maintained during the life of the study (e.g. paper, digital, electronic media, video, audio or photographic):

Initial audio recordings will be stored locally on a password protected computer and later deleted. Transcribed (de-indentified) data will be shared with the research team and saved indefinitely.

5. Where will data be stored including security provisions that will be taken to protect the data (include both paper/hardcopy records and digital/electronic files).

Initial audio recordings will be stored locally on a password protected computer and later deleted. Transcribed (de-indentified) data will be shared with the research team and saved indefinitely.

6. Are there potential ethical or legal circumstances when it would be necessary to break confidentiality (e.g., requirements for mandated reporting or other professional obligations to report)? If so, describe:

No

7. Final disposition: Please describe at what point in time PII and deductive identifiers will be removed from the dataset and/or the records retention plan for the research records:

Once the participants recordings have been transcribed (within 7-days of collecting), the PII and deductive identifiers will be deleted. Transcribed (de-indentified) data will be shared with the research team and saved indefinitely. Data may be published but only de-identified data will be utilized.

Click here to read instructions on how to submit form

INFORMATION SHEET / CONSENT TO PARTICIPATE IN RESEARCH

USABILITY OF A DECISION SUPPORT TOOL FOR THE IMPLEMENTATION OF EXERCISE WITH BLOOD FLOW RESTRICTION

INTRODUCTION

You are being invited to participate in a research study conducted by Mr. Isaac Wedig, a PhD student in the Department of Kinesiology and Integrative Physiology at Michigan Technological University. This study is being conducted as part of his dissertation. Professor Erich Petushek, a faculty member in the Department of Cognitive and Learning Sciences at Michigan Technological University, will be assisting and overseeing the study. This project is funded by the Portage Health Foundation.

Your participation in this study is entirely voluntary. Please read the information below and ask questions about anything you do not understand, before deciding whether or not to participate.

A total of 20 licensed physical therapists will be recruited to participate in the study. Participation will take place entirely online via Zoom. The total time commitment for participating in this study is 1 virtual meeting lasting approximately 30-40 minutes.

PURPOSE OF THE STUDY

The purpose of the study is to assess the usability of a decision support tool (i.e., decision tree/checklist) that aids in the clinical implementation of exercise with blood flow restriction (BFR). This modality involves exercising with a pressurized cuff applied to the upper portion of a limb, which serves to partially limit blood flow going to the working muscles (arterial) and returning to the heart (venous). Exercise with BFR is emerging as an effective way to increase muscle size and strength in healthy and clinical populations and is now endorsed by the American Physical Therapy Association and is utilized in clinical rehabilitation settings. However, implementation remains challenging for practitioners including physical therapists. With this study we are evaluating the efficiency, effectiveness, and satisfaction of a tool that provides a step-by-step guide to implementing BFR exercise safely and effectively in clinical settings. Specifically, the tool aids in conducting medical screening of potential candidates, selecting appropriate equipment for performing BFR, and setting exercising cuff pressures. Results from this study will help to develop a tool that can improve access, safety, and effectiveness of exercise with BFR in clinical settings.

PARTICIPATION REQUIREMENTS

If you choose to be in the study, you will be invited to attend a virtual meeting held on Zoom. During this meeting you will be presented with a tool designed to help clinicians implement exercise with BFR. You will be given a brief overview of the tool and introduced to its purpose. Next you will be asked to use the tool to establish a protocol for implementing BFR with a hypothetical patient. Specifically, you will be asked to 1) determine whether BFR is safe for the patient to engage in, 2) select equipment that you will use to implement BFR, and 3) establish how much pressure will be applied in the cuffs during exercise. Prior to beginning the task, you will be asked to share your audio and turn off your video. The meeting will be recorded. As you work through the task, you will be asked to think aloud and share your thought process. After finishing the task, you will respond to an online survey consisting of 10 questions asking about the effectiveness, efficiency, and satisfaction of using the tool. Reponses to each of these questions will be on a Likert scale (1-5; 1= "Strongly Disagree", 5 = "Strongly Agree"). After completing this survey, you will then be asked to participate in an oral interview by responding to 5 discussion questions that will be prompted by the researchers. These questions will pertain to your thoughts surrounding the utility of the decision support tool for implementing BFR in clinical practice.

RISKS AND DISCOMFORTS
While the investigators will keep your information confidential, please realize that there are risks to participating in internet-based research with regard to potential breaches of privacy or anonymity. Please be sure to close your internet browser once you have finished the survey to protect your privacy. In addition, you can further safeguard your privacy by deleting the webpage history from your browser after closing the survey link. All survey and interview questions will pertain to feedback on the decision support tool (not about you/your personal experiences), thus the nature of this data is not sensitive and wouldn't place you at risk if compromised.

POTENTIAL BENEFITS TO SUBJECTS AND/OR TO SOCIETY
We cannot promise any direct benefit for taking part in this study. However, results will help to develop a tool that can improve access, safety, and effectiveness of exercise with BFR in clinical settings where it can be leveraged to improve rehabilitation.

CONFIDENTIALITY
Interactions with the research team will occur on a password protected Zoom link held on a private MTU Zoom account. During this meeting, you will be asked to turn off your video and share your audio. Your name and audio recordings during the task and interview will be obtained via the Zoom platform. We will protect the confidentiality of your research records by storing the initial audio recordings on a password protected computer. Your audio recordings will be transcribed within 7-days of collection and all personal identifiers will be removed, including any verbalized information disclosing your identity. Audio recordings will be deleted immediately after transcription. Your de-identified transcriptions will be assigned a unique ID code (e.g., Participant 1) to keep your identity secure. There will be no way of re-identifying your transcripts once the ID code is assigned. Survey responses will be collected using Google Forms and will be administered on a secure password protected MTU Google account. A link to the form will be provided in the Zoom chat. Your survey responses will remain confidential, and we will not collect any identifiable information on the form. Your de-identified research data will be kept indefinitely and only individuals on the research team will have access to your data. Below are links to the privacy policies for Zoom and Google which will be used to collect data.

Zoom Privacy Policy: https://explore.zoom.us/en/privacy/

Google Privacy Policy: https://policies.google.com/privacy

Results of this research may be published, but only de-identified data will be used, and your identity will not be shown. Your research data collected in this project may be distributed to other researchers for future studies, but we will not share any information that could identify you.

PARTICIPATION AND WITHDRAWAL
Participating in this study is completely voluntary. Even if you decide to participate now, you may change your mind and stop at any time. You may choose not to answer any of the survey or interview question for any reason.

If you have any questions about this study, please contact:

- Isaac Wedig, MS, CSCS
  Michigan Technological University
  Phone: (906)-458-2778
  Email: ijwedig@mtu.edu

- Erich Petushek, PhD
  Michigan Technological University
  Phone: (906)-487-3204
  Email: ejpetush@mtu.edu

A human research protection program (HRPP) administrator reviewed this project and determined that it is minimal risk and therefore does not require review, approval, or oversight by the Michigan Technological University Institutional Review Board (MTU-IRB). Questions about your rights as a research participant may be directed to the HRPP administrators at Michigan Technological University. They can be reached at (906) 487-2902 or irb@mtu.edu.

If you want a copy of this consent for your records, you can print it from the screen. If you would like documentation linking you to this research study, please email your request to the Principal Investigator, Isaac Wedig, at ijwedig@mtu.edu.

If you wish to participate in this study, please confirm this verbally or insert this confirmation in the chat:

"I confirm that I have read through the consent form and want to participate in this study"

Michigan Technological University

Research Integrity

DATE:	January 13, 2023
TO:	Steve Elmer
FROM:	Christina Lehmann, Director Human Research Protections Program
RE:	M2214, [1984710-1]
TITLE:	Usability of a Decision Support Tool for the Implementation of Exercise with Blood Flow Restriction
SUBMISSION TYPE:	New Project
HRPP ACTION:	Exempt
STATUS:	Exempt

A human research protection program personnel administratively reviewed the above-referenced study project submission. After administrative review it was determined that this project meets the following federal exemption category per 45 CFR 46.104d:

Exemption Category: (3)(i) (A) (B)

> *(3)(i) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met:*
>
> *(A) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;*
>
> *(B) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation;*

This determination is based on no greater than minimal risk to research participants. When a research project is determined to meet the criteria for an exempt status, it means the project as submitted is exempt from Michigan Technological Institutional Review Board (MTU-IRB) oversight and does not require annual continuing review.

This determination only applies to the activities described in this IRBNet submission and does not apply should any changes be made to the project. If changes are being considered, please submit a study modification through IRBNet for review. You can submit a modification by navigating to the initial submission and selecting to "Create a New Package". Be sure to include a "**Renewal, Change, or Closure Request**" form to the new package. **You must receive notification of HRPP determination of "Not Research", "Not HSR", "Exemption", or an MTU-IRB approval PRIOR to implementing change(s).**

While this study does not require MTU-IRB oversight, investigators and study team members must comply with all applicable federal, state, and local laws, as well as FERPA and MTU Policies and Procedures. Studies incorporating human participants requires all team members to complete training to ensure the protection of human subjects and adherence to the ethical principles explained in the Belmont Report. MTU utilizes CITI Program (citiprogram.org) to provide these training courses and

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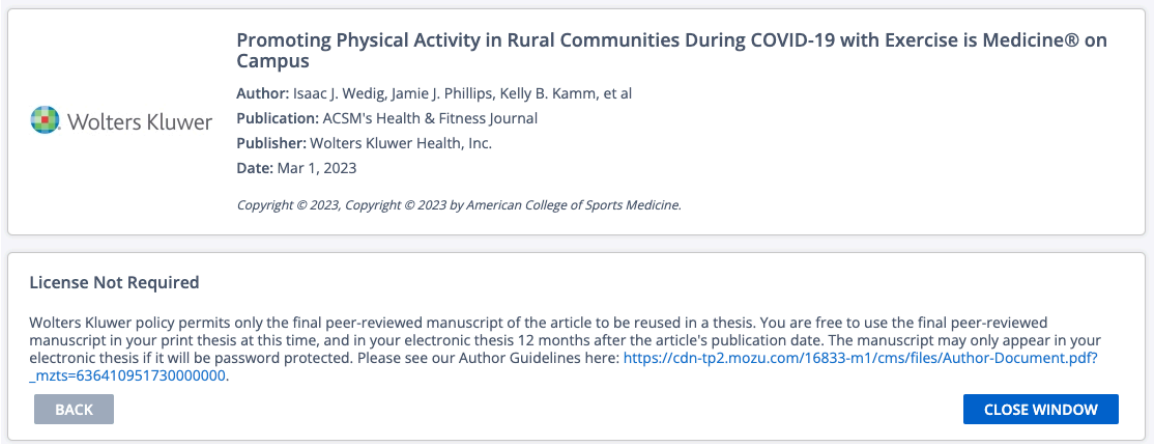
906-487-2902 | f. 906-487-1979 | **mtu.edu**

receives notifications of CITI training courses completed.

If you have any questions or need guidance on human subject research training, please contact HRPP personnel at 906-487-2902 or send an e-mail message to irb@mtu.edu.

G Reuse Permissions

G.1 Study 1



Promoting Physical Activity in Rural Communities During COVID-19 with Exercise is Medicine® on Campus

Wolters Kluwer

Author: Isaac J. Wedig, Jamie J. Phillips, Kelly B. Kamm, et al
Publication: ACSM's Health & Fitness Journal
Publisher: Wolters Kluwer Health, Inc.
Date: Mar 1, 2023

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