

# Exercise Testing and Microvascular Assessment in ICU Survivors to Investigate ICU-Acquired Weakness

Britney Paige Blunderfield

A Thesis submitted to the Faculty of Graduate and Postdoctoral Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE

Department of Physiology and Pathophysiology

University of Manitoba

Winnipeg



**University  
of Manitoba**

Copyright © 2025 by Britney Paige Blunderfield

## Abstract

**Background:** After prolonged intensive care unit (ICU) admission, 50% of survivors develop ICU-acquired weakness (ICU-AW), causing disability up to 5-years post-ICU discharge.

However, its underlying mechanisms remain unclear. ICU-AW research has yet to examine systemic and peripheral factors influencing the oxygen delivery pathway, commonly studied in exercise science. However, the lack of standardized follow-up protocols for this population restricts the quantitative evaluation of peak oxygen uptake ( $\dot{V}O_{2peak}$ ), on/off oxygen uptake ( $\dot{V}O_2$ ) kinetics, and skeletal muscle oxygenation. Recently, we published a standardized single-session exercise test (CPET) protocol in healthy-young-adults with unpublished near-infrared spectroscopy (NIRS) data. **Objective:** This thesis aims to (1) develop a standardized, single-session CPET protocol tailored to ICU-survivors for integrated assessment of  $\dot{V}O_{2peak}$ ,

$\dot{V}O_2$  kinetics, and localized skeletal muscle oxygenation; and (2) analyze retrospective NIRS data from Santana et al., (2025). **Methods:** Key adaptations from Santana et al., (2025) involve: proposing a literature-derived ICU correction factor to determine constant work rate (CWR) at 30%  $\dot{V}O_{2reserve}$ ; and proposing an incremental ramp protocol based on self-reported functional status to individualize each ramp protocol (5, 10, 15, or 20W.min<sup>-1</sup>); with NIRS placed on the vastus lateralis muscle to assess tissue saturation index (TSI) and deoxy-hemoglobin (HHb). Retrospective analysis of healthy NIRS data ( $n=11$  males and  $n=9$  females) involve reporting TSI<sub>peak</sub> and HHb on/off-kinetics from an upright cycle ergometer combined single-session.

**Results:** Developed and applied the ICU-Combined Assessment of cardioRespiratory Exercise (ICU-CARE) CPET protocol to collect preliminary ICU-survivor data ( $n=2$ ), suggesting that NIRS data can be measured with adequate  $\dot{V}O_2$  data in a single-session on/off kinetics assessment which can be fitted mono-exponentially. Supporting the application of NIRS, the

healthy retrospective analysis demonstrates that TSI and HHb can be measured within the protocol proposed by Santana et al., (2025), reporting: HHb kinetics fitted monoexponentially (on-kinetics  $n=5$  females,  $n=7$  males; off-kinetics  $n=3$  females,  $n=7$  males);  $TSI_{peak}$  [%] at  $\dot{V}O_{2peak}$   $74.4 \pm 14.4$  ( $n=5$  females),  $57.3 \pm 5.0$  ( $n=7$  males). **Conclusions:** Conducted a retrospective NIRS analysis and developed a standardized single-session ICU-CARE CPET protocol to quantify  $\dot{V}O_{2peak}$ , on/off  $\dot{V}O_2$  kinetics, and skeletal muscle microvascular oxygenation for ICU-survivors to enable future ICU-AW research.

## Acknowledgments

Foremost, I would like to express my special thanks to my co-supervisors, Dr. Asher Mendelson and Dr. Rodrigo Villar. Their limitless desire to stay on the forefront of research provided an opportunity to learn and conduct integrative research on cardiorespiratory and muscular pathophysiology, using translational approaches from exercise science to design a streamlined yet comprehensive ICU follow-up protocol. Truly meaningful research, and I am grateful for both of your consistent support.

To my committee members, Dr. David Christiansen, Dr. Kristine Cowley, and Dr. Todd Duhamel, thank you for your scholarly insights and feedback, as well as Dr. James Longstaffe, Dr. Ian Dixon, and Karin Nowak-Bailey for supporting my academic journey. To my colleagues in both the CPER lab and Critical Care lab, Jefferson, Isuru, Amirali, Dihogo, Edgar, Faith, Raju, Julia and others, your willingness to share ideas, provide feedback, and engage in scientific discussion greatly enriched my experience.

To my family, your unwavering support as I transitioned from student-athlete to a graduate student and assistant coach at the University of Manitoba has been a constant source of strength and motivation. The impact sport has made in my life has instilled resilience, discipline, consistency, and teamwork - qualities that have empowered me to move forward and give back to our community. This accomplishment is ours. As a proud Bisons Women's Soccer alum, I am honored to present this final thesis, representing both the CPER lab and HSC Critical Care lab.



Cardiorespiratory &  
Physiology of Exercise  
Research Lab



## Table of Contents

|                                                                                        |    |
|----------------------------------------------------------------------------------------|----|
| Abstract .....                                                                         | 2  |
| Acknowledgments.....                                                                   | 4  |
| List of Tables .....                                                                   | 7  |
| List of Figures .....                                                                  | 8  |
| List of Abbreviations .....                                                            | 10 |
| CHAPTER ONE: Introduction .....                                                        | 11 |
| CHAPTER TWO: Literature Review .....                                                   | 16 |
| 2.1 Advances in Critical Care Unit Survivorship.....                                   | 16 |
| 2.2 Shift from Survival to Recovery .....                                              | 16 |
| 2.3 ICU-Acquired Weakness.....                                                         | 18 |
| 2.3.1 Risk Factors.....                                                                | 20 |
| 2.3.2 Shift from Isolated Skeletal Muscle Biology towards Integrative Physiology ..... | 23 |
| 2.4 Role of Oxygen Delivery Pathway.....                                               | 23 |
| 2.4.1 Circulatory Overview .....                                                       | 24 |
| 2.4.2 Microcirculation Overview .....                                                  | 25 |
| 2.4.3 Microvascular-Myocyte Oxygen Exchange.....                                       | 28 |
| 2.5 Skeletal Muscle Microcirculation in Chronic Disease and Critical Illness.....      | 29 |
| 2.6 CPET and NIRS Assessment Methods .....                                             | 31 |
| CHAPTER THREE: Statement of the Problem.....                                           | 45 |
| 3.1 Research Questions, Objectives and Hypothesis .....                                | 45 |
| 3.2 Organization of this Thesis .....                                                  | 46 |
| 3.3 Thesis Deliverables .....                                                          | 47 |
| CHAPTER FOUR: Protocol Development .....                                               | 48 |

|                                                                                          |     |
|------------------------------------------------------------------------------------------|-----|
| 4.1 Rationale for ICU-survivor Protocol Development .....                                | 48  |
| 4.2 Key Protocol Adaptations .....                                                       | 49  |
| 4.2.1 ICU-Survivor Specific <b>VO<sub>2</sub>Peak</b> Correction Factor.....             | 52  |
| 4.2.2 Work Rate Intensity and Ramp Increments Based on Perceived Exercise Capacity ..... | 55  |
| 4.3 Healthy Protocol and Other ICU-survivor Adaptations.....                             | 59  |
| 4.4 ICU-CARE CPET Preliminary Implementation Procedures .....                            | 64  |
| 4.4 Retrospective Healthy NIRS Sample Data Acquisition.....                              | 73  |
| CHAPTER FIVE: Results .....                                                              | 78  |
| 5.1 ICU-survivor – <b>VO<sub>2</sub></b> Preliminary Results.....                        | 78  |
| 5.1.1 Case Study 1: 64-Year-Old Female .....                                             | 79  |
| 5.1.2 Case Study 2: 34-Year-Old Male .....                                               | 82  |
| 5.1.3 ICU-survivor – NIRS Preliminary Results.....                                       | 85  |
| 5.3 Healthy – Retrospective NIRS Data Analysis.....                                      | 91  |
| CHAPTER SIX: DISCUSSION .....                                                            | 97  |
| 6.1 Main Findings .....                                                                  | 97  |
| 6.2 Identified Gaps .....                                                                | 97  |
| 6.3 Clinical Relevance of ICU-survivor <b>VO<sub>2</sub>peak</b> .....                   | 98  |
| 6.4 Protocol Comparison: Healthy vs. ICU survivor .....                                  | 98  |
| 6.5 Strengths and Limitations.....                                                       | 102 |
| 6.6 Practical Implications and Future Directions .....                                   | 104 |
| CONCLUSIONS .....                                                                        | 105 |
| REFERENCES .....                                                                         | 106 |

## List of Tables

|                                                                                                                         |    |
|-------------------------------------------------------------------------------------------------------------------------|----|
| Table 1. Summary of CPET studies in ICU-survivor population, reporting absolute or predicted VO <sub>2</sub> peak.....  | 41 |
| Table 2. Estimated VO <sub>2</sub> peak in the ICU-survivor population studies. ....                                    | 53 |
| Table 3. Perceived exercise capacity based on the staircase question. ....                                              | 56 |
| Table 4. Modified Medical Research Council (mMRC) Dyspnea Scale.....                                                    | 56 |
| Table 5. Cycle ergometer ramp protocol studies. ....                                                                    | 58 |
| Table 6. Sample characteristics of ICU-survivors ( $n = 2$ ). ....                                                      | 78 |
| Table 7. Cardiopulmonary and Muscle Oxygenation Parameters in ICU Patients at Rest and Peak Exercise.....               | 84 |
| Table 8. Preliminary ICU-Survivor TSI at VO <sub>2</sub> peak .....                                                     | 91 |
| Table 9. Sample characteristics in female, male and combined groups eligible for kinetics analysis ( $n = 12$ )......   | 92 |
| Table 10. Deoxy-hemoglobin ( $\Delta$ HHb) on and off kinetic parameters reported in females, males, and combined. .... | 94 |
| Table 11. Healthy adults TSI at VO <sub>2</sub> peak and $\Delta$ TSI from baseline ( $n = 12$ ) .....                  | 95 |
| Table 12. Healthy adults TSI at VO <sub>2</sub> peak and $\Delta$ TSI from baseline ( $n = 11$ ).....                   | 95 |
| Table 13. Individual on-kinetic parameters for $\Delta$ HHb and VO <sub>2</sub> in Healthy Adults, Combined..           | 96 |

## List of Figures

|                                                                                                                                                                                        |    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 1. Illustration of the oxygen delivery pathway.....                                                                                                                             | 28 |
| Figure 2. Example of Phase I, II, II on-kinetics.....                                                                                                                                  | 34 |
| Figure 3. Example of off-kinetics analysis. ....                                                                                                                                       | 36 |
| Figure 4. Literature-derived timeline for cardiopulmonary exercise test (CPET) post-ICU<br>discharge. ....                                                                             | 42 |
| Figure 5. ICU-CARE-CPET protocol with adaptations from Santana et al. (2025).....                                                                                                      | 51 |
| Figure 6. The ICU-CARE CPET .....                                                                                                                                                      | 52 |
| Figure 7. Equipment used in Santana et al. (2025). ....                                                                                                                                | 61 |
| Figure 8. Standardized single-session cardiopulmonary exercise test for combined assessment of<br>peak oxygen uptake and on/off-kinetics in healthy adults (Santana et al., 2025)..... | 63 |
| Figure 9. First Recruitment Block, ICU-survivor Flow Chart.....                                                                                                                        | 66 |
| Figure 10. Second Recruitment Block, ICU-survivor Flow Chart. ....                                                                                                                     | 68 |
| Figure 11. Flow chart of the Pre-ICU-CARE CPET procedures.....                                                                                                                         | 70 |
| Figure 12. Participant recruitment flow chart for initial NIRS analysis .....                                                                                                          | 73 |
| Figure 13. NIRS data analysis flow chart .....                                                                                                                                         | 75 |
| Figure 14. ICU-CARE-CPET protocol with $\text{VO}_2$ at 3 months (left panel) and 6 months (right<br>panel) post-discharge. ....                                                       | 79 |
| Figure 15. ICU-CARE-CPET protocol with $\text{VO}_2$ overlapped at 3 months and 6 months post-<br>discharge during the ICU-CARE CPET protocol. ....                                    | 80 |
| Figure 16. ICU-CARE CPET protocol $\text{VO}_2$ on-kinetic responses of a 64-year-old female ICU-<br>survivor. At 3 months (left panels) and 6 months (right panels) .....             | 81 |

|                                                                                                                                                                                                          |    |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
| Figure 17. ICU-CARE CPET protocol $\text{VO}_2$ off-kinetics of a 64-year-old female ICU-survivor. At 3 months (left panel) and 6 months (right panel).....                                              | 81 |
| Figure 18. ICU-CARE-CPET protocol $\text{VO}_2$ at 6 months post-discharge of a 34-year-old male ICU-survivor. ....                                                                                      | 82 |
| Figure 19. ICU-CARE CPET protocol $\text{VO}_2$ on kinetics (right panel) and off-kinetics (left panel) of a 34-year-old male ICU-survivor. ....                                                         | 83 |
| Figure 20. ICU-CARE-CPET protocol with NIRS-derived $\Delta\text{HHb}$ and TSI for a 64-year-old female ICU-survivor at 3 months (left panels) and 6 months (right panels) post-discharge .....          | 85 |
| Figure 21. ICU-CARE CPET protocol NIRS-derived $\Delta\text{HHb}$ and TSI on kinetic responses 64-year-old female ICU-survivor at 3 months (left panels) and 6 months (right panels).....                | 87 |
| Figure 22. ICU-CARE CPET protocol NIRS-derived $\text{HHb}$ and TSI off-kinetics 64-year-old female ICU-survivor at 3 months (left panels) and 6 months (right panels) responses.....                    | 88 |
| Figure 23. ICU-CARE-CPET protocol with NIRS-derived $\Delta\text{HHb}$ (left panel) and TSI (right panel) 34-year-old male at 6 months post-ICU discharge. ....                                          | 89 |
| Figure 24. ICU-CARE CPET protocol NIRS-derived $\Delta\text{HHb}$ and TSI on kinetics (left panels) and off-kinetics (right panels) responses for a 34-year-old male at 6 months post-ICU discharge. ... | 90 |
| Figure 25. Retrospective data of a 24-year-old healthy male tissue saturation index (TSI) and deoxy-hemoglobin ( $\Delta\text{HHb}$ ) responses.....                                                     | 93 |

### List of Abbreviations

|                      |                                                       |
|----------------------|-------------------------------------------------------|
| CO                   | Cardiac Output                                        |
| CO <sub>2</sub>      | Carbon Dioxide                                        |
| CWR                  | Constant Work Rate                                    |
| EKG                  | Electrocardiogram                                     |
| HR                   | Heart rate                                            |
| HR <sub>peak</sub>   | Peak Heart Rate                                       |
| ICU-AW               | ICU-acquired weakness                                 |
| ICU-CARE             | ICU Combined Assessment of cardioRespiratory Exercise |
| MET                  | Metabolic Equivalent of Task                          |
| NIRS                 | Near Infrared Spectroscopy                            |
| O <sub>2</sub>       | Oxygen                                                |
| O <sub>2</sub> pulse | Oxygen Pulse                                          |
| RER                  | Respiratory Exchange Ratio                            |
| RPM                  | Revolutions per minute                                |
| RQ                   | Respiratory quotient                                  |
| SBP                  | Systolic Blood Pressure                               |
| SV                   | Stroke Volume                                         |
| DBP                  | Diastolic Blood Pressure                              |
| $\dot{V}CO_2$        | Carbon dioxide output                                 |
| $\dot{V}O_{2peak}$   | Peak oxygen uptake                                    |
| W                    | Watt(s)                                               |

## **CHAPTER ONE: Introduction**

In modern critical care, survival is no longer the ultimate accomplishment (Harvey & Davidson, 2016), it is merely the beginning, where the rise of ICU survivorship forms a unique vulnerable population. Amid a rapidly aging population and modern medicine, more critically ill patients survive (Sayde, 2024), resulting in a growing population with persistent impairments extending beyond ICU stay (Jawa et al., 2025). Following extended ICU admissions, 50% of survivors of critical illness develop generalized skeletal muscle dysfunction, of unknown cause, resulting in functional and physical impairments termed ‘intensive care unit-acquired weakness’ (ICU-AW) (Griffiths et al., 2004; Griffiths & Hall, 2010; Jawa et al., 2025). Clinicians currently recognize ICU-AW as a clinical syndrome (Fan et al., 2014) of skeletal muscle and motor nerve dysfunction that develops during and after critical illness (Lad, Saumur, Herridge, dos Santos, et al., 2020). Traditional approaches for studying ICU-AW primarily focus on isolated skeletal muscle pathology, providing a narrow scope that may neglect the in-vivo physiological environment (Mendelson et al., 2023).

ICU-AW research is experiencing a shift from isolated skeletal muscle biology towards the global investigation of the integrated physiological responses throughout the oxygen delivery pathway (Mendelson et al., 2023). Given the consistent findings demonstrating that ICU-survivors face reduced exercise capacity and limited aerobic fitness after critical illness (Benington et al., 2012; Clavario et al., 2021; Joris et al., 2021; Longobardi et al., 2022; Mart et al., 2022; Van Aerde et al., 2021) and lower cardiorespiratory function association with higher mortality rates (Strasser, 2018), it is critical to examine the integrated physiological mechanisms involved in oxygen delivery and utilization through exercise testing, to enable investigation of

systemic factors and a broader investigation of the underlying pathophysiology of ICU-AW that results in decreased exercise tolerance.

Studies of exercise in ICU survivors (Benington et al., 2012; Clavario et al., 2021; Joris et al., 2021; Longobardi et al., 2022; Mart et al., 2022; Van Aerde et al., 2021) often fail to assess local skeletal muscle function – at the microvascular level – crucial to evaluate skeletal muscle oxygen uptake efficiency during exercise. Yet, in diseased states (e.g., chronic heart failure, emphysema, type II diabetes), impaired microvascular oxygen delivery can disrupt the balance between oxygen supply and skeletal muscle demand (Poole & Jones, 2012). Literature suggests that an impediment at any upstream site along the oxygen delivery pathway (i.e., lungs, cardiac, vascular, and microvascular) can result in a decreased oxygen delivery, slowing oxygen uptake kinetics, and ultimately impairing exercise performance (Poole & Jones, 2012). Therefore, isolated skeletal muscle biology may overlook the complex integrated physiological systems required to coordinate oxygen delivery and metabolism to the tissue level during locomotion (Mendelson et al., 2023); an area of research that has not yet been thoroughly evaluated in the ICU-survivor population. An issue, considering ICU-AW prevalence and the lack of effective interventions to rehabilitate skeletal muscle after ICU discharge, is that the pathophysiology of ICU-AW remains poorly understood (Mart et al., 2022), vastly overlooking vascular and systemic factors, particularly microvascular dysfunction and its relationship with ICU-AW.

A method to explore the *physiological knowledge gap*, to allow for a non-invasive assessment of microvascular function in ICU-survivors, is through the application of near-infrared spectroscopy (NIRS). Considering skeletal muscles ability to increase oxygen consumption 100-fold during maximal exercise (Poole et al., 2022), NIRS offers a portable non-

invasive solution providing real-time and high-resolution information of local perfusion of oxygen to the exercising skeletal muscle (Tuesta et al., 2022). Research suggests its application in clinical studies to measure the effects of exercise on muscle oxygenation, hemodynamics, and metabolism in patient populations experiencing central and peripheral vascular alterations (Tuesta et al., 2022).

In both healthy and cardiorespiratory-diseased individuals, cardiorespiratory fitness is one of the strongest independent predictors of overall life expectancy (Strasser, 2018). The cardiopulmonary exercise test (CPET) is a clinical and research assessment tool to assess aerobic fitness and exercise capacity, used to predict health outcomes, diagnose cardiopulmonary dysfunction, functional limitations, and assess interventions (Longobardi et al., 2022). In 2016, the American Heart Association suggested that it is important to assess cardiorespiratory fitness in clinical practice, which led to the rise of CPET use in clinical disease risk prediction and the adoption of larger-scale clinical studies (Ross et al., 2016; Song et al., 2022). Yet, its application has not yet been routinely prescribed in ICU follow-up care. Research and clinical methodologies vary widely, either sacrificing comprehensive data or conducting separate sessions when assessing both on-kinetics (rest-to-exercise transitions at a constant work rate) and off-kinetics (exercise-to-recovery transitions) (Santana et al., 2025). Particularly a barrier to vulnerable populations and clinical research, where multi-session visits may be a less practical method within a clinical setting and a simple design for the participant is preferred (McDonald et al., 2006). Relevant, as ICU follow-up research holds unique challenges in participant recruitment, amid the associated burden of caregivers (Cameron et al., 2016).

A significant *clinical practical gap* remains. For example, literature highlights the lack of standardized ICU follow-up care (Jawa et al., 2025), particularly, a single-session CPET protocol

to assess oxygen transport and utilization comprehensively, where pulmonary and microvascular oxygen kinetics remain under-characterized within the ICU population. A solution that is well established in other chronic cardiorespiratory disease populations (Radtke et al., 2019). Research suggests the use of the CPET as a practical method to assess exercise capacity in ICU-survivors, with benefits including guiding rehabilitation programs (Van Aerde et al., 2021), exercise prescription, and assessing responses to research interventions (Benington et al., 2012). However, many of the established ICU follow-up care clinics lack a formalized process for the implementation of CPET. Therefore, pushing research towards the development of a comprehensive, streamlined, and standardized protocol necessary to ameliorate recruitment and retention (Jawa et al., 2025).

Recently, our team developed a single-session CPET protocol for a combined assessment of  $\dot{V}O_{2\text{peak}}$  and on/off  $\dot{V}O_2$  kinetics in healthy adults on a cycle ergometer (Santana et al., 2025). Given its streamlined, single-session approach, in a weight-bearing exercise, its clinical application holds innate benefits which may similarly provide a systematic methodological approach for studying exercise responses in ICU-survivors. However, to enable further investigation of the physiological underpinnings of ICU-AW, a significant research gap remains. Currently, there is no standardized, single-session protocol integrating CPET-derived oxygen on/off kinetics complemented by quantitative insights provided by NIRS technology to comprehensively assess exercise capacity and skeletal muscle microvascular function tailored to accommodate the ICU-survivor population.

This thesis intends to lay the foundation to allow future research to address both the clinical practice and research gaps. Building upon Santana et al., (2025), key adaptations involve: proposing a literature-derived ICU correction factor to determine constant work rate

(CWR) at 30%  $\dot{V}O_{2reserve}$ ; and proposing an incremental ramp protocol based on self-reported functional status to individualize each ramp protocol (5, 10, 15, or 20W.min<sup>-1</sup>); integrating a NIRS assessment, to provide a patient-centered approach to enable further investigation of ICU-AW. By engaging patients in protocol design, through an individualized approach within a single-session design, in hopes of improving clinical practice and research efficiency in future studies.

To reach this goal, this thesis proposes the development of a comprehensive standardized CPET protocol, measuring peak oxygen uptake ( $\dot{V}O_{2peak}$ ),  $\dot{V}O_2$  on/off-kinetics including an individualized constant work rate, and skeletal muscle oxygenation (tissue saturation index and deoxy hemoglobin) responses in ICU-survivors in a single session. This ICU Combined Assessment of cardioRespiratory Exercise (ICU-CARE) CPET protocol allows evaluation of exercise capacity, how fast and efficiently the cardiorespiratory systems meet muscle O<sub>2</sub> demands of exercise (on-kinetics), how quickly central (i.e., systemic, cardiopulmonary) and peripheral (i.e., local, skeletal muscle) systems recover (off-kinetics), and insight into the microvascular oxygenation responses in ICU-survivors using a direct local measurement. Piloted on two ICU survivor participants before larger-scale implementation for strategic planning purposes. Additionally, a retrospective NIRS data analysis was conducted to determine whether tissue saturation index (TSI) peak and on/off deoxy-hemoglobin (HHb) kinetics in healthy adults could be obtained from our recently published, single-session, combined CPET protocol (Santana et al., 2025). To later serve as a reference to enable future investigation of ICU-AW and/or microvascular dysfunction by comparing healthy and similar data collected in ICU-survivors to determine similarities or deviations of central or peripheral CPET-NIRS derived responses.

## **CHAPTER TWO: Literature Review**

The goal of this chapter is to provide a literature review to support the rationale for this thesis. First, by building upon an overview of ICU survivorship advancement and the emergence of ICU-AW. Followed by the recent transitions in research, regarding the investigation of the physiological mechanisms underlying ICU-AW, including the identification of knowledge gaps. Next, the discussion will transition to reviewing tools for exploring the oxygen delivery pathway that will enable new directions of research, including both local microvascular and global cardiopulmonary assessment methods, to justify thesis deliverables.

### **2.1 Advances in Critical Care Unit Survivorship**

Over the past 60 years, intensive critical care has undergone remarkable advancements in short-term survival, enabling the survival of more severely ill and injured patients (Harvey & Davidson, 2016). Critical illness professionals are starting to recognize that short-term outcomes have drastically improved, increasing critical illness survivorship (Sayde, 2024). For instance, a pivotal point in critical care medicine occurred during the 1952 Copenhagen poliomyelitis epidemic, where anesthesiologist Bjørn Ibsen introduced positive pressure manual ventilation via tracheostomy, significantly reducing mortality rate from ~90% to 25% (West, 2005). Such breakthroughs in technology inspired deeper exploration of human pathophysiology (Adhikari et al., 2010). Having established the increase in ICU survivorship, the next section explores the shift from survival to recovery.

### **2.2 Shift from Survival to Recovery**

Critical care research has primarily focused on vital organs and short-term mortality to achieve a ‘cure’ to attain survivorship, whereas now, there is a demand for enhancing recovery and patient-centered outcomes (Battle et al., 2019; Denehy et al., 2013; Prescott et al., 2019). A

shift that has become more noticeable during the coronavirus disease 2019 (COVID-19) pandemic, as attention expanded from mortality to morbidity focus (Longobardi et al., 2022). As the population ages and ICU survivorship increases (Sayde, 2024), critical care is an increasingly valuable resource in increasing demand. Therefore, critical care must evolve to address these demands that extend beyond the initial critical illness.

Growing attention is now being directed towards the long-term consequences of critical illness, with impairments associated with diminished quality of life (Berney et al., 2012), increased healthcare utilization, as well as a significant socio-economic burden for both patients and their caregivers (Puthuchearry & Denehy, 2015; Tiru et al., 2015). To increase awareness (Harvey & Davidson, 2016), experts at a Society of Critical Care Medicine conference coined the term post-intensive care syndrome (PICS) in 2010 to describe a new persistent decline of physical, cognitive, and mental functioning, for which other causes have been excluded (Smith & Rahman, 2025). PICS remains highly prevalent, as up to 80% of ICU-survivors suffer from cognitive, psychological and functional long-term consequences (Colbenson et al., 2019; Jawa et al., 2025).

Amidst the shift towards recovery (Harvey & Davidson, 2016), there is a growing demand to alleviate PICS by enhancing patient-centered outcomes in ICU-survivors (Battle et al., 2019; Denehy et al., 2013; Prescott et al., 2019). Despite Canada's efforts to begin opening ICU follow-up clinics, there remains a significant gap – the lack of standardized post-ICU follow-up care (Jawa et al., 2025). This is particularly relevant in Manitoba, where the absence of a structured post-ICU care continues to affect patients, despite evidence of long-term consequences lasting up to 5 years post-ICU discharge (Herridge et al., 2011a; Van Aerde et al., 2021).

The rise of ICU survivorship unveils the opportunity to improve the unmet needs of this population. However, the complexity of survivors requires further investigation of PICS before implementing a holistic follow-up clinic. Therefore, this thesis will adopt a step-by-step approach, targeting one aspect of PICS, where the next section explores ICU-AW.

## **2.3 ICU-Acquired Weakness**

### *Definition*

A prominent subdivision of PICS is ‘intensive care unit-acquired weakness’ (ICU-AW) (Jawa et al., 2025) - a syndrome of generalized muscle weakness that emerges during and after critical illness, often involving myopathy and neuropathy, impairing function and quality of life (Fan et al., 2014; Hassan Farhan et al., 2016; Jawa et al., 2025; Schefold et al., 2010; Wang et al., 2020). Subsequent advancements in electrophysiological testing and muscle biopsy techniques in the 1990s and early 2000s further enhanced diagnostic capabilities, permitting subtype CIP (Hassan Farhan et al., 2016); involving critical illness myopathy (CIM), and when CIM and CIP coexist, critical illness neuromyopathy (CINM) (Hassan Farhan et al., 2016).

### *Etiology*

Early understandings of ICU-AW emphasize neuropathy, muscle atrophy and mitochondrial dysfunction (Mendelson et al., 2023). However, recent research now recognizes ICU-AW to be more than just the result of disuse, but instead a distinct pathological syndrome (Lad, Saumur, Herridge, Dos Santos, et al., 2020). Yet, the precise pathophysiological mechanisms remain unclear (Lad, Saumur, Herridge, Dos Santos, et al., 2020). Research suggests that the etiology of ICU-AW is multifactorial (Benington et al., 2012; Lad, Saumur, Herridge, Dos Santos, et al., 2020; Prescott et al., 2019; Vanhorebeek et al., 2020), potentially rooted to both individual factors, such as pre-existing condition, comorbidities, sex, and older

age, as well as ICU-related factors (Herridge et al., 2011a; Hiser et al., 2023; Jawa et al., 2025; Lee et al., 2020; Needham et al., 2012; Salluh et al., 2015; Turnbull et al., 2016). These ICU-related factors include systemic inflammation, such as sepsis-induced systemic inflammation, leading to direct muscle injury and metabolic disturbances (Schefold et al., 2010), often involving prolonged mechanical ventilation (Friedrich et al., 2015), immobility (Hassan Farhan et al., 2016), and the use of corticosteroids as contributing factors to ICU-AW development (Schefold et al., 2010).

### *Symptoms*

ICU-AW symptoms include persistent muscle weakness, reduced mobility, chronic pain, chronic fatigue, reduced exercise capacity and increased exercise intolerance (Fan et al., 2014; Hassan Farhan et al., 2016; Jawa et al., 2025; Schefold et al., 2010; Wang et al., 2020). These symptoms can persist for months to years (Ballve et al., 2017; Herridge et al., 2011b; Jawa et al., 2025), including wide-ranging effects - significantly reducing quality of life, hindering activities of daily living, and delaying return to work (Griffiths et al., 2004; Griffiths & Hall, 2010; Jawa et al., 2025). It also directly contributes to the patient's long-term morbidity and loss of independence (Batt, Herridge, & Dos Santos, 2019; Schefold et al., 2010), causing a strain on caregivers (Herridge et al., 2011) and families (Harvey & Davidson, 2016). All of which contribute to a broader societal and economic burden, as ICU-AW increases readmission rates, increasing healthcare utilization (Hermans et al., 2014), placing a substantial strain on public health resources.

Despite its clinical significance, the classification of ICU-AW remains without consensus for the “gold standard” diagnostic tool, as no single tool can provide a definitive diagnosis of ICU-AW, necessitating a combined approach (Xin et al., 2025; Yang, Li, Jiang, Wang, et al.,

2018). The most widely used method includes manual muscle testing using the Medical Research Council (MRC) sum score, where a score below 48 (out of 60) indicates clinically significant weakness in awake and cooperative patients, limiting its applicability and specificity within ICU settings (Xin et al., 2025). Other methods include electrophysiological testing, histopathological evaluations, inflammatory markers, and ultrasound, which improve specificity (Xin et al., 2025). However, less invasive techniques should be further investigated.

### *Prevalence*

The prevalence of ICU-AW varies by population and clinical context. Most recently, Jawa et al. (2025) reported that ICU-AW affects up to 50% of general ICU-survivors, while Hassan Farhan et al. (2016) reported 56-74% within a surgical ICU context. Among septic patients, Schefold et al. (2010) and Wang et al. (2020) reported that up to 70% of patients acquire this condition, underscoring ICU-AW's high incidence and relevance that remains a pertinent issue today (Schefold et al., 2010; Wang et al., 2020). It is important to identify the risk factors related to ICU-AW, which is discussed in the next section.

#### **2.3.1 Risk Factors**

Influenced by a complex interplay of patient-specific and ICU-related factors, ICU-AW risk factors may include sepsis, prolonged mechanical ventilation, immobility, systemic inflammation, and pharmacologic interventions, such as corticosteroids and sedatives. Next is a brief overview of the risk factors and their association with ICU-AW.

### *Sepsis*

Defined by multi-organ failure, a significant risk factor for developing ICU-AW is sepsis (Rozenberg et al., 2023). Historically, clinicians have documented observations of unexplained weakness in critically ill patients. A “rapid loss of flesh” was reported to be linked with sepsis as

early as 1892 (Osler W. D., 1892), laying the foundation of muscle wasting and its link with critical illness complications. The word ‘sepsis’ derives from an ancient Greek word, referring to ‘rot’, ‘decomposition’, or ‘decay’ in the presence of bacteria (Geroulanos & Douka, 2006). The modern definition of sepsis is termed a life-threatening organ dysfunction caused by the dysregulated host response to infection (Singer et al., 2016) that can cause a cascade of events, such as systemic inflammation, muscle breakdown, impaired contractility, and reduced capacity for muscle repair (Batt, Herridge, & dos Santos, 2019; Lad, Saumur, Herridge, dos Santos, et al., 2020). In 2017, the prevalence of sepsis was reported (Rudd et al., 2020), with over 47 million cases and at least 11 million sepsis-related deaths, accounting for 1 in 5 of all deaths globally, establishing sepsis as a leading global health issue (Rudd et al., 2020). Sepsis remains one of the leading causes of death within the ICU (Scheffold et al., 2010). Notably, research reports that CIP is most commonly associated with severe sepsis, almost five times higher than in patients without multiorgan failure (Hassan Farhan et al., 2016). Involving its inherent systemic complexity, sepsis remains a leading cause of ICU-AW, and is often linked with mechanical ventilation (Scheffold et al., 2010; Wang et al., 2020; Yang, Li, Jiang, Wang, et al., 2018).

### *Mechanical Ventilation*

Prolonged mechanical ventilation in ICU patients  $\geq 7$  days is the prior threshold for the development of ICU-AW (Herridge et al., 2016). Mechanical ventilation, even after as little as two days, causes rapid atrophy of respiratory musculature due to automatic unloading (Smith & Rahman, 2025). One study suggests that CT scans reveal diaphragm thinning at an average rate of 6% per day in medical ICU patients ( $n = 7$ ) (Grosu et al., 2012). Strikingly, ICU-AW occurs in 25% to 75% mechanically ventilated patients (Fan et al., 2014). Additionally, the administration of opiates and sedatives has been found to exacerbate disuse and atrophy,

dampening neural activity of the respiratory musculature, further complicating efforts to wean patients from ventilators (Hassan Farhan et al., 2016; Smith & Rahman, 2025), exacerbating both pulmonary and systemic inflammation, and inducing proinflammatory cytokine expression in peripheral blood (Dhanireddy et al., 2006).

### *Systemic Inflammation*

Whether driven by sepsis, trauma, or the physiological stress of critical illness, persistent systemic inflammation, including elevated levels of tumor necrosis factor-alpha (TNF- $\alpha$ ), interleukin-6 (IL-6), IL-1 $\beta$  and IL-10, leads towards myopathy and neuropathy, resulting in poor oxygenation of local tissues, which may further exacerbate the development of ICU-AW (Guo et al., 2024). Inflammation is managed with corticosteroids (Yang, Li, Jiang, & Xi, 2018).

### *Treatment Using Corticosteroids*

Due to its anti-inflammatory and anti-fibrotic effects, the use of corticosteroids is a key treatment for critically ill patients (Yang, Li, Jiang, & Xi, 2018). For example, corticosteroid therapy results in a shorter duration of mechanical ventilation, faster resolution for patients in shock, and shorter ICU hospitalization, yet its side effects remain controversial. Research suggests a significant association between corticosteroid use and ICU-AW (Yang, Li, Jiang, & Xi, 2018). Furthermore, recent research has also increasingly focused on the role of immobilization in ICU-AW (Chambers et al., 2009; Needham, 2008).

### *Immobilization*

Prolonged bed rest and immobilization can rapidly weaken the muscles of ICU patients (Smith & Rahman, 2025). Research shows that muscle mass can decrease by approximately 2% per day (Hassan Farhan et al., 2016), with patient immobilization leading to over 10% muscle loss, linked to functional impairment (Puthuchear et al., 2013; Vanhorebeek et al., 2020). The

effects of immobility has led to the promotion of sedative interruption and early rehabilitation therapy (Fan et al., 2014). However, ICU-AW is suspected to be more complex than simply a muscle atrophying condition, requiring further investigation (Lad, Saumur, Herridge, Dos Santos, et al., 2020). Emerging research is now shifting from isolated skeletal muscle biology towards a more integrated physiological response investigation (Mendelson et al., 2023).

### **2.3.2 Shift from Isolated Skeletal Muscle Biology towards Integrative Physiology**

ICU-AW has long been recognized as a pathological condition affecting skeletal muscle, characterized by localized neuromuscular impairments, such as CIM, CIP, or their combination (Hassan Farhan et al., 2016). Yet, research focused on isolated skeletal muscle biology may overlook complex and integrated physiological systems responsible for coordinating oxygen delivery to the terminal sites of utilization. A site otherwise known as the microvascular-myocyte oxygen exchange (Hirai et al., 2019). This perspective has led to a shift in research focus from local skeletal muscle biology towards the investigation of integrative physiologic responses across the oxygen delivery and utilization pathways (Mendelson et al., 2023). Prompting a shift beyond cellular and structural skeletal muscle pathology towards examining how impairments across these pathways may drive the symptoms of ICU-AW (Mendelson et al., 2023).

### **2.4 Role of Oxygen Delivery**

Oxygen transport relies heavily on the coordinated interactions between the cardiovascular, pulmonary, and peripheral systems (Roy & Secomb, 2021), to deliver this fundamental molecule necessary to sustain energy production throughout the body, to tolerate functional independence (Tuesta et al., 2022). Fundamental to understanding exercise in health and disease populations (Dominelli et al., 2021). The next section discusses a brief overview of the pulmonary, cardiovascular, and peripheral systems.

### 2.4.1 Circulatory Overview

The circulatory system supports tissue metabolism by transporting oxygen and nutrients to tissues and removing metabolic waste products through a highly integrated transport network, crucial for maintaining cellular homeostasis (Rademakers et al., 2019). Blood circulation occurs through two interconnected loops: pulmonary circulation, which enables gas exchange in the lungs, and systemic circulation, which distributes oxygenated blood to tissues (Ainab et al., 2025).

#### *Pulmonary System*

The pulmonary system is responsible for oxygen diffusion from lungs into the bloodstream (Amador et al., 2025). Blood consists of white blood cells, platelets, plasma and red blood cells (RBC) (Jyoti Batra et al., 2022). RBCs contain millions of molecules of hemoglobin, a protein carrier that binds oxygen in the lungs, and transports oxygen within arteries towards the last step of the oxygen delivery pathway – the diffusion of oxygen from capillaries to cells, utilized within mitochondria for oxidative metabolism, a form of ATP generation through oxidative phosphorylation, enabling greater energy production than through anaerobic metabolic pathways (Pittman, 2011). Any dysfunction of the pulmonary system, for example, caused by tissue damage affecting lung structure or weakness of the respiratory muscle, can limit arterial oxygen content, reducing overall oxygen delivery which may influence the oxygen cascade and peak oxygen uptake (Roy & Secomb, 2021).

#### *Cardiovascular System*

The cardiovascular system is responsible for transporting oxygenated blood to peripheral systems (Roy & Secomb, 2021). In healthy individuals, macrocirculation regulates whole-body blood flow and perfusion pressure (Joyner & Limberg, 2014). However, cardiac dysfunction, as

seen in chronic heart failure patients, results in a reduced oxygen supply to peripheral tissues, both at rest and during exercise, due to a diminished ejection fraction, stroke volume, and a heart rate response, insufficient to compensate for the reduced stroke volume, which is often linked to exercise intolerance (Poole et al., 2012).

### *Peripheral System*

The peripheral system, including muscles and microcirculation, plays a vital role in the autoregulation of oxygen extraction at the tissue level (Mendelson et al., 2023). Skeletal muscle has the widest range of oxygen metabolism of any other tissue or organ, and this range of metabolism is needed, as well as increased blood flow to help tolerate exercise or activities of daily living which are performed largely by repetitive and rhythmic skeletal muscle activity (Mendelson et al., 2023). Typically, microcirculation controls the local blood flow distribution (Bagher & Segal, 2011) and oxygen diffusion into tissues (Poole et al., 2022). In healthy individuals, regulation is mediated by microcirculation and mitochondria, the terminal sites of oxygen diffusion and utilization to produce the energy required for muscle contraction (Roy & Secomb, 2021), important for activities of daily living. The next section introduces a brief overview of the microcirculation.

#### **2.4.2 Microcirculation Overview**

Microcirculation is made up of tiny blood vessels, comprising arterioles, capillaries, and venules, which functions to form a metabolic exchange interface between blood and tissues (Mendelson et al., 2023). Specifically, the structure of arterioles are lined with smooth muscle, acting as the primary site of resistance to regulate blood entry to capillaries via vasodilation and vasoconstriction, modulated by myogenic, metabolic, and neurohumoral mechanisms (Roy & Secomb, 2021). Capillaries facilitate metabolic exchange, as its structure is composed of a single

endothelial cell lining with numerous routes optimizing surface area (Wenceslau et al., 2021), arguably the most important of the cardiovascular system to allow for oxygen exchange (Güven et al., 2020). Then, post-capillary venules return deoxygenated blood to larger veins and the heart (Güven et al., 2020). The primary function of microcirculation is to ensure adequate tissue perfusion, to match blood flow and oxygen delivery to meet metabolic demands of the corresponding tissue, playing a major role in organ (dys-)function (Chalkias et al., 2022). Historically, microcirculation has been largely ignored as a therapeutic target, but is being recognized as an area of opportunity to develop targeted evaluation techniques (Edule et al., 2011). In this case, to identify if there is a link between microvascular dysfunction and ICU-AW. The rate of tissue oxygen consumption and oxygen diffusion can be quantitatively described by Fick's Principle and Law of Diffusion, respectively, each operating at different physiological scales.

#### *Fick's Principle and Law of Diffusion*

One of the central concepts in exercise physiology is in understanding how oxygen moves throughout the body and at the tissue level. To help, an explanation of the Fick's Principle and the Fick's Law of Diffusion is included. The Fick's Principle is a foundational concept to quantify oxygen transport from the atmosphere to the peripheral tissues, relevant, as the leg and muscle  $\dot{V}O_2$  relies on this principle (Poole & Jones, 2012). According to the Fick's Principle, the rate of muscle oxygen consumption (in this case,  $\dot{V}O_2$ ) is the product of muscle blood flow ( $\dot{Q}_m$ ) multiplied by the difference between arterial-venous blood ( $CaO_2 - CvO_2$ ):

$$\dot{V}O_2 = \dot{Q}_m \times (CaO_2 - CvO_2)$$

Where:  $\dot{V}O_2$  = oxygen uptake;  $\dot{Q}_m$  = muscle blood flow;  $CaO_2 - CvO_2$  = arteriovenous oxygen difference.

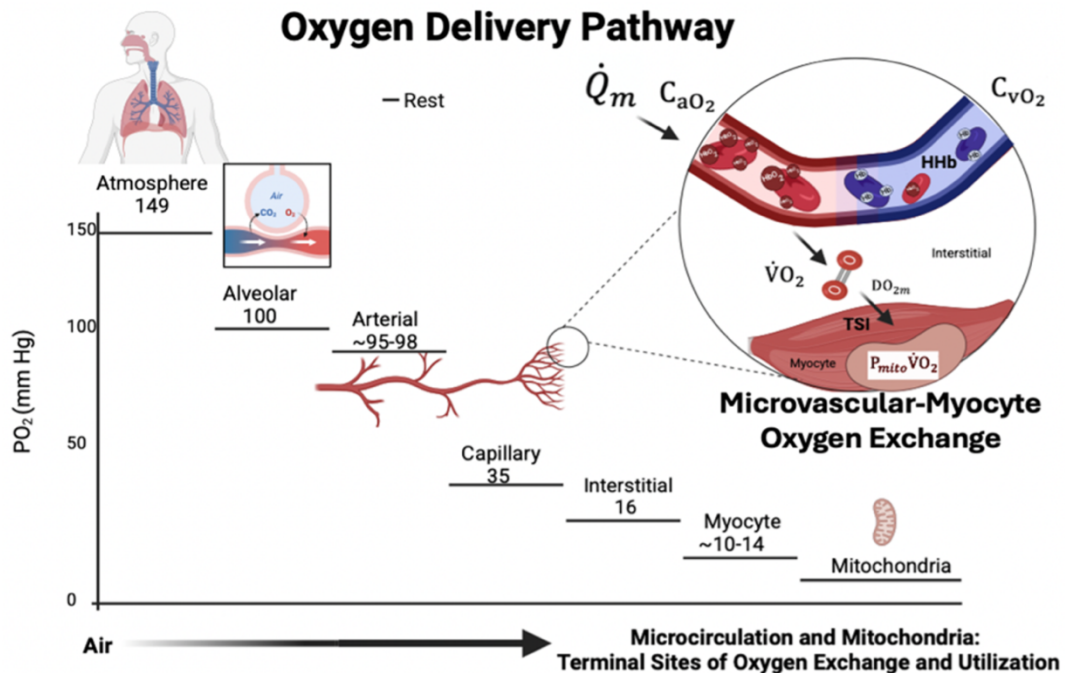
Historically, changes in  $\dot{V}O_{2\text{peak}}$  (exercise training, aging, disease) were attributed to changes in oxygen delivery by changes in muscle's perfusive  $O_2$  flux, whereas now, attention is being shifted to the role of  $O_2$  diffusion capacity (Poole & Musch, 2023). Where, the rate of oxygen diffusion across the microvascular wall towards the myocyte and mitochondria is described by the Fick's Law of Diffusion. According to the Fick's Law of Diffusion, the rate of oxygen diffusion is the product of the muscle oxygen diffusion, multiplied by the difference between microvascular  $PO_2$  and the mitochondrial  $PO_2$  in the equation below:

$$\dot{V}O_2 = DO_{2m} \times (\text{microvascular } P_{mv}O_2 - P_{\text{mito}}\dot{V}O_2)$$

Where:  $DO_{2m}$  = muscle  $O_2$  diffusion ,  $P_{mv}O_2$  = microvascular partial pressure of  $O_2$  ( $PO_2$ );

$P_{\text{mito}}\dot{V}O_2$  = mitochondrial partial pressure of  $O_2$  ( $PO_2$ ).

To conceptualize these central concepts, I have incorporated both in the figure below, demonstrating the pathway of oxygen transport (Barstow, 2019; Hirai et al., 2019; Poole & Jones, 2012).



**Figure 1.** Illustration of the oxygen delivery pathway. Illustration includes the Fick Principle, Fick's Law of Diffusion, HHb and TSI in the oxygen delivery pathway. Arrows depict the last step of the oxygen delivery pathway, where oxygen travels from microcirculation to the mitochondria. Illustration adapted from Hirai et al. (2019) (oxygen cascade, Figure 1 and Figure 4), Barstow et al. (2019) (micro illustration, NIRS data and Fick equations) and Poole and Jones (2012) (Figure 3). Figure generated by Britney Blunderfield with BioRender.

### 2.4.3 Microvascular-Myocyte Oxygen Exchange

Microvascular-myocyte oxygen exchange, the process by which O<sub>2</sub> is transferred from blood to muscle for energy production, is critical for maintaining energy production throughout the body and for muscle function (Tuesta et al., 2022). Skeletal muscles' response from rest to peak exercise can increase oxygen consumption 100-fold (Poole et al., 2022). This increase in oxygen consumption and muscle work correlates with a proportional increase in muscle blood flow and indicates exquisite mechanisms for matching oxygen demand with supply (Murrant &

Sarelius, 2015; Poole & Jones, 2012). Impairment in microvascular-myocyte oxygen exchange leads to weakness and fatigue observed in chronic diseases and critical illness (Barstow, 2019). The next section will briefly introduce skeletal muscle microcirculation in chronic disease and critical illness.

## **2.5 Skeletal Muscle Microcirculation in Chronic Disease and Critical Illness**

Impairments in vascular control mechanisms contribute to exercise limitations in disease conditions (Poole et al., 2021). Disruptions along the oxygen delivery and utilization pathway can impair energy production (Poole & Jones, 2012), leading to fatigue, reduced mobility, and diminished quality of life (Poole et al., 2012). Additionally, bidirectional diseases such as heart failure and frailty show cardiovascular involvement towards symptoms of ‘weakness’ (Talha et al., 2023), yet these have rarely been considered for ICU-AW.

The research focus of ICU-AW on isolated skeletal muscle biology, characterized by changes within the myocyte and myofiber, resulting in the loss of muscle mass and impaired contractility, is now being proposed to broaden its scope (Rozenberg et al., 2023). We know that ICU-survivors experience impaired exercise capacity and reduced muscular oxygen metabolism, suggesting mitochondrial dysfunction (Mart et al., 2022). However, the microcirculatory environment is now an emerging factor in ICU-AW research that researchers should consider (Rozenberg et al., 2023). Drawing from parallels with chronic diseases, such as heart failure and COPD, Mendelson et al. (2023) highlight the need to consider integrative cardiovascular physiology in the pathogenesis of ICU-AW, as there is a likelihood of systemic impairments across the oxygen delivery pathway that may contribute to functional decline in survivors of critical illness (Mendelson et al., 2023). Considering that a dysregulated microvascular and circulatory system plays a significant role in tissue oxygenation and the

pathogenesis of critical illness (Østergaard et al., 2015), the microvascular-myocyte oxygen exchange site should be further investigated within this population.

Sepsis and critical illness trigger an inflammatory cascade, that causes persistent bioenergetic dysfunction, known to induce impaired contractility and structural integrity that may drive the development and the persistent symptoms of ICU-AW (Rozenberg et al., 2023). Microcirculatory disturbances, such as impaired capillary flow and oxygen extraction, are common in sepsis (Rozenberg et al., 2023). It is thought that inflammatory cytokines can damage the endothelial lining of microvessels (Rozenberg et al., 2023), leading to neuromuscular and microcirculatory damage, myopathy and neuropathy, resulting in poor oxygenation of local tissues (Guo et al., 2024). Moreover, prolonged mechanical ventilation can also induce proinflammatory cytokine expression in peripheral blood, further contributing to the pathogenesis of ICU-AW (Dhanireddy et al., 2006).

Reframing ICU-AW as a physiological failure of integrated oxygen supply-demand matching would be a radical change from current perspectives, with the potential to inform new avenues for diagnosis, treatment, and prevention strategies. *As there is currently a paucity of research describing a link between cardiovascular dysfunction and ICU-AW*, particularly how impairments in vascular control mechanisms lead to reduced exercise capacity and worse health outcomes (Dallaire et al., 2017). Therefore, *further investigation is warranted to identify any causal relationships between microvascular dysfunction and ICU-AW*.

Thus, an important research avenue is to further evaluate ICU-AW pathophysiology. As cardiorespiratory fitness is one of the strongest independent predictors of life expectancy in both healthy and cardiorespiratory-diseased individuals (Strasser, 2018), the use of cardiopulmonary fitness and microvascular assessments would be fundamental to advance this type of research in

ICU-survivors. To help identify and account for key limiting factors, this thesis proposes combining the assessment of the respiratory, circulatory and microcirculatory systems, obtained by combining a cardiopulmonary exercise tests (CPET) using a metabolic cart with the application of near-infrared spectroscopy (NIRS), respectively. These assessments will be discussed within the next sections.

## **2.6 Cardiopulmonary Exercise Test and Near Infrared Spectroscopy Assessment Methods**

Currently, there is an urgent need to develop novel interventions that target the underlying mechanisms of ICU-AW, focusing on improving muscle and physical health to improve the lives of survivors of critical illness (Mart et al., 2025). Research encourages the development of methods in which future research can better understand the role of skeletal muscle microcirculation and microvascular link to ICU-AW development and recovery (Rozenberg et al., 2023). While the theory of oxygen delivery and utilization is well established, translating these principles into clinical insight requires appropriate assessment tools. To offer a detailed, non-invasive evaluation of both systemic and local oxygen dynamics, CPET and NIRS will be further discussed to evaluate their application in both clinical and research settings.

Research suggests that identifying methods that benefit patients experiencing ICU-AW is necessary to determine whether the benefits of diagnostic testing for ICU-AW outweigh its burden (Fan et al., 2014). Our team believes that there is strength in integrating both systemic and local assessment methods to better understand ICU-AW across the oxygen delivery pathway, providing novel insights at the cardiovascular, respiratory, and microvascular-myocyte oxygen exchange that could provide a significant opportunity for innovation in post-ICU follow-up care.

The cardiopulmonary exercise test (CPET) is a cycle ergometer-based test that utilizes a metabolic cart for advanced physiological exercise testing, commonly used in research, to study

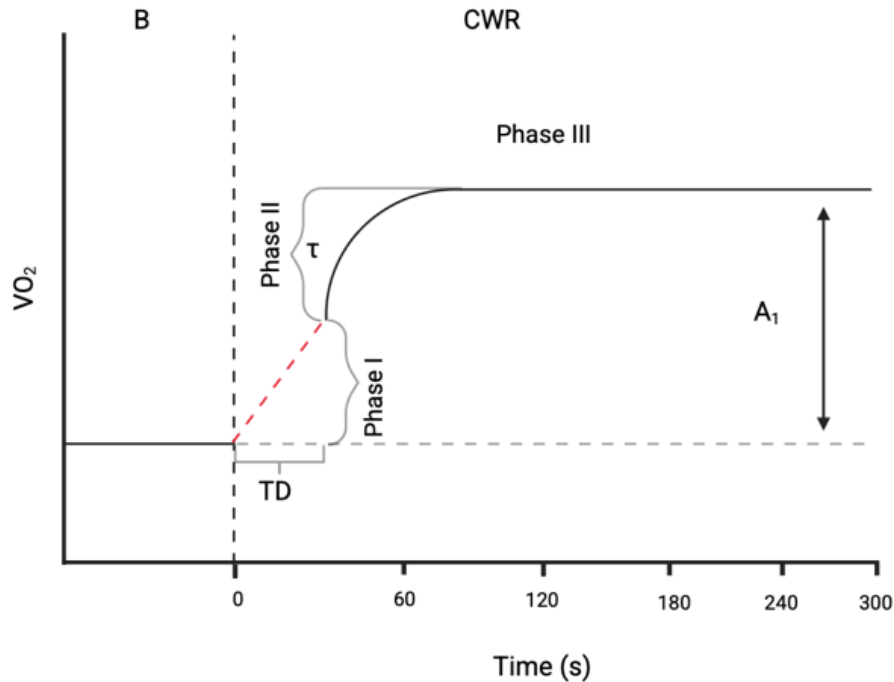
aerobic and anaerobic physiology in athletes, healthy adults (Mazaheri et al., 2021) and clinically in patients with chronic cardiorespiratory disease (Radtke et al., 2019). CPET is a valuable tool to diagnose cardiopulmonary dysfunction, assess functional limitations, exercise capacity and tolerance, evaluate interventions, and predict health outcomes (Longobardi et al., 2022). It analyzes central and peripheral disturbances across multiple systems, helping to identify which component of a patient's physiology (heart, lung, skeletal muscle) is most significantly contributing to exercise intolerance, affecting the rate at which  $\dot{V}O_2$  can adjust to energy demands/workload (Longobardi et al., 2022). A key metric for CPET is  $\dot{V}O_{2peak}$ , defined as the highest  $\dot{V}O_2$  achieved during a symptom-limited test (Poole & Jones, 2017), providing a comprehensive evaluation of cardiovascular fitness, which is often a strong predictor of mortality (Ewert et al., 2022; Mandsager et al., 2018; Nadruz et al., 2017). In addition to 'maximal' testing, 'submaximal' testing can both be assessed in  $\dot{V}O_2$  on and off kinetics analysis, critical to understanding the interplay between various physiological mechanisms vital to sustaining and recovering from locomotion (Grassi et al., 2011; Xu & Rhodes, 1999). Notably, research suggests that in disease or dysfunction states, locus of control of  $\dot{V}O_2$  kinetics can be displaced upstream, whereas in healthy individuals, the locus of control is at the muscle mitochondria (Poole & Jones, 2012).

### *$\dot{V}O_2$ On Kinetics*

At the start of a constant work rate exercise at a light-to-moderate intensity (Garber, 2018), the exponential rise in oxygen uptake towards a steady-state from rest to exercise is described as  $\dot{V}O_2$  on-kinetics (Xu & Rhodes, 1999). It reflects how efficiently the cardiovascular, pulmonary and oxidative phosphorylation responds to a sudden increase in energy demand,

indicating systemic oxygen transport and utilization (Xu & Rhodes, 1999). The transition from rest to constant work rate exercise includes three phases (Reuveny et al., 2022).

The initial rapid increase in  $\dot{V}O_2$  is described as Phase I, cardiodynamic phase (15-30 seconds), reflecting the sudden increase in cardiac output and pulmonary blood flow at exercise onset (Reuveny et al., 2022). Phase II is the primary or fast component, initiated by the arrival of venous return (i.e., from the working muscles to the lung) producing an exponential rise of  $\dot{V}O_2$ , reflecting muscle oxygen uptake (2-3 minutes) (Poole & Jones, 2012). Then, in Phase III, known as the slow component, steady-state occurs when  $\dot{V}O_2$  reaches a plateau, where energy demand meets oxygen supply, achieved by working muscles (4-5 minutes) (Poole & Jones, 2012). At higher constant workload intensities, this steady-state may be delayed or absent, or plateaus then begins drift upwards slowly because of fatigue, as a visual representation of being above anaerobic threshold, demonstrated in Figure 5 from Jones and Poole (2005). However, below anaerobic threshold, a steady-state can be obtained, represented in Phase I, II, II on-kinetics below, in a modified version of Figure 5 from Jones and Poole (2005).



**Figure 2.** Example of Phase I, II, II on-kinetics. Red dotted-line indicates skipping Phase I during kinetics analysis. B = baseline, CWR = constant work rate,  $\tau$  = tau, TD = time delay until exponential increase,  $A_1$  = amplitude from baseline to steady state. Modified from Figure 4 (Jones & Poole, 2005). Generated by Britney Blunderfield using BioRender.

This mono-exponential fitting is characterize by the following parameters:  $A_1$  = Amplitude reached from baseline to steady-state; TD = Time delay taken to the exponential response start;  $\tau$  = time constant, taken to reach 63% of the steady state or final value; MRT = mean response time ( $TD + \tau$ ) (Santana et al., 2025).

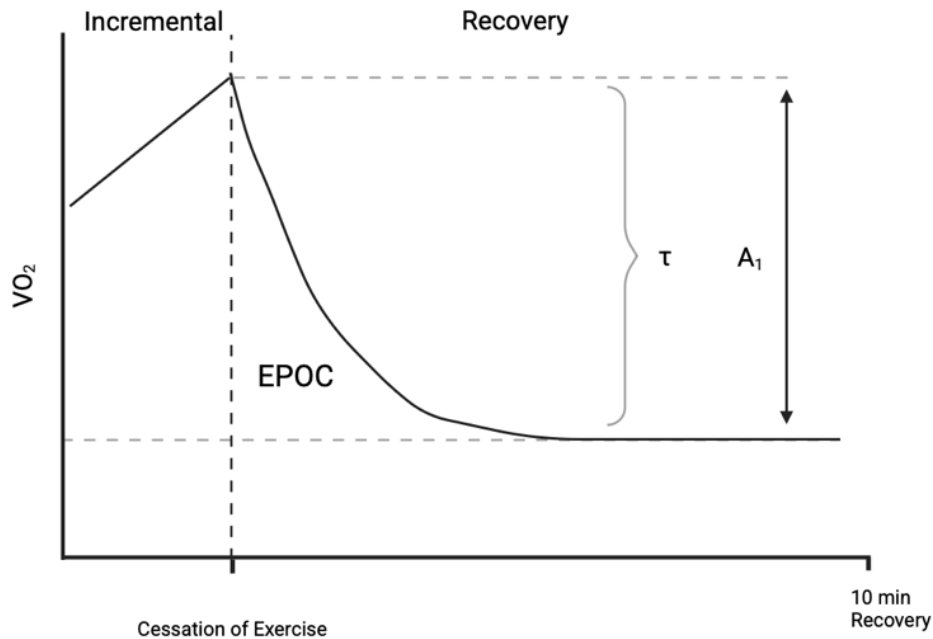
Notably, the rate of the kinetic response can provide physiological insights into systemic efficiency, critical to understanding the interplay between various physiological mechanisms (Grassi et al., 2011; Xu & Rhodes, 1999). Faster  $\dot{V}O_2$  on-kinetics results in a small  $O_2$  deficit, less substrate-level phosphorylation, and high exercise tolerance (Poole & Jones, 2012). In

contrast, slower  $\dot{V}O_2$  on-kinetics refers to a high  $O_2$  deficit, presenting a greater challenge to homeostasis, resulting in poorer exercise tolerance (Poole & Jones, 2012).

### *$\dot{V}O_2$ Off Kinetics*

Following cessation of exercise, the rate at which physiological variables, such as  $\dot{V}O_2$ , descends exponentially returning to baseline is referred to as off-kinetics (Poole & Jones, 2012). Representing the efficiency of metabolic recovery necessary to restore resting-state homeostasis. Historically, Hill and colleagues initially termed as ‘oxygen debt’ (Hill & Lupton, 1923). The sustained elevated  $\dot{V}O_2$  following cessation of exercise (Børsheim & Bahr, 2003) is a phenomenon that was later expanded by Margaria and colleagues (Margaria et al., 1933), proposing that the metabolic recovery process is central to lactate removal, which had prompted Gaesser and Brooks (Gaesser & Brooks, 1984) to introduce the term EPOC (Excess Post-Exercise Oxygen Consumption) to label this phenomenon more comprehensively (Børsheim & Bahr, 2003).

Off-kinetics are evaluated as the time required for variables to return to equilibrium after exercise by measuring the exponential time constant of the tau ( $\tau$ ) curves (Vianna et al., 2014). In diseased states, such as chronic heart failure, emphysema [chronic obstructive pulmonary disease (COPD)] and type II diabetes, and aging populations, slower kinetics reflect higher  $O_2$  deficit due to decreased muscle  $O_2$  delivery (Poole & Jones, 2012). A higher  $\tau$  implies slower kinetics, associated with functional impairments and a higher risk of mortality (Vianna et al., 2014)



**Figure 3.** Example of off-kinetics analysis. EPOC = Excess Post-Exercise Oxygen Consumption,  $\tau$  = tau,  $A_1$  = amplitude. Generated by Britney Blunderfield using BioRender.

### *Traditional vs. Single-Session Cardiopulmonary Exercise Test*

The traditional approach to evaluating both  $\dot{V}O_{2peak}$  and on/off  $\dot{V}O_2$  kinetics requires multiple exercise sessions, by first measuring  $\dot{V}O_{2peak}$  to then prescribe a CWR as a percentage of an individual's personal  $\dot{V}O_{2peak}$  (Santana et al., 2025). Unfortunately, a multi-session approach may limit recruitment and compliance, particularly problematic for ICU-follow up clinical research, as ICU survivors face unique needs, even extending to caregivers who may face depressive symptoms at least 1 year following discharge and may not choose to come voluntarily (Cameron et al., 2016).

Recently, two studies further developed CPET methodology by developing a single session CPET (Longobardi et al., 2022; Santana et al., 2025). To improve feasibility within a clinical setting, a novel single-session CPET protocol was developed previously by researchers

on a treadmill CPET (Longobardi et al., 2022). However, some methodological challenges including impeding off-kinetics analysis due to the inclusion of an active recovery period (1-minute), a short CWR duration (3-minute), which may affect the ability to achieve steady state, and most prominently, when equivalent work rates between participants have not yet been achieved, limiting the ability to compare on-kinetics data across cohorts, affecting the generalizability of the combined on/off  $\dot{V}O_2$  kinetics single session (Santana et al., 2025). Highlighting these methodological challenges has led to our recently published work to advance protocol standardization in Santana et al., (2025), discussed in the next section.

When these metrics,  $\dot{V}O_{2peak}$  and on/off  $\dot{V}O_2$  kinetics, are evaluated in a single session, the most important methodological challenge is to determine or estimate the constant work rate (CWR) without a prior maximal CPET to obtain  $\dot{V}O_{2peak}$  values. The single session has been done by previous researchers (Grassi et al., 2011; Hughson, 2009; Longobardi et al., 2022) and use a uniform CWR regardless of fitness level and subjective parameters, preventing accurate data comparison between participants. Moreover, the phases of the exercise (i.e., CWR, ramp, and recovery) within a single session protocol require standardization, since a relatively short CWR or the implementation of an active recovery can compromise data analyses when evaluating on/off kinetics (Longobardi et al., 2022; Santana et al., 2025).

#### *Recent Advances in Protocol Standardization for ICU survivors*

A crucial step towards addressing methodological challenges in protocol standardization is to resolve relative CWR to promote generalizability while also promoting patient recruitment and retention from a single session (Santana et al., 2025). Our recent publication in the healthy adult population by Santana and colleagues (2025) (Santana et al., 2025) built upon the novel work of Longobardi and colleagues' single-session concept (Longobardi et al., 2022), by

changing the modality from treadmill to an upright cycle ergometer, employing a longer on-transient phase of 5 minutes to allow more time for individuals to reach a steady state, including a constant work rate at a relative intensity across the cohort, followed by the 20 Watts/min incremental phase to attain  $\dot{V}O_{2peak}$ . Lastly, offering an off-transient phase excluding the active recovery component to allow for a more accurate off kinetics analysis.

Results of this study were derived from healthy participants and analysis included on/off  $\dot{V}O_2$  kinetics with mono-exponential fittings, with no significant differences between predicted and measured  $\dot{V}O_{2peak}$  ( $p = 0.47$ ). Results included a strong correlation ( $r = 0.88$ ) and good agreement between the calculated/actual individuals' 30%  $\dot{V}O_{2reserve}$ , where the measured exercise intensity at CWR closely matched the target of 30%, indicating that results had high similarity between predicted and measured values (Santana et al., 2025). Based upon this successful development of a standardized single-session CPET protocol for a combined assessment of  $\dot{V}O_{2peak}$  and on/off  $\dot{V}O_2$  kinetics, in this healthy population (Santana et al., 2025), a next logical step is to adapt this fundamental protocol for use in those with low peak oxygen uptake caused by disease.

This thesis builds upon the protocol developed by Santana et al., (2025) in a healthy-young-adult population, incorporating key adaptations, such as integrating NIRS technology, proposing a literature-derived ICU correction factor to determine constant work rate (CWR) at 30%  $\dot{V}O_{2reserve}$ , and proposing an incremental ramp protocol based on self-reported functional status to individualize each ramp protocol (5, 10, 15, or 20W.min<sup>-1</sup>). These key adaptations developed within the ICU-CARE CPET protocol development study aims to advance patient-centered research through a more individualized approach in hopes of improving clinical practice and research efficiency in future studies.

### *ICU-Survivor Cardiopulmonary Exercise Test*

Consistent findings indicate that ICU-survivors face reduced exercise capacity and limited aerobic fitness after critical illness (Benington et al., 2012; Clavario et al., 2021; Joris et al., 2021; Longobardi et al., 2022; Mart et al., 2022; Van Aerde et al., 2021), with reduced  $\dot{V}O_{2peak}$  often falling below 80-85% of predicted values derived from a variety of equations not yet standardized within ICU survivor CPET studies (Benington et al., 2012; Mart et al., 2022; Van Aerde et al., 2021). Table 1 provides information regarding  $\dot{V}O_{2peak}$  values, percentage of predicted values in the ICU-survivor population CPET literature review. For example, median relative  $\dot{V}O_{2peak}$  in one study was 12.6 ml/kg/min which would be classified as low exercise capacity ( $\dot{V}O_{2peak} < 80\%$ ) compared to predicted peak values, with well over half of all those examined, ( $n = 11/14$ , median age 63 at 6 months post-ICU) below this threshold (Mart et al., 2022). Supporting the need for a standardized and specialized CPET protocol for this population.

The CPET has not yet been routinely prescribed in ICU follow-up care, despite its ability to assess exercise capacity in ICU-survivors, with benefits including guiding rehabilitation programs (Van Aerde et al., 2021), exercise prescription, and assessing interventions (Benington et al., 2012). Research and clinical methodologies vary widely, either sacrificing comprehensive data or conducting separate sessions when assessing both on-kinetics and off-kinetics.

Conducting multi-session visits may be a barrier to patients participating in clinical research, particularly for ICU follow-up over a longitudinal period due to the associated burden of time, effort for both the patient as well as their caregivers (Cameron et al., 2016). Since longitudinal follow-up care is imperative for long-term well-being within this vulnerable population, researching the development of a comprehensive, streamlined, and standardized protocol to ameliorate recruitment and retention is necessary (Jawa et al., 2025). Notably, Santana et al.

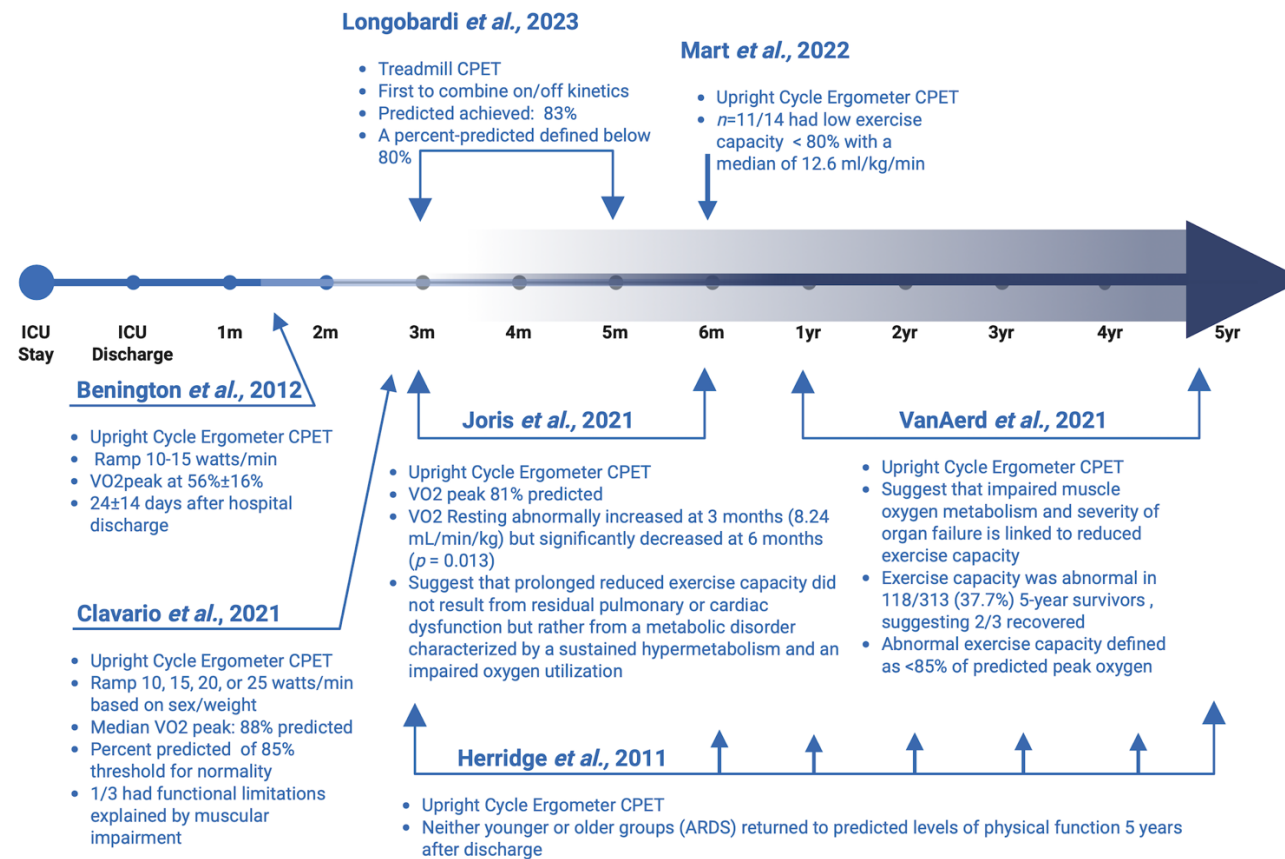
(2025) suggest that the single-session protocol design may enable greater recruitment, amid its combined design, to enhance detail for clinical application.

Figure 4 shows the timeline of testing for these studies and demonstrates that survivors show reduced peak values despite some improvement – however, given these wide ranging and variable results, without clear explanation as to which underlying mechanisms may be responsible, it is important to develop a standardized test to track improvement for such underlying mechanisms. Where, NIRS may be one method to provide local insight.

**Table 1.** Summary of CPET studies in ICU-survivor population, reporting absolute or predicted  $\dot{V}O_{2peak}$ 

| CPET Study & Modality                     | ICU Population                                                                                                                                                                                                                                         | Absolute or % Predicted $\dot{V}O_{2peak}$ (mL/kg/min)                                                                                                                                                                                                                                                                                       |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Benington et al., 2012<br>Cycle Ergometer | $n = 50$ General Adult ICU Survivors (median age, 57 years), mechanically ventilated $\geq 5$ days, within 6 weeks post-discharge                                                                                                                      | $56\% \pm 16\%$ of predicted                                                                                                                                                                                                                                                                                                                 |
| Clavario et al., 2021<br>Cycle Ergometer  | $n = 200$ COVID-19 survivors, 3-month follow-up                                                                                                                                                                                                        | Median 88% of predicted.<br>85% is considered the threshold for normality; 49% of participants were below the threshold. 1/3 had functional limitations explained by muscular impairment                                                                                                                                                     |
| Longobardi et al., 2023<br>Treadmill      | $n = 35$ COVID-19 survivors, 3–5 months post-discharge; $n = 18$ healthy individuals matched for sex, age, comorbidities, and physical activity level with no prior history of SARS-CoV-2 infection were recruited.                                    | 83% of predicted. A percent-predicted $\dot{V}O_{2peak}$ defined below 80%.<br>Protocol Relevance: Constant workload exercise incorporated for assessing both $\dot{V}O_{2peak}$ and on/off transient $\dot{V}O_2$ kinetics                                                                                                                  |
| Mart et al., 2022<br>Cycle Ergometer      | $n = 14$ ICU survivors, 6 months post-ICU (range 4.5–7 months), enrolled adults aged 18+, median age 63 [50–76], treated for respiratory failure (mechanical ventilation) and/or shock (need for vasopressors) from medical, surgical, and trauma ICUs | Priori defined cutoff of $\dot{V}O_{2peak} < 80\%$ predicted (Wasserman, 2012). Patient percent $\dot{V}O_{2peak}$ predicted achieved: 79% or $n = 11/14$ had low exercise capacity $\dot{V}O_{2peak} < 80\%$ with a median $\dot{V}O_{2peak}$ of 12.6 mL/kg/min                                                                             |
| Van Aerd et al., 2021<br>Cycle Ergometer  | $n = 313$ ICU survivors, 1–5 years post-ICU; $n = 40$ CPET 1-year follow up; 49 sedentary matched controls                                                                                                                                             | Abnormal exercise capacity is defined as peak oxygen consumption ( $\dot{V}O_{2peak}$ ) $< 85\%$ of predicted peak oxygen consumption ( $\%pred\dot{V}O_{2peak}$ ), based on the historic sedentary population.<br>Patient percent $\dot{V}O_{2peak}$ predicted achieved: Exercise capacity was abnormal in 118/313 (37.7%) 5-year survivors |

The following figure demonstrates the scarce, yet vital research conducted to date (from my knowledge) of CPET in the ICU-survivor population.



**Figure 4.** Literature-derived timeline for cardiopulmonary exercise test (CPET) post-ICU discharge. Generated by Britney Blunderfield with BioRender.

## *Near-Infrared Spectroscopy in Exercise Science*

One method to explore the ICU-AW physiological knowledge gap is through the application of NIRS. NIRS is an important tool used to monitor muscle oxygenation in real-time through the detection of light absorption changes through biological tissue, with a high level of reliability (Grassi & Quaresima, 2016; Hamaoka et al., 2007; Tuesta et al., 2022). Specifically, it allows non-invasive quantification of skeletal muscle oxygenation using a near infrared light, penetrating ~700–900 nm absorbed by main chromophores (hemoglobin and myoglobin), to enable greater insight into the underlying control mechanisms influencing perfusion, diffusion, oxygen delivery, and oxidative metabolism (Barstow, 2019). Informing a broad spectrum of contexts, ranging from athletics to the intensive care unit (Mirsajadi et al., 2024) or within emergency fields (Barstow, 2019).

Research suggests that examining oxygen utilization in thigh muscles, particularly with NIRS placed on the vastus lateralis (Gildea et al., 2021; Koga et al., 2017; Murias et al., 2013), is crucial to better understanding peripheral factors contributing to exercise intolerance, as described in the Type 2 Diabetes (T2D) incremental cycle ergometer study (Miyamoto et al., 2020). Which has further contributed to advancing our pathophysiological understanding about T2D through the investigation of oxygen uptake kinetics to partly explain the link between T2D and its potential underlying mechanisms of exercise intolerance (Miyamoto et al., 2020). Within the T2D study, the NIRS was placed on the vastus lateralis at the midpoint between the greater trochanter and lateral patella after measuring subcutaneous tissue thickness (Miyamoto et al., 2020). Another study suggested the application process of shaving and cleaning the skin, using an adhesive marker to measure roughly 10cm above the knee joint, securing NIRS with velcro straps and adhesive tape with a black cloth around the probe to prevent any contamination from

ambient light, sampled at a 10Hz frequency (Zuccarelli et al., 2020). This was the first study to assess muscle  $\dot{V}O_2$  recovery kinetics using a NIRS repeated occlusions method, where findings suggest the feasibility and utility of NIRS as a functional evaluation tool of skeletal muscle oxidative metabolism (Zuccarelli et al., 2020). The next section discusses NIRS usage within the ICU-survivor context.

### *Near-Infrared Spectroscopy in ICU-survivor Population*

Recent studies (Benington et al., 2012; Clavario et al., 2021; Joris et al., 2021; Longobardi et al., 2022; Mart et al., 2022; Van Aerde et al., 2021) have only infrequently assessed local skeletal muscle function to assess skeletal muscle microvascular oxygenation. Mendelson et al. (2023) recommend the application of NIRS, because NIRS is a well-established adjunct tool in exercise science (Barstow, 2019; Grassi & Quaresima, 2016; Poole & Jones, 2012). Research suggests that directly applying NIRS to skeletal muscle within this population will enable a more detailed evaluation of local microvascular oxygen delivery and utilization, used to provide quantitative insights to complement CPET systemic evaluation (Mendelson et al., 2023). To enable greater insight into the underlying control mechanisms influencing perfusion, diffusion, oxygen delivery, and oxidative metabolism - the microvascular oxygenation responses in ICU-survivors - to advance ICU-AW pathophysiology research.

To summarize, addressing challenges to research, particularly in protocol standardization for ICU follow-up care, is not only driven by the scarcity of research to describe the link between microvascular dysfunction and ICU-AW, but the absence of standardization for combining CPET and NIRS assessments within an inclusive and streamlined framework.

## CHAPTER THREE: Statement of the Problem

Although ICU-AW is well recognized, the literature continues to lack a comprehensive, standardized method to assess its physiological underpinnings. This becomes an issue when it restricts the ability to evaluate the full impact of critical illness, hindering the development of targeted rehabilitation strategies. Therefore, there is a need to develop a standardized method to enable further investigation of the relationship between ICU-AW, the role of microvascular dysfunction, impaired exercise capacity, and oxygen uptake kinetics in ICU survivors. Currently, the literature lacks a standardized, single-session CPET protocol tailored to the ICU-survivor population, for simultaneous determination of peak oxygen uptake and  $\dot{V}O_2$  kinetics that integrates local skeletal muscle oxygenation assessment, to allow comparison across research studies and clinical settings. There is currently a paucity of research to consider the link between microvascular dysfunction to ICU-AW, particularly while using dynamic, non-invasive measurements (e.g., NIRS, metabolic cart) within a combined single-session CPET assessment.

### 3.1 Research Questions, Objectives and Hypothesis

This thesis is divided into two research questions with their respective objectives and hypotheses, as follows:

**Research Question 1:** Can a standardized, single-session ICU-CARE CPET protocol combining peak oxygen uptake ( $\dot{V}O_{2peak}$ ), oxygen on/off-kinetics ( $\dot{V}O_2$ ), and localized skeletal muscle oxygenation in ICU survivors be developed?

**Objective 1:** The first objective is the development of a standardized, single-session ICU-CARE CPET protocol that combines peak oxygen uptake ( $\dot{V}O_{2peak}$ ), oxygen uptake ( $\dot{V}O_2$ ) on/off-kinetics, and localized skeletal muscle oxygenation (TSI; HHb) measurements, tailored to ICU survivors.

**Hypothesis 1:** I hypothesize that the standardized ICU-CARE CPET proposed protocol can be developed to quantitatively assess  $\dot{V}O_{2peak}$ ,  $\dot{V}O_2$  on/off-kinetics and localized skeletal muscle oxygenation (TSI and HHb) observed from ICU survivors preliminary results, adapting from Santana et al. (2025) protocol.

**Research Question 2:** Can TSI<sub>peak</sub> and HHb on/off kinetics be obtained from retrospective data in healthy adults, using a single, combined CPET protocol as described by Santana et al. (2025)?

**Objective 2:** The second objective is to conduct a retrospective analysis of healthy adults to determine TSI<sub>peak</sub> and HHb on/off kinetics within a single, combined CPET session, based on the study by Santana et al. (2025).

**Hypothesis 2:** I hypothesize that it is possible to derive TSI<sub>peak</sub> and HHb on/off kinetics from the healthy adult, combined single-session CPET from a retrospective analysis of Santana et al., (2025).

### 3.2 Organization of this Thesis

This thesis is organized according to the Faculty of Graduate Studies (FGS) outlines at the University of Manitoba, and divided into 6 chapters, as follows:

**Chapter 1** introduces the rise of ICU survivorship, highlighting the persistent burden of ICU-AW and identifying knowledge gaps, to introduce the proposal for the development of the ICU-CARE CPET protocol, intended to support future research and clinical interventions in ICU follow-up care.

**Chapter 2** reviews the literature to justify the proposed research and protocol introduced within the first chapter. Reviewing the evolution of critical care, the rise of ICU survivorship, the emergence of ICU-AW, its multifactorial etiology and long-term consequences, its emerging risk

factors, the transition of research focus towards the role of microvascular dysfunction and ICU-AW, evaluating the oxygen delivery pathway using tools such as CPET and NIRS.

**Chapter 3** presents an overview of the statement of the problem, knowledge gaps identified in the ICU literature, research questions, objectives and hypotheses.

**Chapter 4** outlines the development of the standardized single-session CPET measuring peak oxygen uptake, oxygen on/off-kinetics in healthy controls derived from the unpublished retrospective NIRS data, providing the foundation for a detailed methodology of the standardized ICU-CARE CPET, developed to quantitatively assess  $\dot{V}O_{2peak}$ ,  $\dot{V}O_2$  on/off-kinetics, and localized skeletal muscle oxygenation (TSI and HHb) in ICU survivors.

**Chapter 5** presents skeletal muscle oxygenation peak and on/off kinetics obtained from retrospective data in healthy adults, using a single, combined CPET protocol. Additionally, the inclusion of preliminary data from the ICU-CARE CPET protocol, including ICU survivors' NIRS and  $\dot{V}O_2$  data is displayed.

**Chapter 6** reviews the objectives and hypotheses, discusses and provides observations of its clinical application, practical implications, and future directions.

### **3.3 Thesis Deliverables**

The deliverables of this thesis involve (1) a detailed description of the single session, standardized framework (ICU-CARE-CPET protocol), integrating  $\dot{V}O_{2peak}$ ,  $\dot{V}O_2$  on/off-kinetics, HHb on/off-kinetics, and  $TSI_{peak}$  with potential clinical and research implementation, and (2) retrospective NIRS data quantitative analysis in young healthy adults to demonstrate that  $TSI_{peak}$  and HHb on/off kinetics parameters, can be obtained within a combined, single-session CPET protocol.

## CHAPTER FOUR: Protocol Development

This section introduces the development of the ICU Combined Assessment of cardio-Respiratory Exercise (ICU-CARE) CPET protocol. It describes key protocol features and adaptations proposed from the Santana et al. (2025) protocol in healthy population. The aim is to promote standardization within an inclusive framework for ICU survivors, enabling the investigation of ICU-AW pathophysiology in future studies.

### 4.1 Rationale for ICU-survivor Protocol Development

The lack of standardization in ICU follow-up care (Jawa et al., 2025), specifically for combining assessments of  $\dot{V}O_{2peak}$ ,  $\dot{V}O_2$  on/off-kinetics post-ICU discharge, and the scarcity of research to describe the link between microvascular dysfunction and ICU-AW, reduced exercise capacity and worse health outcomes (Dallaire et al., 2017) that can persist up to 5 years following ICU discharge (Herridge et al., 2011a; Van Aerde et al., 2021), has driven a new protocol development. Past CPET studies report reduced exercise capacity and limited aerobic fitness (Benington et al., 2012; Clavario et al., 2021; Joris et al., 2021; Longobardi et al., 2022; Mart et al., 2022; Van Aerde et al., 2021). Yet, ICU-AW underlying mechanisms, particularly beyond skeletal muscle biology, remain underexplored amid scarce adoption of CPET for ICU-survivors. For these reasons, we have decided to propose the ICU-CARE CPET study.

This protocol was developed based on the studies of Longobardi et al. (2022) and Santana et al. (2025), both exploring single-session CPET. Longobardi et al. used a single-session treadmill CPET incorporating a 3-minute moderate-intensity walk (below ventilatory threshold) before the incremental phase and a 6-minute recovery period (1 minute active and 5 minutes passive) in survivors of severe COVID-19 about 3-6 months after hospitalization ( $n = 53$ ). Our research team then recently published the development of a standardized and single-

session cycle ergometer protocol in healthy adults ( $n = 20$ ), as indicated above (Santana et al., 2025). In brief, this CPET protocol consisted of 3 minutes of rest seated in a chair ( $\dot{V}O_{2\text{rest}}$ ), 3 minutes of baseline seated on the cycle ergometer (no pedaling), 5 minutes of CWR at 30% estimated  $\dot{V}O_{2\text{reserve}}$  (60 rpm), incremental phase ( $20 \text{ W} \cdot \text{min}^{-1}$ ) to attain  $\dot{V}O_{2\text{peak}}$ , and 10 minutes of passive recovery. Based on the results, it was concluded that the proposed protocol provided a systematic and standardized single-session CPET for the combined assessment of  $\dot{V}O_{2\text{peak}}$  and  $\dot{V}O_2$  on/off-kinetics (Santana et al., 2025). Both studies provided the single-session foundation that has led to the advancement of the CPET to accommodate the ICU-survivor population, including the addition of NIRS to provide further insights into ICU-AW research. As mentioned by Santana et al. (2025), the selection of a specific equation to determine  $\dot{V}O_{2\text{peak}}$  and the determination of the CWR phase are paramount for the development of this protocol. Our group had recently established four steps: (1) prediction of  $\dot{V}O_{2\text{peak}}$ , (2) calculation of  $\dot{V}O_{2\text{reserve}}$ , (3) determination of targeted  $\dot{V}O_{2\text{reserve}}$ , and (4) estimation of work rate in Watts (Santana et al., 2025).

## 4.2 Key Protocol Adaptations

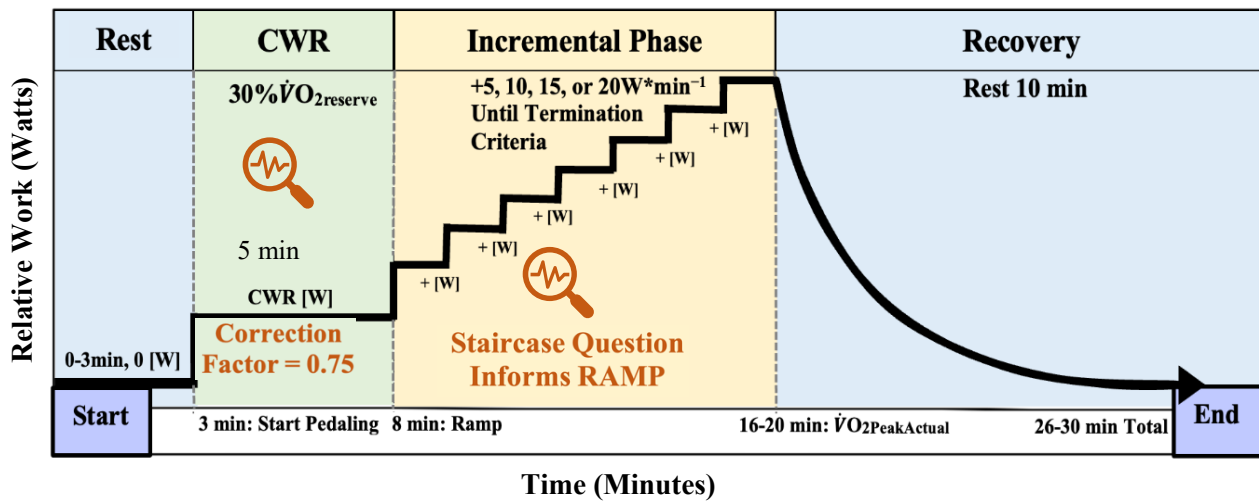
This thesis builds upon Santana et al., (2025), incorporating key adaptations, such as integrating NIRS technology, proposing a literature-derived ICU correction factor to determine constant work rate (CWR) at 30%  $\dot{V}O_{2\text{reserve}}$ , and proposing an incremental ramp protocol based on self-reported functional status to individualize each ramp protocol (5, 10, 15, or  $20 \text{ W} \cdot \text{min}^{-1}$ ). The primary goal of this ICU Combined Assessment of cardioRespiratory Exercise (ICU-CARE) CPET protocol is to develop a comprehensive, standardized protocol, combining the quantitative evaluation of  $\dot{V}O_{2\text{peak}}$ ,  $\dot{V}O_2$  on/off-kinetics, and skeletal muscle oxygenation (TSI and HHb), tailored to ICU-survivors in a single session. Designed to overcome the

limitations of traditional approaches to CPET and  $\dot{V}O_2$  kinetics, such as multiple clinical research or hospital lab visits, longer data collection, recruitment and compliance issues (Longobardi et al., 2022; Santana et al., 2025), as well as to improve overall efficiency within clinical settings (Longobardi et al., 2022). CPET is currently being studied within the ICU-survivor population, within the same time period as proposed in this study, yet lacks standardization and the direct measurement of local skeletal muscle oxygenation (Herridge et al., 2011a; Joris et al., 2021; Longobardi et al., 2022; Mart et al., 2022).

The validity and utility of the ICU-CARE CPET protocol may be assessed by determining whether combined measurements of the physiological responses ( $\dot{V}O_{2peak}$ ,  $\dot{V}O_2$  on/off-kinetics, TSI and HHb), within a single-session, produces physiologically appropriate, interpretable and clinically meaningful data which may efficiently inform follow-up assessment. The ICU-CARE CPET protocol wishes to advance patient-centered research through a more individualized approach to improve clinical practice and research efficiency in future studies, which may enable more advanced investigation of ICU-AW and its associated pathophysiology (Mendelson et al., 2023).

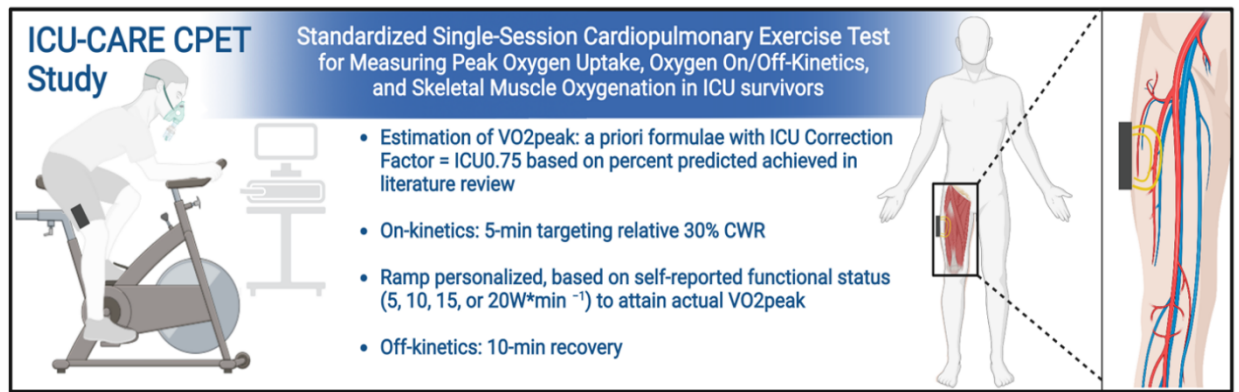
Figure 5 displays the ICU-CARE CPET protocol, including key adaptations to assess  $\dot{V}O_{2peak}$ ,  $\dot{V}O_2$  on/off kinetics, and microvascular oxygenation in ICU-survivors, including: (1) insertion of an ICU-survivor specific  $\dot{V}O_{2peak}$  correction factor and the determination of the work rate intensity based on the ICU-survivor specific  $\dot{V}O_{2peak}$  to be used in the CWR phase, and (2) the increments during the ramp protocol phase based on ICU-survivors' perceived exercise capacity. Thus, the ICU-CARE-CPET protocol for ICU-survivors consists of: (i) *Baseline phase*: 3 minutes baseline  $\dot{V}O_2$  measurements, no pedaling, seated on the bike; (ii) *Constant Work Rate phase* (CWR; on-kinetics): 5 minutes pedalling at 60 rpm and

30%  $\dot{V}O_{2\text{reserve}}$  ( $\dot{V}O_{2\text{peak predicted}} - \dot{V}O_{2\text{rest}}$ ), whereby  $\dot{V}O_{2\text{peak predicted}}$  is estimated a priori using the correction factor of 0.75 based on ICU-survivor  $\dot{V}O_{2\text{peak}}$  (equations 1 and 2); (iii) *Incremental phase (ramp)*:  $\dot{V}O_{2\text{peak}}$  is assessed through a ramped cycling exercise, based on self-reported functional status until volitional exhaustion or if any termination criteria are met, as described above; and (iv) *Recovery phase (off-kinetics)*: 10 minutes passive recovery (no pedaling). The Orange words in this figure represent the protocol adaptations from Santana et al.(2025) study.



**Figure 5.** ICU-CARE-CPET protocol with adaptations from Santana et al. (2025). Created in BioRender by Britney Blunderfield.

The next figure represents the summary of the standardized, single-session ICU-CARE CPET protocol, combining the assessment of  $\dot{V}O_{2peak}$ ,  $\dot{V}O_2$  on/off kinetics, and NIRS derived skeletal muscle oxygenation (HHb and TSI) in ICU-survivors.



**Figure 6.** ICU Combined Assessment of cardioRespiratory Exercise (ICU-CARE) CPET protocol. The ICU-CARE CPET offers a comprehensive, standardized, CPET-NIRS protocol, measuring  $\dot{V}O_{2peak}$ ,  $\dot{V}O_2$  on/off kinetics, and skeletal muscle oxygenation in ICU-survivors. This illustration was created in BioRender by Britney Blunderfield.

The next section describes the key adaptations to accommodate this protocol to the ICU-survivor population, based on a literature review.

#### 4.2.1 ICU-Survivor Specific $\dot{V}O_{2peak}$ Correction Factor

The ICU-survivor specific  $\dot{V}O_{2peak}$  correction factor was derived from a literature review (Table 2). It was developed to reflect more closely the  $\dot{V}O_{2peak}$  of the ICU-survivor population. Research suggests that 1/3 ICU-survivors experience reduced  $\dot{V}O_{2peak}$  (Van Aerde et al., 2021), often falling below 80-85% of predicted values (Benington et al., 2012; Mart et al., 2022; Van Aerde et al., 2021). Based on these studies, the use of a correction factor of 0.75 (75%) was adopted to account for the reduced  $\dot{V}O_{2peak}$  range reported in the ICU-survivor population.

**Table 2.** Estimated  $\dot{V}O_{2peak}$  in the ICU-survivor population studies.

| Study                 | Population                                                                                                           | Defined Abnormal $\dot{V}O_{2peak}$                                                          |
|-----------------------|----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Clavario et al., 2021 | $n = 200$ ; COVID-19 Survivors; 3-month follow-up                                                                    | 85% of the $\dot{V}O_{2peak}$ predicted is considered the threshold for normality            |
| Mart et al., 2022     | $n = 14$ ; ICU-survivors; 6-month post-ICU (range 4.5-7 months)                                                      | Used a priori defined cutoff below 80% predicted                                             |
| VanAerd et al., 2021  | $n = 313$ ; ICU-survivors; 1-5 years post-ICU;<br>$n = 40$ ; CPET 1-year follow up;<br>49 sedentary matched controls | Abnormal exercise capacity below 85% of predicted based on the historic sedentary population |

The ICU-specific  $\dot{V}O_{2peak}$  correction factor is incorporated into equations 1 and 2 (step 1) as described below.

1. *ICU-Survivor Prediction Equation for  $\dot{V}O_{2peak}$ .* Sex-specific equations (Eq. 1a and Eq. 1b),

currently used in clinical practice within the Ultima™ CardiO2® software's Wasserman equation, are used to predict  $\dot{V}O_{2peak}$  as a normative value. Please note, future testing is shifting towards an updated equation using Canadian adult ( $\geq 40$  years of age) normative (50<sup>th</sup> percentile) and sex-specific equations to predict  $\dot{V}O_{2peak}$  (Lewthwaite et al., 2020).

Subsequently, an ICU correction factor of 0.75 (ICU0.75) is used to account for an average of 25%  $\dot{V}O_{2peak}$  reduction in ICU-survivors, previously described in the literature (Longobardi et al., 2022; Mart et al., 2022)(Van Aerde et al., 2021). Equations 1 and 2 are provided below.

**Eq. 1a***Estimated  $\dot{V}O_{2peak}$  (Female)*

$$\dot{V}O_{2peak} = ((43 + \text{Body Mass [kg]}) \times (22.78 - 0.17 \times \text{Age})) \times \text{ICU}0.75$$

**Eq. 1b***Estimated  $\dot{V}O_{2peak}$  (Male)*

$$\dot{V}O_{2peak} = (\text{Weight [kg]} \times (50.72 - 0.372 \times \text{Age})) \times \text{ICU}0.75$$

Where age (years), body mass (kg) and ICU0.75 = ICU correction factor of 0.75.

After  $\dot{V}O_{2peak}$  is estimated, the next steps are the calculations of  $\dot{V}O_{2reserve}$  (step 2) and  $\dot{V}O_{2CWR}$  (step 3), as described below.

2.  *$\dot{V}O_{2reserve}$  Calculation.*  $\dot{V}O_{2reserve}$  is calculated as the difference between the estimated  $\dot{V}O_{2peak}$  from either Eq. 1a or 1b and  $\dot{V}O_{2rest}$  ( $\dot{V}O_{2reserve} = \dot{V}O_{2peak} - \dot{V}O_{2rest}$ ). To promote more efficiency within a clinical setting,  $\dot{V}O_{2rest}$  is fixed at 3.5 mL/kg/min (Dominelli et al., 2021).
3.  *$\dot{V}O_{2CWR}$  Calculation.* The target  $\dot{V}O_{2CWR}$  is determined as described in Eq. 2 below. The  $\dot{V}O_{2reserve}$  obtained in step 2, described above, is multiplied by the desired intensity. For the development of this protocol, 30%  $\dot{V}O_{2reserve}$  is selected because it represents light intensity exercise according to the American College of Sports Medicine (ACSM) (Garber, 2018). Also, in this intensity, participants may perform the CWR exercise phase below the ventilatory anaerobic threshold (Albouaini et al., 2007) allow them to achieve a steady state  $\dot{V}O_2$  within 5 minutes, while minimizing interference with the subsequent progressive incremental phase (ramp) of the protocol.

**Eq. 2**

$$\dot{V}O_{2CWR} = [(\dot{V}O_{2peak} - \dot{V}O_{2rest}) \times (\%desired\ intensity)] + \dot{V}O_{2rest}$$

Where  $\dot{V}O_{2peak}$  [mL/kg/min] is the value estimated in step 1 for ICU-survivors;  $\dot{V}O_{2rest}$  [mL/kg/min] is the value of oxygen uptake at rest (3.5 mL/kg/min), and % desired intensity, expressed in decimals, is the desired intensity relative to the individual's  $\dot{V}O_{2reserve}$ .

4. *Estimation of work rate in Watts.* The work rate in Watts (W) is obtained by using the individual's body mass and the  $\dot{V}O_2$  (mL/kg/min), as described in equation 3 (Garber, 2018).

**Eq. 3**

$$Work\ rate\ [W] = \frac{body\ mass \times (\dot{V}O_{2CWR} - 7)}{1.8} \times 0.164$$

Where the individual's body mass is expressed in kilograms (kg) and the  $\dot{V}O_2$  (mL/kg/min) is the target  $\dot{V}O_{2CWR}$  obtained in step 3 (Eq. 2). The result of Eq. 3 determines the CWR (W) performed during the ICU-CARE-CPET protocol on the cycle ergometer.

#### **4.2.2 Work Rate Intensity and Ramp Increments Based on Perceived Exercise Capacity**

Since there is a higher prevalence of exercise intolerance and impaired muscle strength post-ICU (Clavario et al., 2021; Van Aerde et al., 2021), it was decided to use ICU-survivors' perceived functional exercise capacity to determine the ramp during the incremental phase of the ICU-CARE-CPET protocol. This approach allows for a more individualized adjustment of the incremental work rate to match individuals' perceived exercise capacity. To do so, the responses obtained during the recruitment process from the self-reported staircase question (Glaab & Taube, 2022) and the modified Medical Research Council (mMRC) dyspnea scale (Yorke et al., 2022) inform a more appropriate ramp selection. For the staircase question, participants are

asked, “How many floors can you walk up quickly without stopping?”. Based on their responses, the increments are defined as follows (Table 3).

**Table 3.** Perceived exercise capacity based on the staircase question.

| Floors | Intensity           |
|--------|---------------------|
| 1      | 5 W/min; 50 W       |
| 2      | 10 W/min; 100 W     |
| 3      | 15 W/min; 125-150 W |
| 4      | 20 W/min; 200 W     |

W/min = Watt increase per minute for ramp protocol, based on staircase question.

For the mMRC dyspnea scale, participants' severity of breathlessness is reported based on activity descriptors and mMRC grade between 0-4 with their respective Watt equivalent (Table 4).

**Table 4.** Modified Medical Research Council (mMRC) Dyspnea Scale.

| Grade | Activity Descriptor                                                                         | RAMP                                      |
|-------|---------------------------------------------------------------------------------------------|-------------------------------------------|
| 0     | Strenuous activity, not troubled by breathlessness<br>(e.g., cycling, shoveling heavy snow) | 20 W/min                                  |
| 1     | Walking up an incline causes shortness of breath                                            | 15 W/min                                  |
| 2     | Walking two blocks and experiencing breathlessness                                          | 10 W/min                                  |
| 3     | Walking short distances and needs to catch breath<br>(e.g., 100ft, or room to room)         | 5 W/min for females<br>10 W/min for males |
| 4     | Can't get dressed or shower without symptoms                                                | No CPET                                   |

W/min = Watt increase per minute for ramp protocol, based on mMRC Dyspnea Scale.

The ramp component of the ICU-CARE-CPET protocol was based on previously published studies in the ICU-survivor population using a cycle ergometer ramp protocol (Table 5). Notably lacking specific methodological implementation of ramp modification and selection, based upon our current knowledge.

**Table 5.** Cycle ergometer ramp protocol studies.

| Study                  | Population                                                                                                                                                        | CPET Cycle Ergometer Ramp Protocol                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Benington et al., 2012 | General Adult ICU-survivors: $n = 50$<br>Median age: 57 years<br>Mechanically ventilated: $\geq 5$ days<br>Post-discharge: 6 weeks                                | Ramp: 10-15 W/min<br>( <i>not specified</i> )                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Clavario et al., 2021  | $n = 200$<br>COVID-19 survivors<br>Median age: 58.8<br>Post-discharge: 3 months<br>29 mechanically ventilated,<br>21 of 29 below 85% predicted $\dot{V}O_{2peak}$ | Ramp: 10, 15, 20, or 25 W/min based on sex and body mass<br>( <i>not specified</i> )                                                                                                                                                                                                                                                                                                                                                                                                       |
| Glaab & Taube, 2022    | Practical guide to CPET in adults, no specific population                                                                                                         | 1. Resting phase (2-3 min)<br>2. Unloaded phase (2-3 min, 0-15 W) cadence 55-70 rpm<br>3. Incremental exercise phase: 5, 10, 15, or 20 W/min based on stair-climbing ability ( $10 \pm 2$ min, or for at least 5 min in severely restricted patients). A continuous incrementing ramp protocol (increase of work rate, e.g., every 2–15 s or minute-by-minute e.g., 5–30 W/min) to symptom-limited maximum exercise.<br>4. Recovery phase (cool down period: 3-5 min, unloaded pedalling). |
| Pollock et al., 1993   | $n = 31$<br>Male patients with varying chronic airflow obstruction (CAO)<br>Age 39 to 80 years<br>$aFEV1 = 1.6 \pm 0.71$<br>FEV/FVC ratio = $51 \pm 14$           | Stair climbing protocol vs. CPET; Ramp increased by 20 W/min, until exhaustion<br><i>Key findings:</i> Strong linear correlation between the $\dot{V}O_{2peak}$ achieved during stair climbing and leg cycle ergometry for CAO patients.                                                                                                                                                                                                                                                   |

### **4.3 Healthy Protocol and Other ICU-Survivor Adaptations**

#### *Ethics Approval*

The recently published study (Santana et al., 2025) was reviewed and approved by the University of Manitoba Health Research Ethics Board (Ethics approval protocol number HE2022-0058) and agreed with the Declaration of Helsinki.

#### *Study Design*

The development of the standardized, single-session CPET protocol in healthy adults is part of an observational cross-sectional design, using Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Guidelines.

#### *Setting*

Recruitment and data collection took place from July to October 2023 in the Cardiorespiratory Physiology of Exercise Research Laboratory in the Faculty of Kinesiology and Recreation Management at the University of Manitoba. Recruitment was conducted through convenient and snowball sampling methods (Biernacki & Waldorf, 1981). Phone calls, emails, word of mouth, social media platforms (Facebook, Instagram, and X), and promotional materials (e.g., advertisements, flyers, and posters) were used as recruitment strategies. Interested individuals were invited to contact the research team directly via email or telephone.

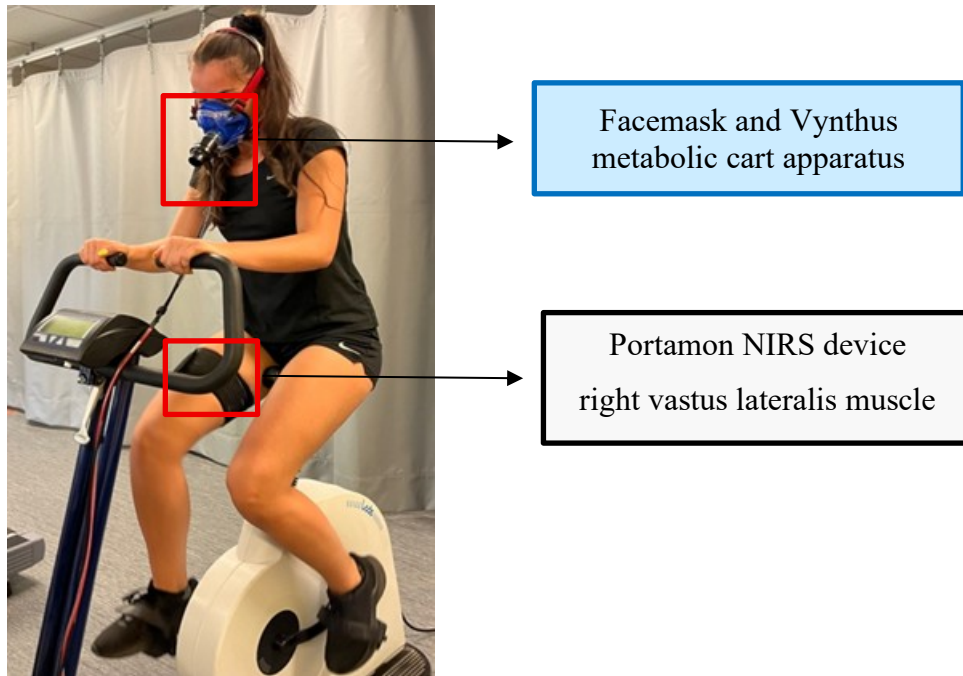
#### *Demographic Information, Safety Procedure, Equipment*

Demographic information and the Get Active Questionnaire (GAC) was collected (Canadian Society for Exercise Physiology, 2021), as well as the Paffenberger Physical Activity Questionnaire (Paffenbarger et al., 1993) prior to testing. To ensure participants' safety, blood pressure ( $SBP_{rest}$  and  $DBP_{rest}$ ) and heart rate ( $HR_{rest}$ ) were measured at rest, following the CSEP guidelines (Canadian Society for Exercise Physiology, 2021). All individuals had values below

the safety cut-offs ( $BP \leq 160/90$  mmHg;  $HR \leq 100$  bpm) (Headley, 2018). Additionally, height (H; m), body mass (BM; kg), and body mass index (BMI;  $\text{kg/m}^2$ ) were measured ( $BMI = BM/H^2$ ).

Then, participants were fitted with an air-cushioned mask and a heart rate (HR) device (Polar system) to monitor ventilatory variables and heart rate, respectively. A bidirectional breath-by-breath volume sensor (DVT Vyntus CPX, Vyaire Medical, Mettawa, Illinois, United States) was used to collect the ventilatory variables. Calibration was done before each test, using the Vyaire SentrySuite software platform on the Vyntus TM, providing automatic calibration and verification procedures.

The CPET was conducted in a quiet room with a controlled temperature of  $21.0 \pm 1.0$  °C, with humidity and barometric pressure at ambient. NIRS Portamon (Artinis Inc, Netherlands) was placed on the vastus lateralis of the participant before the exercise protocol began on the stationary cycle ergometer (Lode Corival, Lode B.V. Medical Technology, Groningen, Netherlands). Pulmonary oxygen uptake ( $\dot{V}O_2$ ) and carbon dioxide output ( $\dot{V}CO_2$ ) were recorded and monitored using the Vyntus TM CPX Metabolic cart (Vyaire Medical, Mettawa, Illinois, United States) (Figure 7).



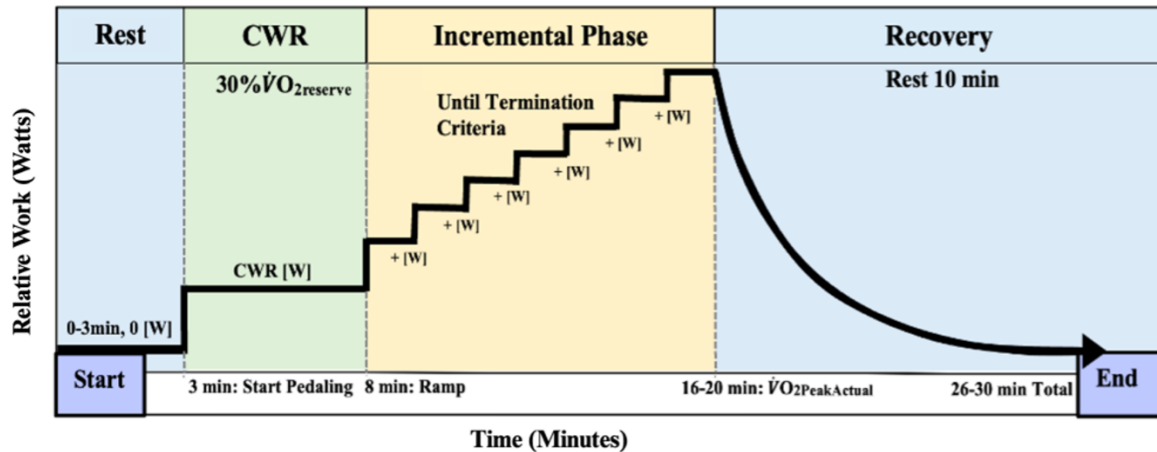
**Figure 7.** Equipment used in Santana et al. (2025). Upright cycle ergometer for CPET. Facemask and metabolic cart apparatus to collect gases. Portamon NIRS system applied to the right vastus lateralis muscle to collect muscle oxygenation.

### *Eligibility*

Eligibility was assessed using a screening tool during the phone calls. Participants identified as female or male (sex assigned at birth), non-smokers and non-pregnant individuals were included in the study. Individuals with orthopedic complications, smoking habits, cardiopulmonary diseases, and long-distance athletes (e.g., runners, cyclists, triathletes) were excluded from the study. Verbal and written information was distributed in detail regarding experimental procedures and potential risks to participation before signing an informed consent form, approved by the Research Ethics Board (REB1, Fort Garry Campus). Participant instructions requested all participants to refrain from consuming alcohol and engaging in vigorous exercise 24 hours leading up to the test, or from consuming a large meal two hours before arrival.

### *CPET Protocol for Healthy Individuals*

Formerly, our research team proposed an approach with four standardized steps to determine the CWR exercise intensity. This protocol consisted of a baseline resting  $\dot{V}O_2$  measurements (average of 6 readings with 30s intervals), while seated in a chair, to estimate the work rate (W) for the CWR phase, before moving to the upright cycle ergometer. For the estimation of work rate to watts, the American College of Sports Medicine (ACSM) metabolic calculations for common physical activities, such as leg cycling, was used to estimate the work rate (i.e., power) (Garber, 2018). After work rate was determined, participants were requested to move and sit on the cycle ergometer for 3 min with no pedaling, considered as baseline measurement. After this baseline period, participants underwent 5 min CWR at an intensity of 30% of their estimated  $\dot{V}O_{2\text{reserve}}$  with a cadence of 60 rpm. Then, the incremental phase started, consisting of progressive resistance increments of 20 W/min until volitional exhaustion or termination criteria met, including inability to maintain cadence ( $< 50$  rpm). After cessation of exercise, a 10 min recovery was administered (off-kinetics) with no pedaling, with participants remaining seated in the bike seat. Figure 8 illustrates the CPET protocol for healthy individuals (Santana et al., 2025).



**Figure 8.** Standardized single-session cardiopulmonary exercise test for combined assessment of peak oxygen uptake and on/off-kinetics in healthy adults (Santana et al., 2025). CWR = Constant Work Rate. Ramp 20 W/min. Created in Biorender by Britney Blunderfield.

### *Other Adaptations*

Referring to Santana et al. (2025), the estimated  $\dot{V}O_{2peak}$  is used to derive the CWR exercise at a similar relative intensity to allow for  $\dot{V}O_2$  on kinetics analysis and comparisons across participants. The selected intensity of 30%  $\dot{V}O_{2reserve}$ , considered a light intensity (Garber, 2018), aimed to maximize the chance that the participants would perform the CWR exercise phase and reach a steady state  $\dot{V}O_2$  within 5 minutes, with minimal interference in the incremental portion of the test (Santana et al., 2025). The estimation of the CWR and an accurate estimation of  $\dot{V}O_{2peak}$  are critical points for implementing a single-session CPET protocol for the combined assessment of  $\dot{V}O_{2peak}$  and  $\dot{V}O_2$  on/off-kinetics (Santana et al., 2025). There are a few small details that have been adapted from the healthy study for the ICU-CARE CPET protocol development, as follows:

(1) Recommended by the supervising clinicians, the protocol was slightly adapted, using a fixed 3.5 mL/kg/min  $\dot{V}O_{2rest}$ , a standard resting value (Dominelli et al., 2021), that involves the participant to remain seated on the upright cycle ergometer for less time, to streamline the exercise protocol within a clinical setting.

(2) Formerly, the sex-specific refined version of the estimated  $\dot{V}O_{2peak}$  Hansen/Wassermann equation used in the healthy protocol is noted to be most accurate for work rates between 50-200 Watts (Garber, 2018). The estimated  $\dot{V}O_{2peak}$  equation required a more tailored approach for ICU survivors, as pilot data collection revealed the need for a lower Watt range. Therefore, the pilot data was collected using the estimated  $\dot{V}O_{2peak}$  equation provided within the Ultima™ Cardio2® software's Wasserman equation (Eq. 1a and Eq. 1b) that is currently used in clinical practice at St. Boniface Hospital, used to predict  $\dot{V}O_{2peak}$  as a normative value. However, nearing the end of my master's program, the equation has since been updated with a sex-specific Canadian adult ( $\geq 40$  years old) equation, to be tested in future studies (Lewthwaite et al., 2020).

#### **4.4 ICU-CARE CPET Preliminary Implementation Procedures**

Planning to implement the ICU-CARE CPET, careful consideration was taken of several factors; ethical approval, data collection setting, inclusion and exclusion criteria, recruitment strategy, CPET modality and equipment, safety and termination criteria, pre-test instructions, pre-CPET evaluation checklist, provided below.

##### **Ethical Approval**

The ICU-CARE CPET study was approved by the University of Manitoba Health and Institutional Research Ethics Boards (HS25592; SH2022-187; RRC 2023/2119). Registered in clinicaltrials.gov under the clinical study ID NCT06193980.

## **Study Settings**

Preliminary recruitment and data collection occurred during a single visit to the Pulmonary Function Lab at St. Boniface Hospital in Winnipeg, Manitoba, Canada. This preliminary cohort had initiated recruitment from the previous MIMICS study cohort, including patients monitored in the ICU between July 2022 and July 2025.

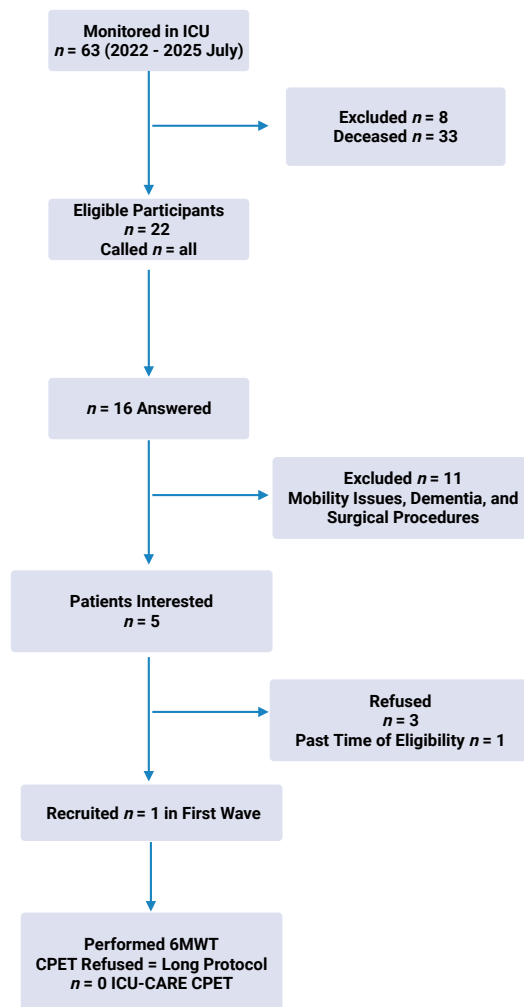
## **Preliminary Recruitment and Eligibility**

Preliminary recruitment was conducted during ICU stay, with researchers screening potential participants for willingness to join follow-up and meeting the study criteria. After three months post-ICU discharge, participants are contacted through phone calls to determine ongoing willingness and ability to participate in the ICU-CARE CPET study.

Volunteer participants are ICU survivors of both sexes (18+ years) who have answered the self-reported functional ability questionnaire and have been mechanically ventilated for  $\geq 7$  days, consistent with the threshold for the development of ICU-AW (Herridge et al., 2016). Participants will be excluded if experiencing significant orthopedic or musculoskeletal impairment affecting mobility, have a medical history of neuromuscular disease, have ongoing respiratory limitations (i.e., supplemental oxygen), have an adipose tissue thickness (ATT) of  $\geq 12.5$  mm, considered less reliable for skeletal muscle NIRS measurements (Van Der Zwaard et al., 2016), or if participant's primary residence is a significant distance from Winnipeg. Individuals will also be excluded if they report not being able to climb at least one flight of stairs, indicative of their limited exercise tolerance and exercise capacity (Glaab & Taube, 2022; Yorke et al., 2022).

Sixty-three participants monitored during their ICU stay from January 2022 to July 2025 were contacted, of whom forty-one ICU-survivors were excluded (33 deceased; 8 did not meet

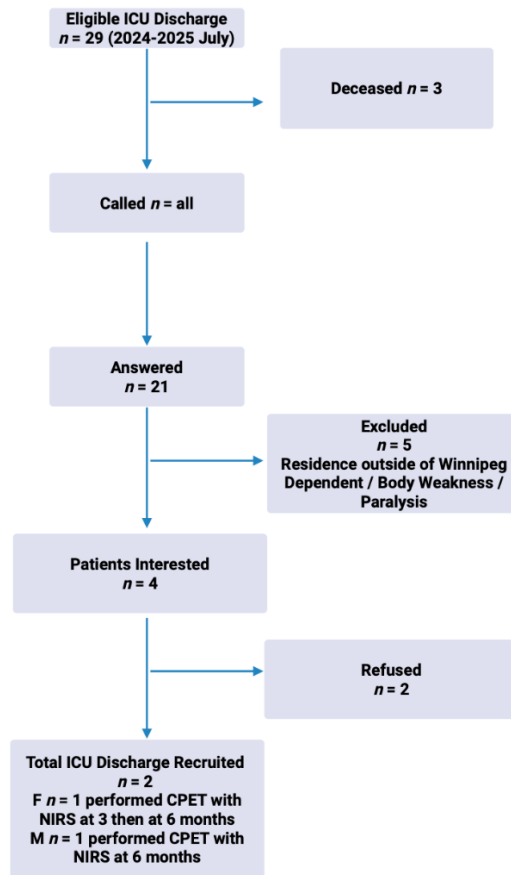
eligibility criteria). From the twenty-two ICU-survivors remaining, sixteen answered the phone call, then another 11 individuals were excluded due to mobility issues, leaving 5 participants eligible to participate. However, after further contact, 3 individuals refused to participate in the study, and another one was beyond the time of study inclusion criteria. Only one participant accepted to join the study (2% retention rate) within the first wave of recruitment, executed the 6-minute walk test, yet the length of the protocol caused the participant and caretaker to withdraw from the CPET portion ( $n = 0$ ) (Figure 9).



**Figure 9.** First Recruitment Block, ICU-survivor Flow Chart. Created with BioRender by Britney Blunderfield.

Data collection was discontinued in 2024 due to difficulties in recruitment, assessment space, and the necessity to reevaluate the plan and make appropriate changes. After many discussions with supervisors and approval of the committee members, it was decided that the protocol should be streamlined and shortened. Thus, the 6-minute walk test and lunch were removed from the study.

After this change, a preliminary recruitment was resumed. In this new recruitment attempt, 29 ICU-survivors (2024-2025 cohort) were contacted, where 3 individuals passed away, 5 resided outside Winnipeg, and 19 refused to participate in the study, resulting in two participants recruited (Figure 10).



**Figure 10.** Second Recruitment Block, ICU-survivor Flow Chart. Created with BioRender by Britney Blunderfield.

During the second wave of recruitment, two ICU-survivors have completed the ICU-CARE CPET protocol. A 64-year-old female underwent the ICU-CARE CPET at 3- and 6-month post-ICU discharge, while a 35-year-old male was assessed only at 6 months post-ICU discharge.

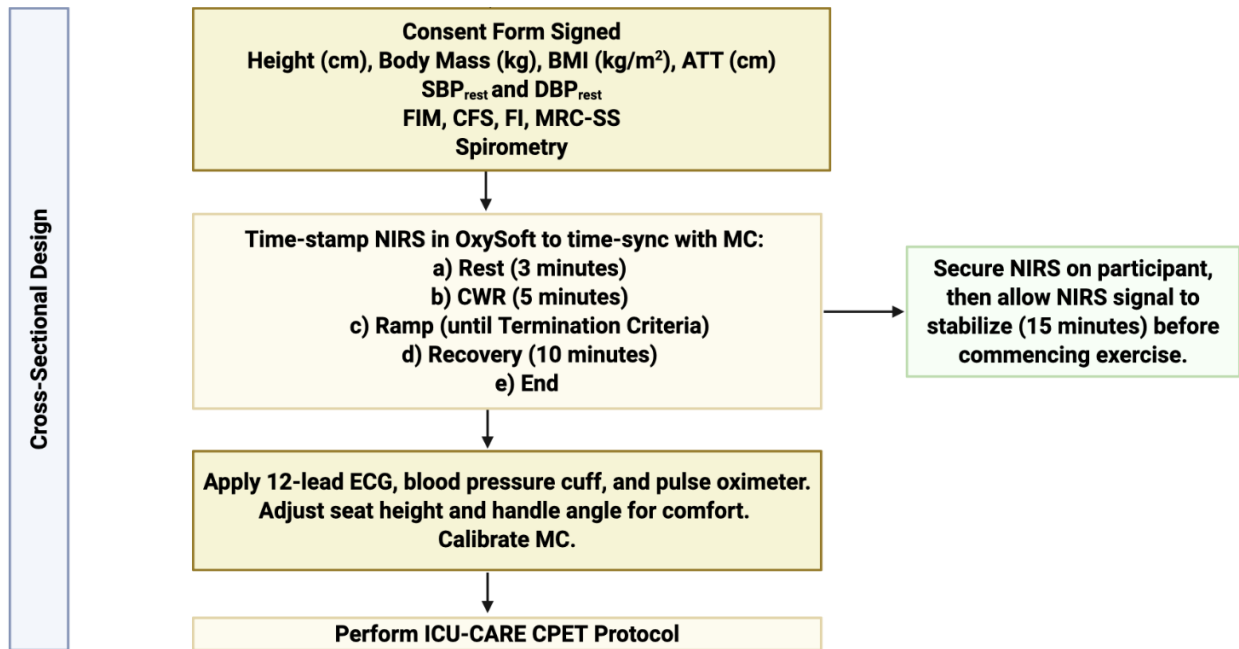
## Procedures

Participants received detailed information regarding the study procedures and potential risks before agreeing to attend the assessment day. Participants were asked for relevant hospital and post-ICU discharge information regarding length of ICU stay, readmission(s), intubation

period, concurrent illness, list of medications, and to acquire a recent blood test if available. Participants were also asked, “how many floors can you walk up quickly without stopping?”. This specific information was used to prescribe the work rate intensity (W/min) and increment for the ramp portion of the test (see incremental phase for more details).

Specific pre-test instructions are communicated at least 24 hours leading up to the single session through a phone call appointment. Participants must wear athletic clothing, such as a loose-fitting t-shirt, shorts, and running shoes, must avoid eating, drinking, or smoking within two hours before the test, avoid alcohol consumption, strenuous exercise 24 hours prior to the appointment, avoid makeup and lotions, maintain a regular sleep and a regular dietary pattern the day before the test.

Written informed consent is signed on the day of testing. Potential risks are stated during recruitment and before the start of the test session. This exercise test is anticipated to have minimal risk of cardiac event ( $< 0.1\%$ ) and extremely low risk of death ( $< 0.01\%$ ), according to the American Thoracic Society (ATS) (“ATS/ACCP Statement on Cardiopulmonary Exercise Testing,” 2003). CPET is routinely administered within patient populations, including those experiencing advanced cardiorespiratory disease, cardiac (Segreti et al., 2021) and lung transplantation (Schwaiblmair et al., 1999), as well as within advanced heart failure management patients (Landsteiner et al., 2025). Figure 11 displays the pre-ICU-CARE CPET procedures.



**Figure 11.** Flow chart of the Pre-ICU-CARE CPET procedures.

After signing the informed consent form, height (cm) and body mass (kg) are measured using a stadiometer and a scale, respectively. BMI is determined with the following formula:  $\text{BMI (kg/m}^2\text{)} = \text{body mass/height}^2$ . Following, resting systolic ( $\text{SBP}_{\text{rest}}$ ) and diastolic ( $\text{DBP}_{\text{rest}}$ ) blood pressure, and heart rate ( $\text{HR}_{\text{rest}}$ ) are measured prior to exercise following the ATS/ACCP guidelines (“ATS/ACCP Statement on Cardiopulmonary Exercise Testing,” 2003) to ensure participant safety. The Medical Research Council sum score (MRC-SS) (Hermans & Van Den Berghe, 2015) is reported because it is a tool commonly used to diagnose and track the development of ICU-AW (Connolly et al., 2012; Kleyweg et al., 1991). The Functional Independence Measure (FIM) questionnaire is assessed to track ICU survivors’ ability to carry out activities of daily living (Dos Santos et al., 2016; Herridge et al., 2016). FIM score, even early after ICU discharge, has been shown to predict long-term disability in a cohort of ICU survivors (Herridge et al., 2016). The Clinical Frailty Scale (CFS) is used because it is a simple clinician-based tool to quickly evaluate the overall frailty score, based on a 9-point scale, in

addition to the detailed Frailty Index (FI), both previously validated in critically ill population (Heyland et al., 2015; Muscedere et al., 2022).

The ICU-CARE CPET protocol was conducted using an upright cycle ergometer (Lode Corival | CPET, Lode B.B. Medical Technology, Netherlands), in a quiet room with controlled temperature of  $22.0 \pm 1.0$  °C, and humidity and barometric pressure at ambient conditions. Medical personnel and research staff are present throughout the protocol to ensure continuous monitoring and participant safety. Termination criteria follow the standard ATS/ACCP guidelines (ATS/ACCP Statement on Cardiopulmonary Exercise Testing, 2003), including: chest pain suggestive of ischemia, ischemic electrocardiogram (ECG) changes, complex ectopy, second or third-degree heart block, a fall in SBP by 20 mmHg from the highest value during the test, hypertension (SBP  $\geq 250$  mmHg; DBP  $\geq 120$  mmHg diastolic), severe desaturation (indicated by pulse oximetry, arterial oxygen saturation (80%) with symptoms of severe hypoxemia), sudden pallor, loss of coordination, mental confusion, dizziness or presyncope, and signs of respiratory failure (ATS/ACCP Statement on Cardiopulmonary Exercise Testing, 2003). Furthermore, testing is terminated when participants request to stop (volitional exhaustion), or develop significant discomfort preventing continued exercise, abnormal pain, shortness of breath preventing continued exercise, light-headedness, dizziness, or inability to sustain 60 rpm cadence ( $\pm 10$  rpm).

### **Data Acquisition**

Ventilatory parameters collected and monitored include the pulmonary oxygen uptake ( $\dot{V}O_2$ ), carbon dioxide output ( $\dot{V}CO_2$ ), minute ventilation ( $\dot{V}E$ ), breathing rate (BR), and the respiratory exchange ratio (RER) using the Ultima™ Cardio2® gas exchange analysis system metabolic cart (MC) (MGC Diagnostics, Minnesota, USA). These ventilatory parameters are

collected using a fitted air-cushioned face mask (preVent<sup>®</sup>, Minnesota, USA) and a bidirectional breath-by-breath volume sensor (preVent<sup>®</sup>, Minnesota, USA). For procedural compliance with the recommended ATS/ERS pulmonary function acceptability & repeatability guidelines, before each test, the Ultima<sup>™</sup> Cardio2<sup>®</sup> undergoes calibration by using automated gas and flow calibrations, along with quality assurance, as described in the user manual.

HR is continuously monitored using a 12-lead Mortara ECG embedded in the Ultima<sup>™</sup> Cardio2<sup>®</sup> system (*Metabolic with 12 lead ECG Ultima<sup>™</sup> Cardio2<sup>®</sup> Gas Exchange Analysis System Two Technologies in a Singular All-in-One Powerful Cardiorespiratory Diagnostic System.*, n.d.), and blood pressure is recorded every 2 minutes using the Tango M2 Stress Test Monitor (SunTech Medical, Morrisville SC) system during the ICU-CARE CPET protocol.

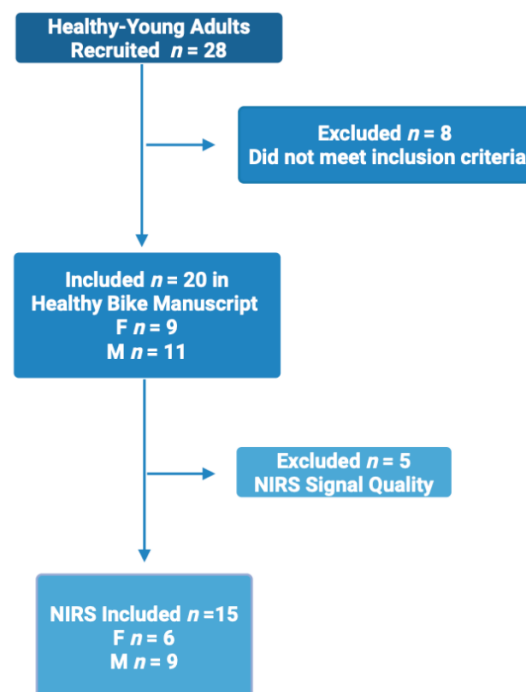
For NIRS application process: first conduct an ATT measurement using the Sonosite PX Ultrasound System (FUJIFILM Sonosite, Inc., USA), where three ATT measurements are retrieved using light pressure to record the average ATT for each participant (Tandirerung et al., 2024). To measure microvascular oxygen delivery and local tissue utilization in skeletal muscle during exercise (Ferreira et al., 2007; Perrey, 2024), a portable, wireless NIRS device (PortaMon, Artinis Inc, Netherlands) is placed on the vastus lateralis muscle (Gildea et al., 2021; Koga et al., 2017; Murias et al., 2013) 12-14 cm above the knee, secured by a dark band to minimize motion artifacts during cycling exercise and ambient light interference. The deepest transmitter penetration of the NIRS is selected to minimize the influence of skin blood flow over the area of interest (Beltrame et al., 2017). The NIRS device is warmed up for ~ 30 minutes prior to data collection. To ensure sufficient NIRS signal penetration, an ATT of  $\geq 12.5$  mm is considered less reliable for skeletal muscle NIRS measurements (Van Der Zwaard et al., 2016).

In this case, a sensitivity analysis is conducted with both the inclusion and exclusion of these subgroups ( $\leq 12.5$  mm;  $\geq 12.5$  mm) in the cohort outcomes.

#### 4.4 Retrospective Healthy NIRS Sample Data Acquisition

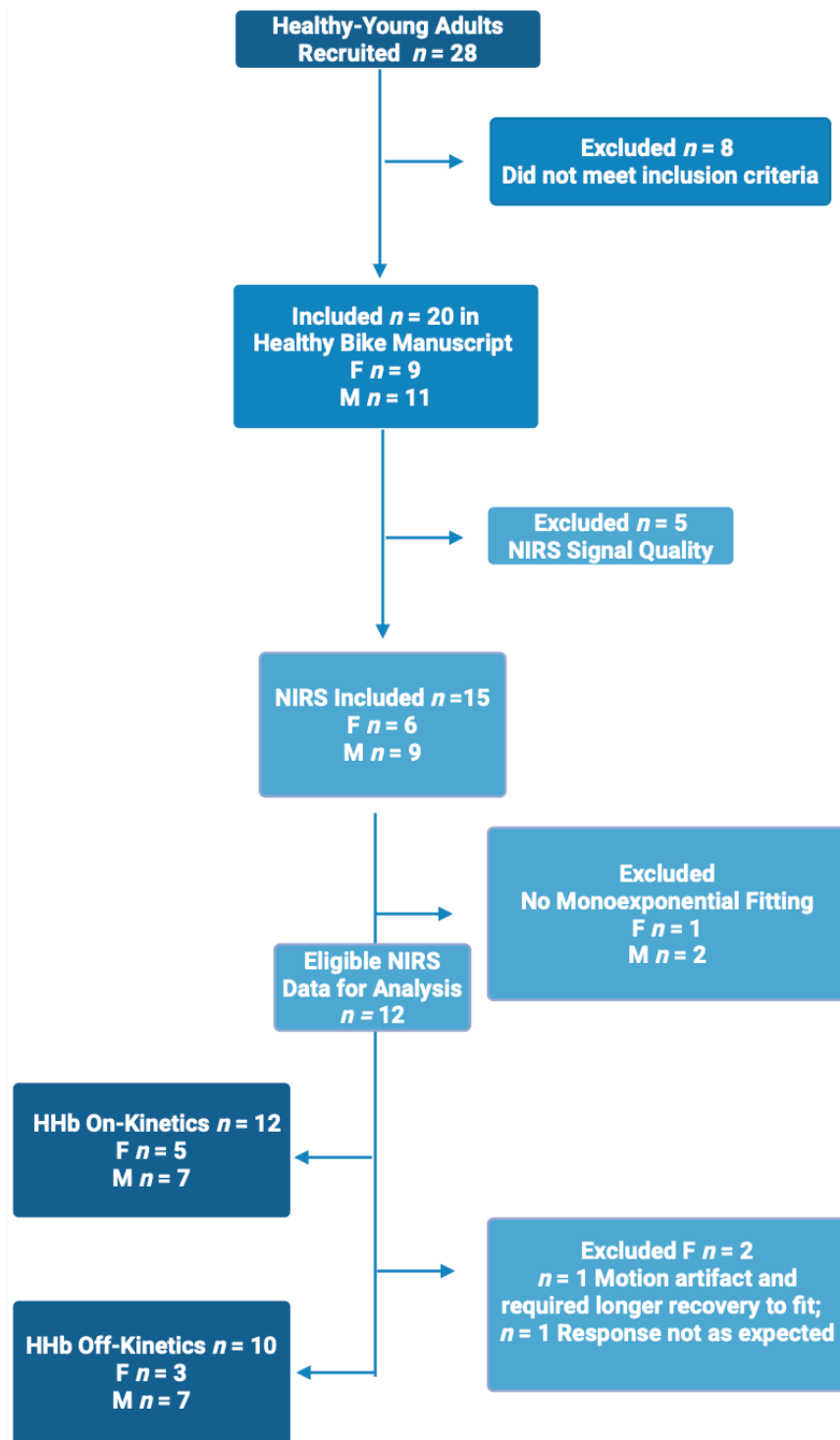
This section describes the sample data acquisition of healthy NIRS analysis derived from a dataset that has not been analyzed or published from our previous published work (Santana et al., 2025) .

Initially, a total of 28 healthy adults were recruited, of whom 8 participants were excluded because they did not meet the inclusion criteria, leaving 20 participants for analysis in the previously published manuscript (Santana et al., 2025). Of the 20 participants, 5 were excluded due to poor NIRS signal quality ( $n=3$  females and  $n=2$  males), leaving 15 participants for the final NIRS dataset analysis (Females:  $n=6$ , Males:  $n=9$ ) (Figure 12).



**Figure 12.** Participant recruitment flow chart for initial NIRS analysis. Created in Biorender by Britney Blunderfield.

For the HHb on kinetics analysis, 3 participants were excluded due to failure in fitting a monoexponential expected response (Female:  $n = 1$ , Males:  $n = 2$ ), essential for kinetics analysis (Beltrame et al., 2017), leaving 12 participants for the on kinetics analysis (Females:  $n = 5$ , Males:  $n = 7$ ). Of the 12 participants, 2 females were excluded from the off-kinetics analysis; one due to motion artifact and an extended recovery period that was not recorded under the time frame of the protocol, and another due to failure in matching the expected physiological pattern response during recovery (HHb increase rather than decrease) and not fitting a monoexponential expected response. The following flow chart (Figure 13) illustrates the NIRS data analysis process and reasoning for participant exclusion to ensure that only high-quality physiological data is included within the final analysis.



**Figure 13.** NIRS data analysis flow chart. Created in BioRender by Britney Blunderfield.

*Note:* In this thesis, the TSI kinetics analysis was not conducted as HHb is already being examined in detail, because TSI is derived from the relative concentrations of oxygenated (O<sub>2</sub>Hb) and deoxygenated hemoglobin (HHb) and all procedures and analysis would be similar; thus, inherently redundant to report it. Please refer to the TSI calculation:

$$TSI (\%) = \left( \frac{[O_2Hb]}{[O_2Hb] + [HHb]} \right) \times 100$$

#### *Data sampling rate and pre and post-processing procedures*

The primary variables are NIRS-derived HHb and TSI data, with analysis procedures following the  $\dot{V}O_2$  analysis previously conducted on healthy adults (Santana et al., 2025). Including  $\dot{V}O_2$  on-kinetics,  $\dot{V}O_{2peak}$ , and  $\dot{V}O_2$  off-kinetics within a single bout, with key adaptation is reporting HHb on/off-kinetics and TSI<sub>peak</sub> values. Measured non-invasively with a sample rate of 10 Hz, NIRS is transmitted wirelessly into OxySoft software and time-synched with the metabolic cart in real-time with a marker placed by research staff. Program NIRS computer with key commands were used: a) rest (no pedaling): 3-minutes, b) CWR: 5-minutes, c) ramp: until termination criteria, d) recovery (no pedaling): 10-minutes, e) end ICU-CARE-CPET.

NIRS data is exported from the OxySoft to Excel, adjusted for timestamps, and data analysis is conducted using a customized LabVIEW code (LabView v20.0.01, National Instruments Corp, United States). The filtering process includes removal of outliers, moving average procedures, and linear interpolation. Removal of outlier NIRS data is done by applying 2 standard deviations (SD) in a window size of 7 s, then applying a 350 s moving average. Data is linearly interpolated to provide second-by-second (1 Hz resampling) values (Gildea et al., 2021), time-aligned at zero to match the beginning of the exercise. The NIRS signal is normalized using a 60 s average before the exercise begins. The data is analyzed by detecting the nadir, occurring

after a sudden decrease in HHb signal, excluding the data that are not associated with muscular  $\dot{V}O_2$  dynamics, referring to the muscle pump (Beltrame et al., 2017).

After the nadir, HHb increases monoexponentially, representing the  $\dot{V}O_2$  dynamics occurring upon the onset of exercise (DeLorey et al., 2003; Murias et al., 2011, 2014; Tschakovsky et al., 2006). To determine the quality of the fitting, the analysis of residuals, the degree of linear correlation between the experimental data and fitted function ( $r$ ), the 95% confidence interval band ( $CI_{95}$ ), and the significance level ( $p$ -value) of the estimated parameters are used (Beltrame et al., 2017). Reported  $\Delta TSI$  [%], to evaluate tissue oxygen saturation fluctuation within the skeletal muscle, is calculated as the difference between baseline (average 30 seconds before CWR) and end of exercise (30-second average before start of recovery), as described in the equation below:

$$\Delta TSI [\%] = TSI_{peak} - TSI_{bl}$$

Where  $TSI_{peak}$  is the 30-second average before  $\dot{V}O_{2peak}$ ;  $TSI_{bl}$  is the TSI baseline using a 30-second average before commencing exercise.

## CHAPTER FIVE: Results

This chapter describes the key results from (1) the preliminary results of  $\dot{V}O_2$  kinetics regarding the ICU-CARE CPET protocol for ICU-survivors, and (2) the healthy adults using the standardized, single session CPET protocol related to NIRS-derived HHb and TSI data.

### 5.1 ICU-Survivor: $\dot{V}O_2$ Preliminary Results

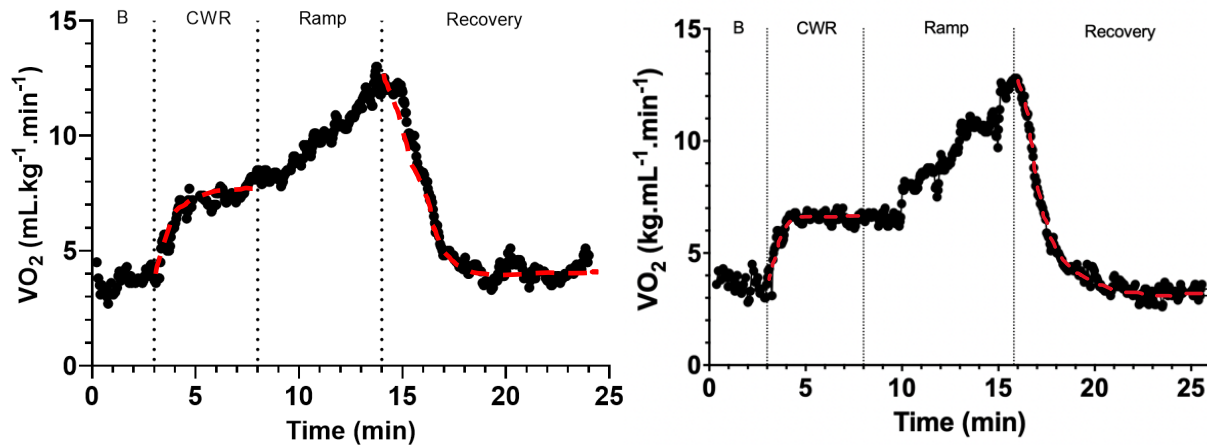
Preliminary data from two participants and three ICU-CARE-CPET protocols were collected as a pilot study to create a more streamlined implementation process to capture ICU-survivors' recovery after hospital discharge. Table 6 presents the ICU-survivors sample characteristics related to age, height, body mass, BMI, heart rate at rest, and systolic and diastolic blood pressure at rest.

**Table 6.** Sample characteristics of ICU-survivors ( $n = 2$ ).

| Mean $\pm$ SD              |                    |                  |
|----------------------------|--------------------|------------------|
|                            | Female ( $n = 1$ ) | Male ( $n = 1$ ) |
| Age [years]                | 64                 | 35               |
| Height [cm]                | 177.5              | 184.0            |
| Body mass [kg]             | 102.4              | 105.4            |
| BMI [kg/m <sup>2</sup> ]   | 31.1               | 31.8             |
| HR <sub>rest</sub> [bpm]   | 74                 | 83               |
| SBP <sub>rest</sub> [mmHg] | 125                | 158              |
| DBP <sub>rest</sub> [mmHg] | 72                 | 98               |

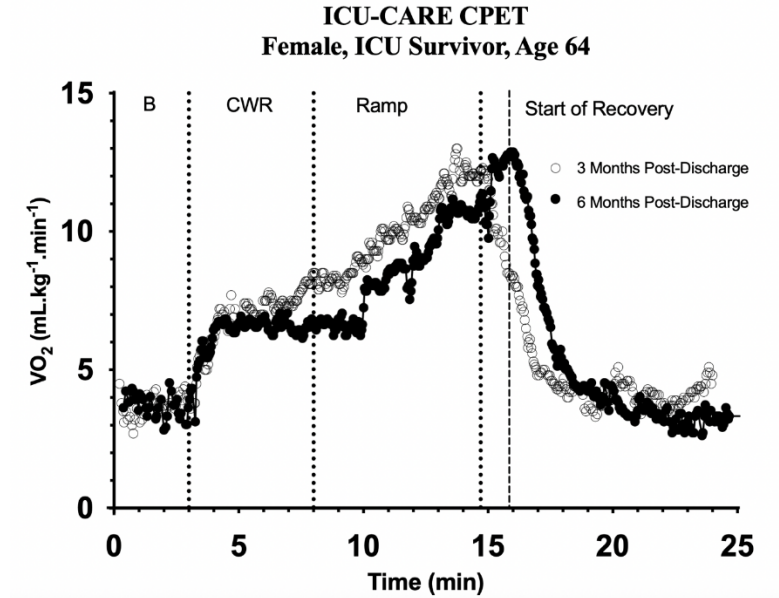
### 5.1.1 Case Study 1: 64-Year-Old Female

The first participant was a 64-year-old female who performed the ICU-CARE-CPET at 3 months and 6 months post-ICU discharge.  $\dot{V}O_2$  is illustrated in Figure 14. In both tests, it is possible to observe a monoexponential-like response during the CWR phase (on kinetics), an increase during the incremental phase, and another monoexponential-like response during the recovery phase (off-kinetics). The specific parameters for each fitting for ICU survivors are not reported, as that is not an objective and beyond the scope of this master's thesis, but rather a 'proof-of-concept'.



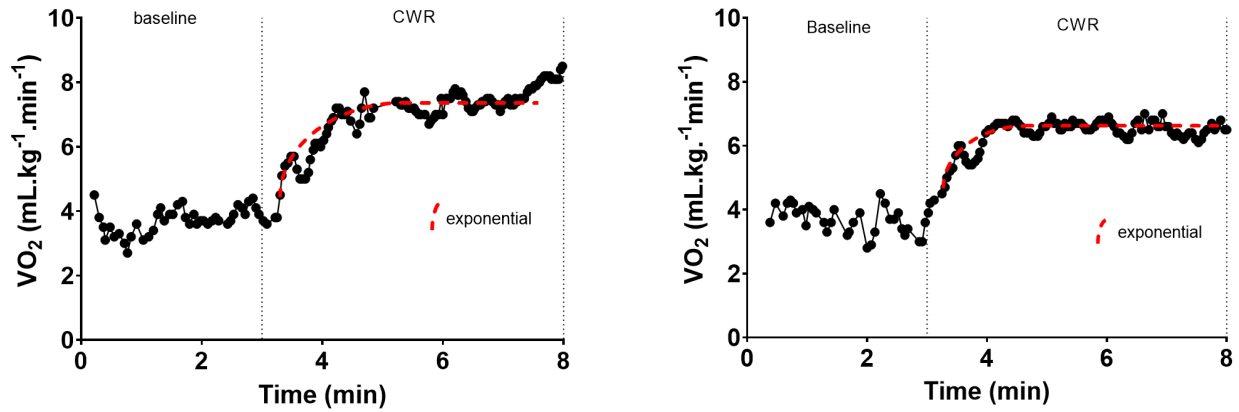
**Figure 14.** ICU-CARE-CPET protocol with  $\dot{V}O_2$  at 3 months (left panel) and 6 months (right panel) post-discharge. Red curved lines represent mono-exponential fitting.

Then next figure displays the comparison between 3 and 6 months post-discharge during the ICU-CARE-CPET protocol. Arguably, observations suggest there isn't a clear plateau at 3 months for the female during the CWR phase.

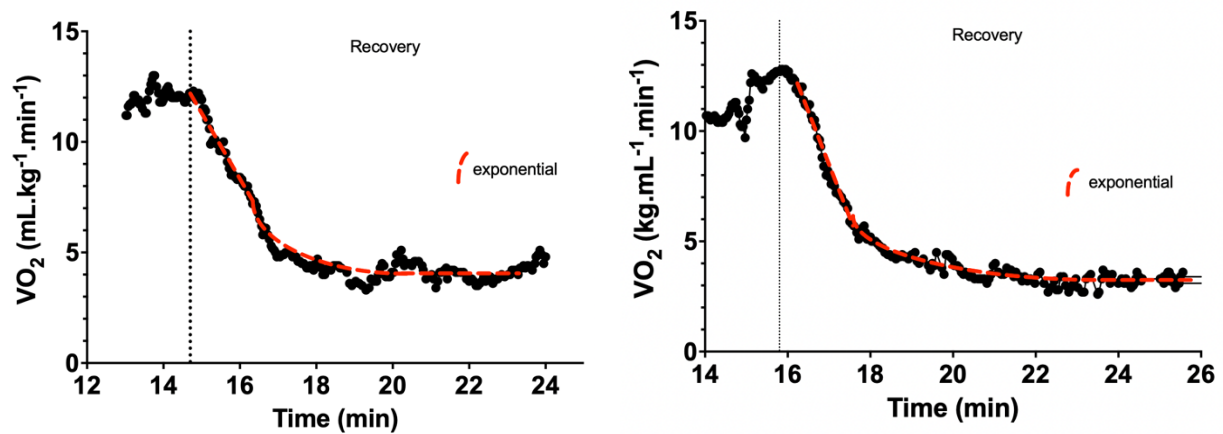


**Figure 15.** ICU-CARE-CPET protocol with  $\dot{V}O_2$  overlapped at 3 months and 6 months post-discharge during the ICU-CARE CPET protocol.

With the same data, the next figures (16 and 17) display the  $\dot{V}O_2$  on and off kinetic responses of a 64-year-old female ICU-survivor during the ICU-CARE CPET protocol, to allow for a clearer visual of the data presented.



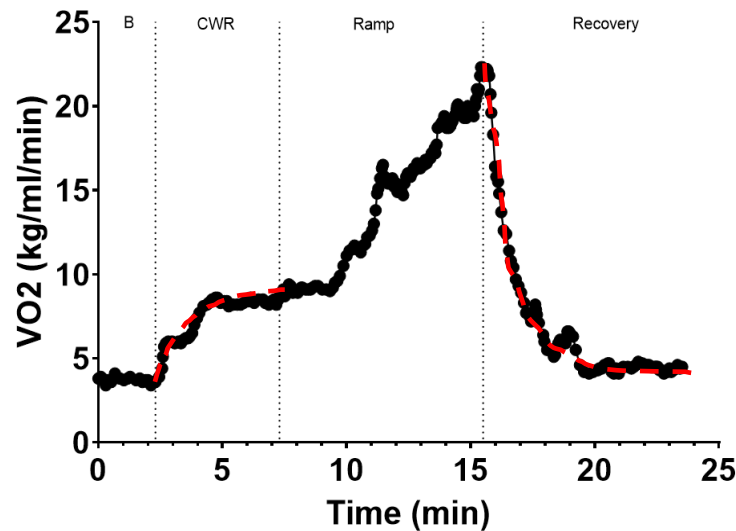
**Figure 16.** ICU-CARE CPET protocol  $\dot{V}O_2$  on-kinetic responses of a 64-year-old female ICU-survivor. At 3 months (left panel) and 6 months (right panel). Dashed lines indicate the onset of exercise. Red curved lines represent mono-exponential fitting.



**Figure 17.** ICU-CARE CPET protocol  $\dot{V}O_2$  off-kinetics of a 64-year-old female ICU-survivor. At 3 months (left panel) and 6 months (right panel) responses. Dashed lines indicate cessation of exercise. Red curved lines represent mono-exponential fitting.

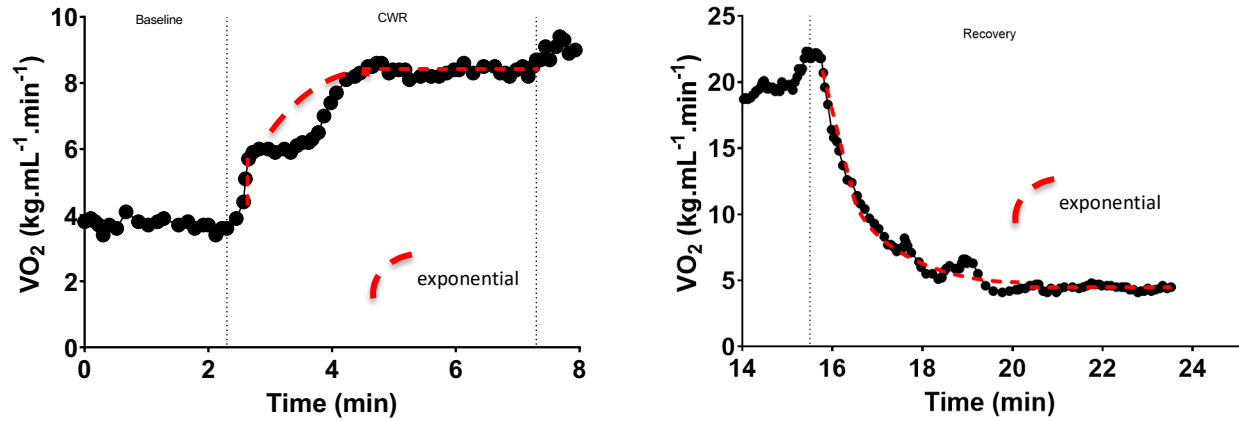
### 5.1.2 Case Study 2: 34-Year-Old Male

Figure 18 displays the  $\dot{V}O_2$  responses during the ICU-CARE-CPET protocol of a 34-year-old male at 6 months post-ICU discharge and did not participate at 3 months as this was not an objective of this thesis, but an ‘in-addition’ to the set objectives for planning purposes for future research. Relative  $\dot{V}O_{2peak}$  was 22.3 mL/kg/min and absolute  $\dot{V}O_{2peak}$  was 2.36 L/min, being lower than the normative values expected for his age ( $44.7 \pm 7.4$  mL/kg/min or  $3.4 \pm 0.6$  L/min) (Wagner et al., 2021). The  $\dot{V}O_{2peak}$  was 50% of the relative predicted  $\dot{V}O_{2peak}$  (22.3 mL/kg/min vs.  $44.7 \pm 7.4$  mL/kg/min) and 69% of the absolute predicted  $\dot{V}O_{2peak}$  (2.36 L/min vs.  $3.4 \pm 0.6$  L/min). These values indicate reduced cardiorespiratory fitness and exercise capacity.



**Figure 18.** ICU-CARE-CPET protocol  $\dot{V}O_2$  at 6 months post-discharge of a 34-year-old male ICU-survivor. Red curved lines represent mono-exponential fitting.

Figure 19 represents the  $\dot{V}O_2$  on and off kinetic responses of a 34-year-old male ICU-survivor during the ICU-CARE CPET protocol.



**Figure 19.** ICU-CARE CPET protocol  $\dot{V}O_2$  on kinetics (right panel) and off-kinetics (left panel) of a 34-year-old male ICU-survivor. Dashed lines indicate the onset of exercise (on-kinetics) or cessation of exercise (off-kinetics). Red curved lines represent mono-exponential fitting.

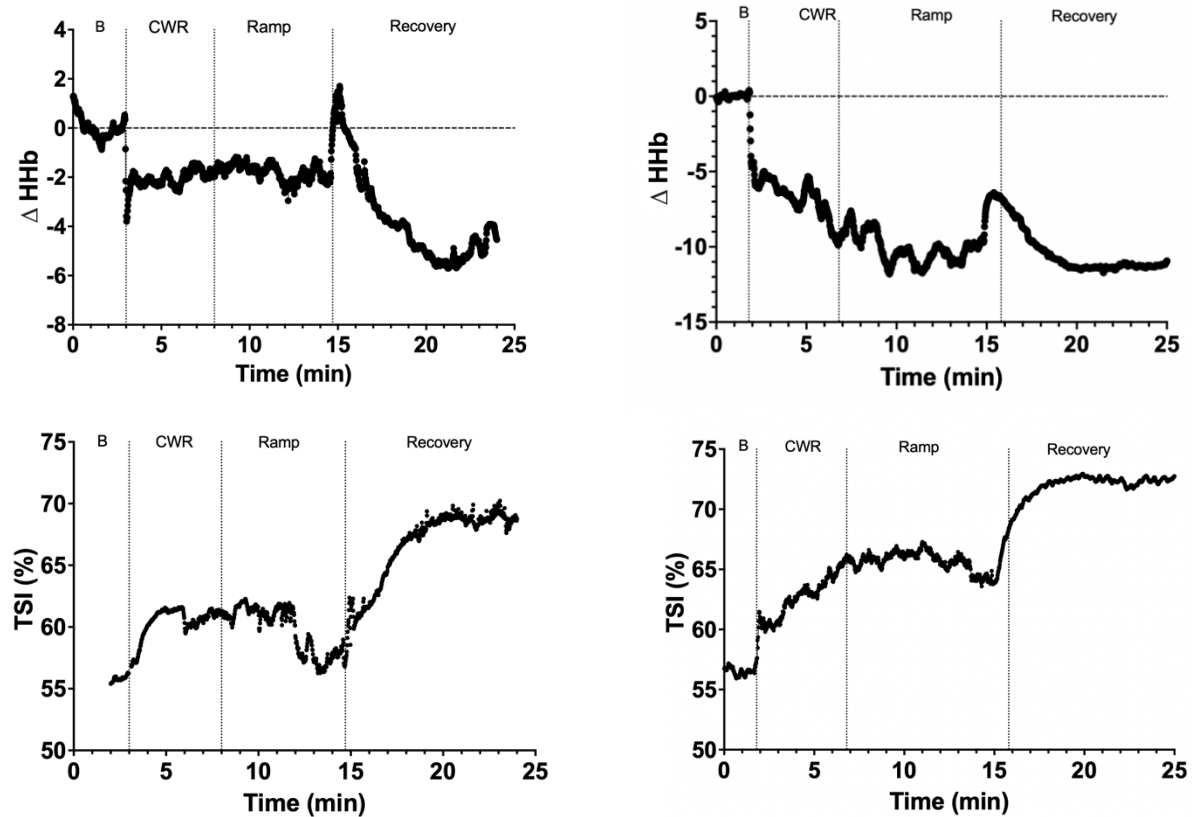
The next table describes cardiopulmonary and muscle oxygenation variables from the ICU-CARE CPET sessions at two time points (baseline and peak exercise).

**Table 7.** Cardiopulmonary and Muscle Oxygenation Parameters in ICU Patients at Rest and Peak Exercise

| ICU Patient | Post-Discharge | Baseline → Peak Exercise |           |             |             |             |                      |                     | ATT (mm) | NIRS Reliability |
|-------------|----------------|--------------------------|-----------|-------------|-------------|-------------|----------------------|---------------------|----------|------------------|
|             |                | O <sub>2</sub> Pulse     | HR (bpm)  | RER         | Vt (L)      | RR (br/min) | SpO <sub>2</sub> (%) | VE/VCO <sub>2</sub> |          |                  |
| F, 64y      | 3 mo           | 5 → 11                   | 80 → 118  | 0.84 → 1.02 | 0.85 → 1.81 | 6 → 28      | 96 → 91              | 47 → 37             | 9.7      | Reliable         |
| F, 64y      | 6 mo           | 6 → 12                   | 73 → 119  | 0.87 → 1.07 | 0.95 → 1.75 | 17 → 29     | 92 → 87              | 44 → 34             | 12.5     | Less Reliable    |
| M, 34y      | 6 mo           | 4 → 13                   | 107 → 178 | 0.89 → 1.11 | 1.39 → 3.10 | 9 → 24      | 100 → 99             | 30 → 29             | 10.8     | Reliable         |

### 5.1.3 ICU-Survivor – NIRS Preliminary Results

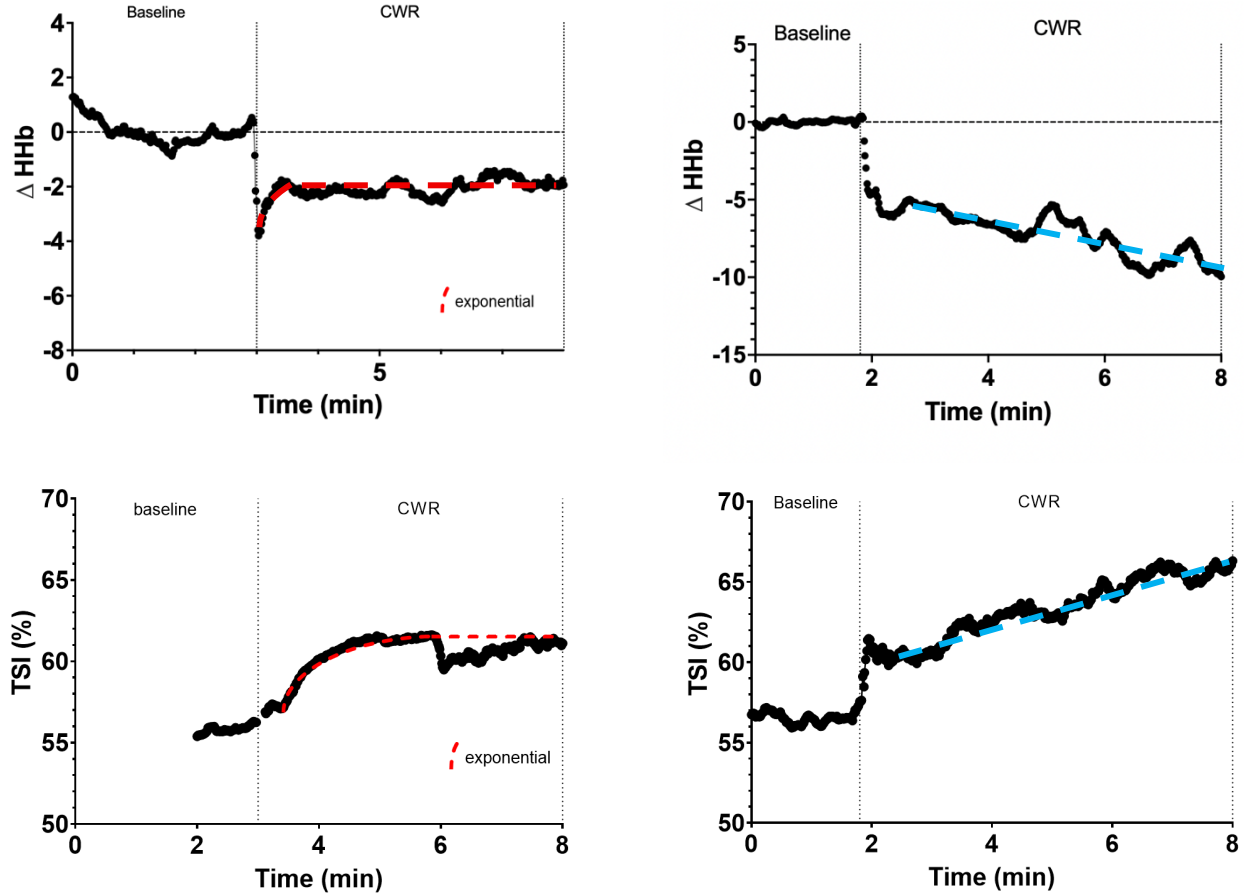
The following figure shows HHb and TSI retrieved from the entire protocol for the female ICU-survivor at 3 months (left) and at 6 months (right) post-discharge.



**Figure 20.** ICU-CARE-CPET protocol with NIRS-derived  $\Delta\text{HHb}$  and TSI for a 64-year-old female ICU-survivor at 3 months (left panels) and 6 months (right panels) post-discharge. For  $\Delta\text{HHb}$  graphs, negative  $\Delta\text{HHb}$  represents decreased values compared to baseline, while positive  $\Delta\text{HHb}$  represents increased values compared to baseline.

All HHb data has been normalized to baseline. In the upper right graph of Figure 20, at 6 months, the HHb NIRS signal appears to have downshifted. Considering literature suggests ATT of  $\geq 12.5\text{mm}$  can derive less reliable skeletal muscle NIRS measurements (Van Der Zwaard et

al., 2016), being the case at 6 months, this may have impacted NIRS signal quality during data collection, compared to an ATT of 9.7mm at 3 months. Therefore, the linear relationships at 6 months may have been caused by a NIRS signal drift, with observable NIRS signal connection issues during data collection that may have derived less a reliable measurement. A monoexponential-like responses can be observed during the transition from rest to exercise (CWR phase), except for  $\Delta\text{HHb}$  and TSI at 6 months. At 6 months,  $\Delta\text{HHb}$  showed fast desaturation followed by a smaller, continuous desaturation over time (2-8 minutes). TSI showed a fast increase, short stabilization from minute 2 to minute 3, followed by a more continuous linear increase until minute 8 during the CWR phase of the protocol (Figure 21).



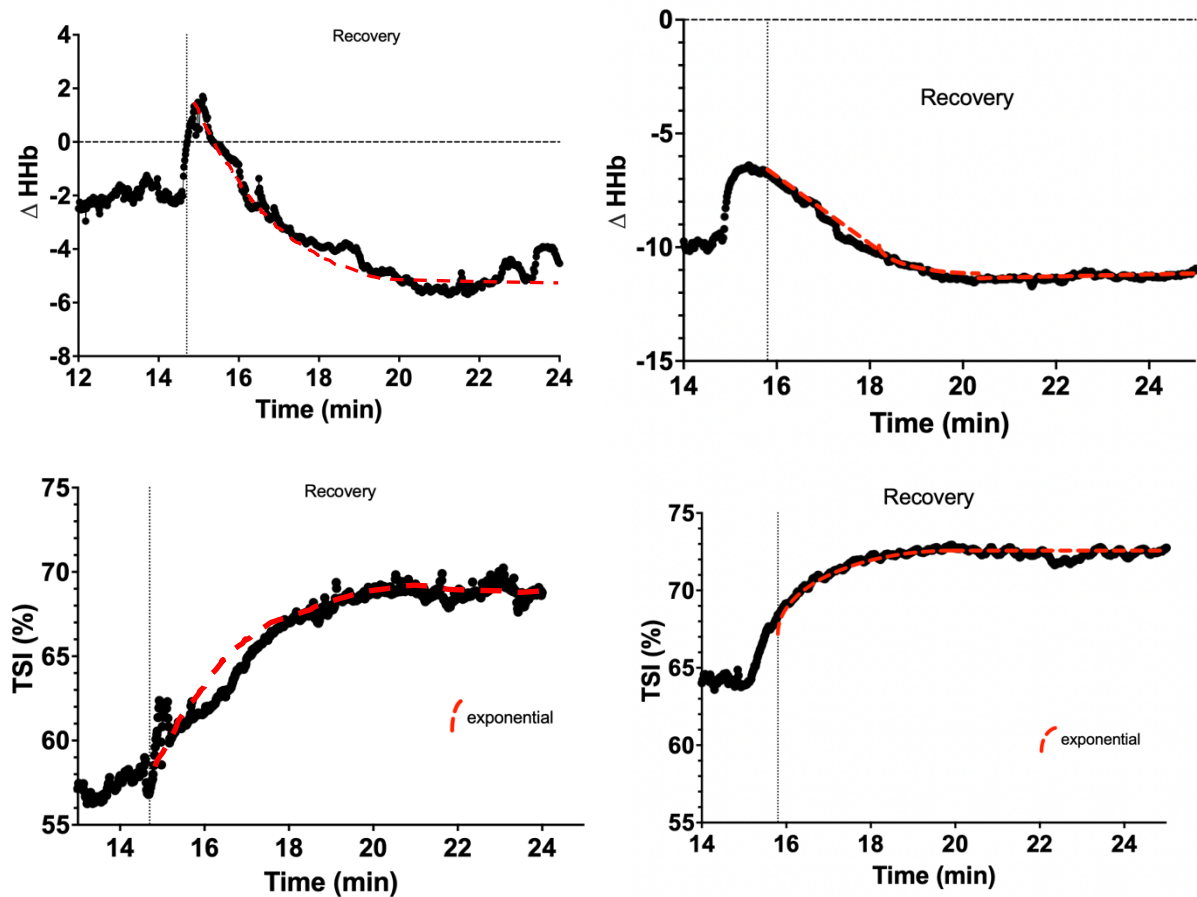
**Figure 21.** ICU-CARE CPET protocol NIRS-derived  $\Delta \text{HHb}$  and TSI on kinetic responses 64-year-old female ICU-survivor at 3 months (left panels) and 6 months (right panels). Dashed vertical lines indicate the onset of exercise. Red curved lines represent monoexponential fitting in the left panels. Blue dashed line in right panels showcase a linear relationship.

During exercise, the expected response of TSI is to progressively decrease in incremental exercise, arriving at a minimum plateau near peak exercise, reflecting the balance between delivery and utilization of oxygen in working skeletal muscle (Van Hooff et al., 2022). During exercise, HHb is expected to increase with increase in workload (Agbangla et al., 2017).

During recovery, the expected response of TSI after cessation of peak exercise is to increase, however within a patient population, reoxygenation is delayed, and anticipated to have

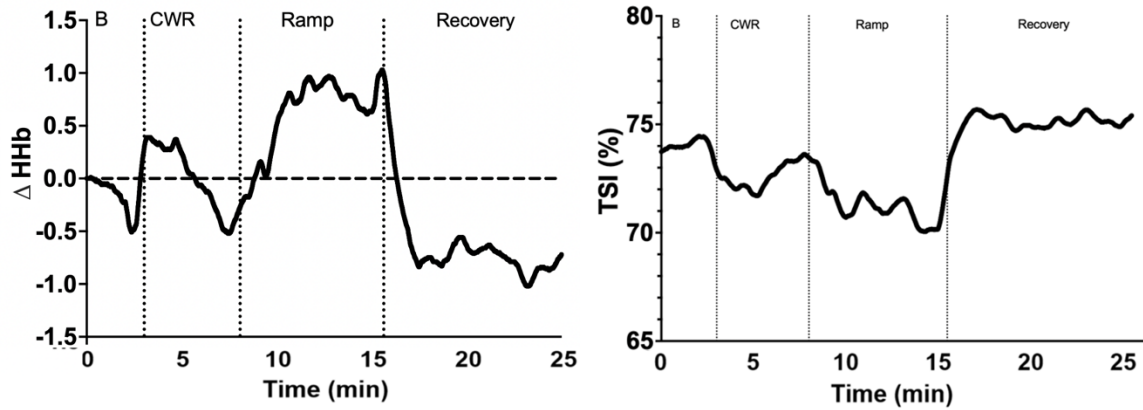
a larger time delay than healthy controls (Van Hooff et al., 2022). During recovery, HHb is expected to decrease, however within a patient population, a slower recovery of deoxygenation is anticipated, potentially suggesting intrinsic muscle dysfunction impacting muscle recovery (Azevedo et al., 2016).

The ICU-CARE CPET protocol responses regarding NIRS-derived  $\Delta\text{HHb}$  and TSI off kinetics are presented in Figure 22. A monoexponential-like response during the transition from exercise to recovery is noticeable at 3- and 6-month post-ICU discharge.

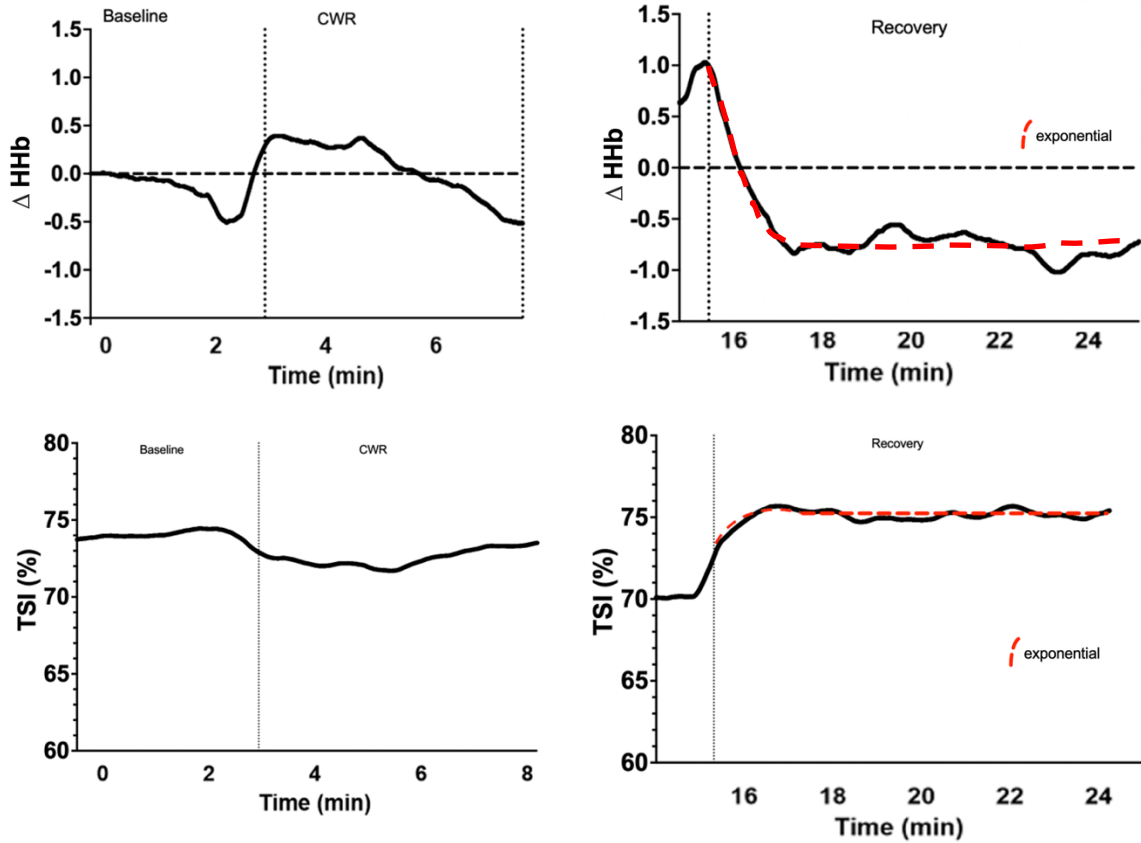


**Figure 22.** ICU-CARE CPET protocol NIRS-derived HHb and TSI off-kinetics 64-year-old female ICU-survivor at 3 months (left panels) and 6 months (right panels) responses. Dashed lines indicate cessation of exercise. Red curved lines represent monoexponential fitting.

The following figure displays the NIRS-derived  $\Delta\text{HHb}$  and TSI responses during the ICU-CARE-CPET protocol of a 34-year-old male at 6 months post-ICU discharge.



**Figure 23.** ICU-CARE-CPET protocol with NIRS-derived  $\Delta\text{HHb}$  (left panel) and TSI (right panel) 34-year-old male at 6 months post-ICU discharge.



**Figure 24.** ICU-CARE CPET protocol NIRS-derived  $\Delta\text{HHb}$  and TSI on kinetics (left panels) and off-kinetics (right panels) responses for a 34-year-old male at 6 months post-ICU discharge. Dashed lines indicate the onset of exercise (on-kinetics) or cessation of exercise (off-kinetics). Red curved lines represent monoexponential fitting.

Figure 24 shows the ICU-CARE CPET protocol related NIRS-derived  $\Delta\text{HHb}$  and TSI on/off kinetic responses. A monoexponential fitting was noticeable in all the variables, except  $\Delta\text{HHb}$  and TSI on kinetics. HHb showed a monoexponential-like response from ~ minute 2 to minute 5 (3 minutes) with signs of desaturation from minute 5 to minute 7 (end of the CWR phase). TSI did not demonstrate the expected increased response; instead, there was a slight reduction in TSI values until almost minute 6, then a slight increase from minute 6 to minute 7. This interpretation of a single bout should be further investigated when more data is obtained.

Next, the preliminary ICU-survivor NIRS-derived TSI obtained at  $\dot{V}O_{2peak}$  calculated from the average of the last 20 seconds of exercise, aligning with the  $\dot{V}O_{2peak}$  data analysis (Santana et al., 2025).

**Table 8.** Preliminary ICU-Survivor TSI at  $\dot{V}O_{2peak}$ .

| ICU-survivor NIRS parameters at $\dot{V}O_{2peak}$ (Mean) |                    |             |                  |
|-----------------------------------------------------------|--------------------|-------------|------------------|
| Variables                                                 | Female ( $n = 1$ ) | Same Female | Male ( $n = 1$ ) |
|                                                           | 3 Months           | 6 Months    | 6 Months         |
| TSI Baseline [%]                                          | 55.8               | 56.4        | 74.0             |
| TSI [%] at $\dot{V}O_{2peak}$                             | 57.5               | 68.2        | 72.7             |

TSI = Tissue Saturation Index;  $\dot{V}O_{2peak}$  = Peak Oxygen Uptake

The change in TSI at  $\dot{V}O_{2peak}$  between 3 and 6 months in the female ICU survivor can demonstrate how this protocol can report the local assessment of their underlying physiological status to evaluate whether recovery is progressing or regressing, to inform clinicians for prognostic considerations. Future research should track recovery and investigate its impact on prognostic considerations to better understanding its findings and impact/utility within a clinical setting.

### 5.3 Healthy – Retrospective NIRS Data Analysis

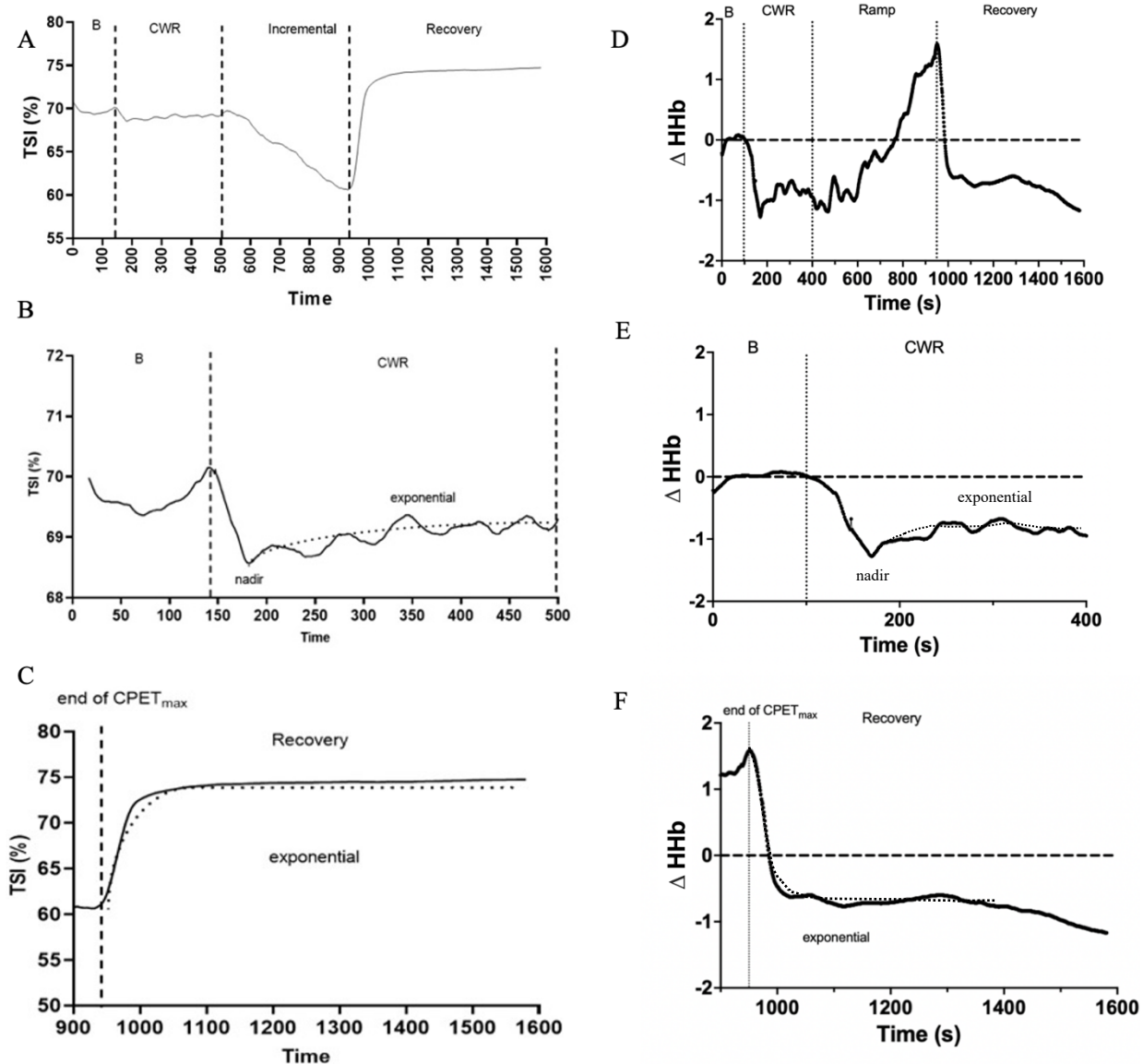
The following table showcases the sample characteristics of the healthy participants included in the retrospective analysis regarding age, height, body mass, BMI, resting heart rate, and resting systolic and diastolic blood pressure.

**Table 9.** Sample characteristics in female, male and combined groups eligible for kinetics analysis ( $n = 12$ ).

| Mean $\pm$ SD              |                    |                  |                       |
|----------------------------|--------------------|------------------|-----------------------|
|                            | Female ( $n = 5$ ) | Male ( $n = 7$ ) | Combined ( $n = 12$ ) |
| Age [years]                | 27.6 $\pm$ 7.23    | 26.1 $\pm$ 4.6   | 26.8 $\pm$ 5.58       |
| Height [cm]                | 1.68 $\pm$ 0.08    | 1.75 $\pm$ 0.06  | 1.72 $\pm$ 0.08       |
| Body mass [kg]             | 58.0 $\pm$ 6.6     | 78.09 $\pm$ 12.1 | 69.7 $\pm$ 14.2       |
| BMI [kg/.m <sup>2</sup> ]  | 20.5 $\pm$ 1.07    | 25.5 $\pm$ 2.53  | 23.4 $\pm$ 3.22       |
| HR <sub>rest</sub> [bpm]   | 71.8 $\pm$ 12      | 71.6 $\pm$ 10.8  | 71.7 $\pm$ 10.8       |
| SBP <sub>rest</sub> [mmHg] | 107 $\pm$ 5.27     | 132 $\pm$ 8.54   | 121 $\pm$ 14.7        |
| DBP <sub>rest</sub> [mmHg] | 67.4 $\pm$ 7.73    | 76 $\pm$ 6.98    | 72.4 $\pm$ 8.24       |

BMI = Body Mass Index; HR<sub>rest</sub> = Heart Rate at rest; SBP<sub>rest</sub> = Systolic Blood Pressure at rest; DBP<sub>rest</sub> = Diastolic Blood Pressure at rest.

The next figure showcases an example of NIRS-derived  $\Delta$ HHb and TSI responses within the entire CPET single-session protocol (Figure 25. A and D), on-kinetics phase (Figure 25. B and E) and off-kinetics phase (Figure 25. C and F) in a 24-year-old male. The four phases of the protocol include baseline, constant work rate (CWR), incremental and recovery phases. CWR (on-kinetics) is monoexponentially fitted at nadir (dotted line), as well as recovery (off-kinetics; dotted line), illustrating that it is possible to obtain kinetic parameters from NIRS-derived data generated from a retrospective dataset from Santana et al., 2025.



**Figure 25.** Retrospective data of a 24-year-old healthy male tissue saturation index (TSI) and deoxy-hemoglobin ( $\Delta\text{HHb}$ ) responses. With the four phases of the protocol, baseline, constant work rate (CWR), incremental and recovery phase (A and D). TSI and  $\Delta\text{HHb}$  on-kinetics monoexponentially fitted at nadir during constant work rate (CWR) phase (B and D). TSI and  $\Delta\text{HHb}$  recovery, reflecting off-kinetics fitted monoexponentially (C and F). Dotted black lines represent a monoexponential fitting function in this healthy figure example.

Table 10 presents the specific parameters used to perform the  $\Delta\text{HHb}$  kinetics analysis, selected to evaluate on- and off-kinetic responses during CWR and recovery phases of the single-session CPET protocol using NIRS.

**Table 10.** Deoxy-hemoglobin ( $\Delta\text{HHb}$ ) on and off kinetic parameters reported in females, males, and combined.

| Parameters from $\Delta\text{HHb}$ kinetics analyses (Mean $\pm$ SD) |                                    |                                  |                                       |
|----------------------------------------------------------------------|------------------------------------|----------------------------------|---------------------------------------|
| <b><math>\Delta\text{HHb}</math> on-kinetics</b>                     | <b>Female (<math>n = 5</math>)</b> | <b>Male (<math>n = 7</math>)</b> | <b>Combined (<math>n = 12</math>)</b> |
| $A_1$ [ $\text{mL.kg}^{-1}.\text{min}^{-1}$ ]                        | $0.9 \pm 0.5$                      | $3.6 \pm 2.4$                    | $2.5 \pm 2.3$                         |
| TD [s]                                                               | $1.4 \pm 0.4$                      | $4.3 \pm 2.8$                    | $3.1 \pm 2.6$                         |
| $\tau$ [s]                                                           | $28.4 \pm 6.6$                     | $38.7 \pm 11.4$                  | $34.4 \pm 10.9$                       |
| MRT [s]                                                              | $29.9 \pm 6.8$                     | $43.0 \pm 10.7$                  | $37.5 \pm 11.3$                       |
| <b><math>\Delta\text{HHb}</math> off-kinetics</b>                    | <b>Female (<math>n = 3</math>)</b> | <b>Male (<math>n = 7</math>)</b> | <b>Combined (<math>n = 10</math>)</b> |
| $A_1$ [ $\text{mL.kg}^{-1}.\text{min}^{-1}$ ]                        | $6.6 \pm 1.6$                      | $16.8 \pm 7$                     | $13.8 \pm 7.93$                       |
| *TD [s]                                                              | $0 \pm 0$                          | $0 \pm 0$                        | $0 \pm 0$                             |
| $\tau$ [s]                                                           | $85.1 \pm 65.8$                    | $48.8 \pm 24.9$                  | $59.7 \pm 47.2$                       |
| MRT [s]                                                              | $85.1 \pm 65.8$                    | $48.8 \pm 24.9$                  | $59.7 \pm 47.2$                       |

$A_1$  = Amplitude; TD = Time Delay;  $\tau$  = time constant; HHb = deoxyhemoglobin; MRT = mean response time (TD +  $\tau$ ). \*TD is zero during off-kinetics because the recovery process begins immediately following exercise. Therefore, there is no observable delay between the start of the “off” phase and the decline in HHb.

Table 11 shows the NIRS-derived TSI obtained at  $\dot{V}O_{2\text{peak}}$  calculated from the average of the last 20 seconds of exercise, aligning with the  $\dot{V}O_{2\text{peak}}$  data analysis (Santana et al., 2025), as well as the difference between baseline and TSI [%] at  $\dot{V}O_{2\text{peak}}$ .

**Table 11.** Healthy adults TSI at  $\dot{V}O_{2\text{peak}}$  and  $\Delta\text{TSI}$  from baseline ( $n = 12$ ).

| $\Delta\text{TSI}$ (Mean $\pm$ SD)   |                    |                  |                       |
|--------------------------------------|--------------------|------------------|-----------------------|
| Variables                            | Female ( $n = 5$ ) | Male ( $n = 7$ ) | Combined ( $n = 12$ ) |
| TSI Baseline [%]                     | 73.0 $\pm$ 2.62    | 66.6 $\pm$ 8.34  | 69.2 $\pm$ 7.17       |
| TSI [%] at $\dot{V}O_{2\text{peak}}$ | 74.4 $\pm$ 14.4    | 57.3 $\pm$ 4.99  | 64.4 $\pm$ 12.9       |
| $\Delta\text{TSI}$ [%]               | 1.44 $\pm$ 11.99   | -9.30 $\pm$ 4.19 | -4.83 $\pm$ 9.61      |

TSI = tissue saturation index.

However, an outlier was identified in the TSI data ( $\text{TSI}_{\text{peak}} = 100\%$ ), where typically,  $\text{TSI}_{\text{peak}}$  values are at  $\sim 70$ . If this participant is excluded,  $\text{TSI}_{\text{peak}}$  values change from  $74.4 \pm 14.4$  to  $68.0 \pm 2.2$  in females and from  $64.4 \pm 12.9$  to  $57.3 \pm 6.77$  in the combined sample (Table 12).

**Table 12.** Healthy adults TSI at  $\dot{V}O_{2\text{peak}}$  and  $\Delta\text{TSI}$  from baseline ( $n = 11$ ).

| $\Delta\text{TSI}$ (Mean $\pm$ SD)   |                    |                  |                       |
|--------------------------------------|--------------------|------------------|-----------------------|
| Variables                            | Female ( $n = 4$ ) | Male ( $n = 7$ ) | Combined ( $n = 11$ ) |
| TSI Baseline [%]                     | 71.9 $\pm$ 1.42    | 66.6 $\pm$ 8.34  | 68.5 $\pm$ 7.05       |
| TSI [%] at $\dot{V}O_{2\text{peak}}$ | 68.0 $\pm$ 2.22    | 57.3 $\pm$ 4.99  | 57.3 $\pm$ 6.77       |
| $\Delta\text{TSI}$ (%)               | -3.89 $\pm$ 1.45   | -9.30 $\pm$ 4.19 | -7.33 $\pm$ 4.31      |

TSI = tissue saturation index.

$\Delta\text{HHb}$  on-kinetics monoexponentially fitted at nadir during CWR phase ( $n = 12$ ) and  $\Delta\text{HHb}$  off-kinetics fitted monoexponentially ( $n = 10$ ), and  $\dot{\text{V}}\text{O}_2$  was modelled monoexponentially, removing the initial cardiogenic phase (20 s) for healthy adults from Santana et al. (2025). As the fitting window began at the onset of the primary exponential response, the time delay (TD) can be zero, particularly in younger participants and those with faster responses (e.g., higher levels of physical activity). Next is a table reporting the mean and standard deviation of on-kinetics variables from exponential fitting, including individual  $\dot{\text{V}}\text{O}_2$  data from Santana et al. (2025), next to the individual female, male, and combined parameters from NIRS collected during Santana et al. (2025).

**Table 13.** Individual on-kinetic parameters for  $\Delta\text{HHb}$  and  $\dot{\text{V}}\text{O}_2$  in healthy-young-adults, combined.

| Parameters     | A1                 |                            | TD (s)             |                            | $\tau$ (s)         |                            | MRT (s)            |                            |
|----------------|--------------------|----------------------------|--------------------|----------------------------|--------------------|----------------------------|--------------------|----------------------------|
| Participant ID | $\Delta\text{HHb}$ | $\dot{\text{V}}\text{O}_2$ | $\Delta\text{HHb}$ | $\dot{\text{V}}\text{O}_2$ | $\Delta\text{HHb}$ | $\dot{\text{V}}\text{O}_2$ | $\Delta\text{HHb}$ | $\dot{\text{V}}\text{O}_2$ |
| F3             | 0.5                | 9.1                        | 1.3                | 0                          | 34.1               | 29.9                       | 35.4               | 29.9                       |
| F5             | 0.7                | 4.7                        | 1.0                | 0                          | 26.0               | 13.3                       | 27.0               | 13.3                       |
| F9             | 1.2                | 6.8                        | 1.5                | 0                          | 35.1               | 19.5                       | 36.6               | 19.5                       |
| F12            | 1.8                | 6.8                        | 2.2                | 0                          | 30.0               | 19.1                       | 32.2               | 19.1                       |
| F13            | 0.2                | 8.2                        | 1.0                | 8.3                        | 17.0               | 18.5                       | 18.0               | 26.8                       |
| M4             | 8.0                | 10.4                       | 8.9                | 7.2                        | 25.2               | 37.0                       | 34.1               | 44.2                       |
| M7             | 2.1                | 9.0                        | 1.5                | 0                          | 57.4               | 28.8                       | 58.9               | 28.8                       |
| M8             | 1.8                | 7.6                        | 2.7                | 3.1                        | 37.0               | 20.5                       | 39.7               | 23.6                       |
| M9             | 4.7                | 11.6                       | 6.9                | 0                          | 46.4               | 20.3                       | 53.3               | 20.3                       |
| M10            | 0.4                | 6.9                        | 1.1                | 0                          | 26.1               | 13.3                       | 27.2               | 13.3                       |
| M11            | 2.8                | 7.8                        | 2.8                | 0                          | 48.3               | 30.5                       | 51.1               | 30.5                       |
| M15            | 5.2                | 10.1                       | 6.2                | 0                          | 30.2               | 16.7                       | 36.4               | 16.7                       |
| <b>Mean</b>    | <b>2.5</b>         | <b>8.3</b>                 | <b>3.1</b>         | <b>1.6</b>                 | <b>34.4</b>        | <b>22.3</b>                | <b>37.5</b>        | <b>1.7</b>                 |
| <b>SD</b>      | <b>2.3</b>         | <b>1.9</b>                 | <b>2.6</b>         | <b>3.0</b>                 | <b>10.9</b>        | <b>7.5</b>                 | <b>11.3</b>        | <b>0.7</b>                 |

A1 = amplitude; TD = time delay;  $\tau$  = time constant; MRT = mean response time.

## CHAPTER SIX: DISCUSSION

### 6.1 Main Findings

This thesis describes the development of a standardized, single-session ICU-CARE CPET protocol specifically tailored to the ICU-survivor population. Reporting data generated using that protocol for two ICU-survivors, signifying strong contributions to suggest that this protocol offers a novel standardized approach. Findings suggests that NIRS data was measured with adequate  $\dot{V}O_2$  data which can be fitted mono-exponentially showcased in preliminary ICU survivor ( $n = 2$ ) data. Regarding the healthy retrospective NIRS analysis, data reported  $TSI_{peak}$  [%] at  $\dot{V}O_{2peak}$  ( $74.4 \pm 14.4$   $n=5$  females;  $57.3 \pm 5.0$   $n=7$  males) and  $\Delta HHb$  on/off-kinetics (on-kinetics  $n=5$  females,  $n=7$  males; off-kinetics  $n=3$  females,  $n=7$  males), suggesting that this protocol can allow mono-exponential fitting. These findings suggest that this protocol may enable quantification of  $TSI_{peak}$ ,  $\Delta HHb$  and  $\dot{V}O_2$  on/off-kinetics using a combined single-session CPET-NIRS protocol, producing physiologically appropriate and interpretable data to inform future research and improve clinical practice.

### 6.2 Identified Gaps

Two significant gaps were identified in the ICU-AW literature, both representing barriers to advancing research in this field: a clinical-practical gap and a physiological knowledge gap. To enable deeper investigation into the underlying physiological processes of ICU-AW, we must first acknowledge the lack of a standardized, combined single-session CPET protocol that facilitates consistent and patient-centered assessment. Additionally, the limited application of NIRS in this population during exercise to provide quantitative insights into muscle oxygenation further constrains our understanding of the physiological mechanisms underlying ICU-AW.

### 6.3 Clinical Relevance of ICU-survivor $\dot{V}O_{2peak}$

Ewert et al. (2022) confirms  $\dot{V}O_{2peak}$  as a strong predictor of survival for people with cardiorespiratory disease, where the threshold for prognostic of 5-year survival for COPD patients is 14.6 mL/kg/min (Ewert et al., 2022), with ICU survivors frequently falling within a similar concerning and elevated risk category. ICU-survivors demonstrate markedly reduced  $\dot{V}O_{2peak}$ , ranging from 6 weeks up to 5 years post-discharge (Benington et al., 2012; Clavario et al., 2021; Herridge et al., 2011a; Joris et al., 2021; Longobardi et al., 2022; Mart et al., 2022; Van Aerde et al., 2021). For example, Benington et al. (2012) reported  $13.8 \pm 4.0$  mL/kg/min at 6 weeks post-discharge. Mart et al. (2022) observed a median  $\dot{V}O_{2peak}$  of 12.6 mL/kg/min ( $n = 14$ ) at 6 months post-ICU (Mart et al., 2022). Van Aerde et al. (2021) reported  $24 \pm 9.7$  mL/kg/min at 5 years after ICU-discharge. All these studies reflect a reduced exercise capacity and a limited aerobic fitness following critical illness (Benington et al., 2012; Clavario et al., 2021; Joris et al., 2021; Longobardi et al., 2022; Mart et al., 2022; Van Aerde et al., 2021). Despite some improvement five years post-ICU discharge, ICU-survivor relative  $\dot{V}O_{2peak}$  values remain below healthy norms, underscoring the ongoing impairment after ICU stay, while also highlighting the window of opportunity for rehabilitation and intervention. Notably, a consistent critical limitation across studies is the lack of reported absolute  $\dot{V}O_{2peak}$  values (L/min). Most studies report relative values (mL/kg/min), hindering cross-population comparisons for clinical application. Standardizing both relative and absolute reporting will improve prognostic utility and enhance targeted rehabilitation strategies moving forward.

### 6.4 Protocol Comparison: Healthy vs. ICU-survivor

Building upon the works of Santana et al., (2025) within a healthy population, key adaptations include the integration of NIRS technology, a literature-derived ICU correction

factor to correct for the estimated ICU-survivor  $\dot{V}O_{2\text{peak}}$ , and a functional capacity questionnaire to inform incremental ramp protocol based on self-reported functional status to individualize each ramp protocol (5, 10, 15, or 20W.min<sup>-1</sup>).

One key adaptation that differentiates the ICU-CARE CPET protocol compared to the protocol used in Santana et al. (2025) is the literature-derived ICU correction factor. The purpose of the ICU correction factor is to help estimate  $\dot{V}O_{2\text{peak}}$  below the 80-85% threshold of normality, as an attempt to include this vulnerable population, by accounting for long-term cardiorespiratory impairment repeatedly noted in the literature (Longobardi et al., 2022; Mart et al., 2022; Van Aerde et al., 2021). Reflecting the expected physiological ceiling for ICU-survivors, since a healthy  $\dot{V}O_{2\text{peak}}$  may overestimate aerobic capacity and power of this population. As a result, the ICU correction factor of 0.75 undershoots the so-called threshold of normality (80-85%) by considering the anticipated 25% reduction in  $\dot{V}O_{2\text{peak}}$  within this population. To help tailor Santana et al. (2025) protocol to the ICU survivor population when calculating CWR in four steps.

Regarding the results of the ICU survivor preliminary data, the 64-year-old female's peak workload was 84 W and exercise duration was 11:42 (min:sec) in the first session. In the second session, peak workload was 96 W and exercise duration was 12:58 (min:sec). Relative  $\dot{V}O_{2\text{peak}}$  showed a 1.54% decrease (from 13.0 to 12.8 mL/kg/min), involving a 7 kg increase in body mass between sessions (102.4kg to 109.4kg), potentially reflecting a common ongoing trend of weight-gain post-ICU (Chan et al., 2018; Jaitovich et al., 2019). In contrast, absolute  $\dot{V}O_{2\text{peak}}$  increased 4.48% (from 1.34 to 1.40 L/min), suggesting continued improvement of cardiopulmonary efficiency, despite the increase in body mass.

The  $\dot{V}O_{2\text{peak}}$  estimated with the ICU correction factor was compared with the  $\dot{V}O_{2\text{peak}}$  measured during the ICU-CARE CPET protocol (% difference). At 3 months post-discharge (102.4 kg), the 64-year-old female had an estimated  $\dot{V}O_{2\text{peak}}$  of 11.2 mL/kg/min (1.15 L/min) and a measured 13.0 mL/kg/min (1.34 L/min), representing 0.19 (L/min) absolute difference and 16.5% difference between estimated and measured  $\dot{V}O_{2\text{peak}}$  (L/min), and a 1.8 (mL/kg/min) difference (16.1%) from priori equation in metabolic cart. At 6 months post-discharge (109.4 kg), the same participant had an estimated  $\dot{V}O_{2\text{peak}}$  of 11.3 mL/kg/min (1.24 L/min) and a measured 12.8 mL/kg/min (1.40 L/min), representing a 0.16 (L/min) absolute difference and 12.9% difference between estimated and measured  $\dot{V}O_{2\text{peak}}$  (L/min), and a 1.5 (mL/kg/min) relative (13.3%) difference from priori equation in metabolic cart. Well below the age-matched healthy control CPET study ( $n = 36$ ), where individuals between 60-69 years had average relative  $\dot{V}O_{2\text{peak}}$  values of  $26.3 \pm 5.4$  mL/kg/min and  $1.59 \pm 0.27$  L/min (Wagner et al., 2021), indicating that our female participant experiences limited cardiopulmonary fitness and reduced exercise capacity compared to healthy values.

For example: at 3 months, representing 49.4% of predicted relative  $\dot{V}O_{2\text{peak}}$ , while absolute  $\dot{V}O_{2\text{peak}}$  (1.34 L/min) was 84.3% of the predicted absolute  $\dot{V}O_{2\text{peak}}$ ; at 6 months, the relative  $\dot{V}O_{2\text{peak}}$  declined slightly (12.8 mL/kg/min) to 48.7% of the predicted relative  $\dot{V}O_{2\text{peak}}$ , whereas the predicted absolute  $\dot{V}O_{2\text{peak}}$  (1.40 L/min) improved to 88.1% of predicted at 6 months post-discharge, compared to healthy controls (Wagner et al., 2021). The discrepancy between relative (49.4%  $\rightarrow$  48.7%) and absolute (84.3%  $\rightarrow$  88.1%) values highlights the impact of body mass within the recovery process, while also reinforcing the importance to report both absolute and relative measures in post-ICU recovery assessments, to be able to interpret continued

improvement of cardiopulmonary efficiency (or lack thereof), despite the increase in body mass. This is particularly relevant for critical illness survivors, as rapid muscle wasting during ICU stay is often followed by weight gain that is predominantly composed of an increase in fat mass (Chan et al., 2018; Jaitovich et al., 2019). Collectively, these findings support the need to adapt Santana et al., (2025) healthy-young-adult protocol to the ICU survivor population, within a standardized framework.

Regarding the 34-year-old male, at 6 months post-discharge (105.4 kg), his single session peak workload was 197 W and exercise duration was 13:06 (min:sec). This participant had an estimated  $\dot{V}O_{2peak}$  of 15.8 mL/kg/min (1.67 L/min) compared to a measured  $\dot{V}O_{2peak}$  of 22.3 mL/kg/min (2.36 L/min), representing a 0.69 (L/min) relative difference and 41.3% difference between estimated and measured  $\dot{V}O_{2peak}$  (L/min), and a 6.5 (mL/kg/min) difference (41.1%) from priori equation in metabolic cart. This participant's relative and absolute  $\dot{V}O_{2peak}$  values were lower than the normative values expected for his age ( $44.7 \pm 7.4$  mL/kg/min or  $3.4 \pm 0.6$  L/min) (Wagner et al., 2021). Representing 49.9% of predicted relative  $\dot{V}O_{2peak}$  and 69.4% of the predicted absolute  $\dot{V}O_{2peak}$  at 6 months post-discharge. These results suggest that the methods used for collecting this preliminary data underestimated the actual  $\dot{V}O_{2peak}$  of the ICU survivor (please see implementation limitation in the limitation section below, as the proposed standardization was not fully applied).

The second key adaptation includes the implementation of a self-reported functional capacity questionnaire. The purpose of the self-reported functional capacity questionnaire is to identify an individual's perceived exercise capacity to serve as a tool for participant baseline screening and ramp protocol calibration that aligns with the patient's perceived current

functional status to improve protocol adherence and reliability of CPET outcomes (Glaab & Taube, 2022). During ICU-survivor data collection, each participant self-reported the ability to perform four floors or more without stopping or breathlessness. Although the intended implementation of the individualized work rate increments prescribed based on patients' self-reported functional status (5, 10, 15, or 20W/min) would have prescribed a ramp of 20 W/min, our team decided to take the precautionary approach, described within the limitation section. Together, these key modifications may offer a more tailored and clinically sensitive method to enable a more patient-centered assessment tool for systemic and muscular oxygen dynamic responses to exercise, laying the groundwork for standardized follow-up care and future research in more vulnerable populations (e.g., frailty).

## **6.5 Strengths and Limitations**

The strength of developing the ICU-CARE CPET protocol was to offer a standardized, CPET-NIRS combined single-session to enable the comprehensive assessment of exercise capacity and skeletal muscle microvascular function in the ICU-survivor population, anticipated to be used to compare across research studies and clinical settings. Our team believes that assessing both maximal aerobic exercise capacity ( $\dot{V}O_{2peak}$ ) and  $\dot{V}O_2$  kinetics, complemented with the quantitative insights of NIRS (muscle oxygenation), within a single session, will enable the expansion of vulnerable population research. Not only by having more appeal for recruitment by reducing the number of hospital visits, but also by tailoring the protocol by including the participant within the individualized protocol design.

While the ICU-CARE CPET protocol holds considerable promise, a few limitations should be addressed within future research. Although this protocol is designed to accommodate a wide range of ICU-survivors, inter-participant variability (e.g., comorbidities and exercise

capacity before and after ICU) may impact the generalizability of results. Additionally, researchers must carefully document and adhere to time stamps of the protocol, as these are key for the accurate segmentation to allow for proper data analysis.

Furthermore, our preliminary data collection experience revealed additional limitations when implementing the Santana et al. (2025) protocol to the ICU-survivor population. After our first pilot attempt, our team discovered that the standardization steps proposed in Santana et al., (2025), particularly the Hansen/Wassermann refined equation for an estimated healthy  $\dot{V}O_{2peak}$  equation that is most accurate for work rate 50-200W (Garber, 2018), did not apply as well as hoped for the 64 year-old female ICU survivor. Our team manually attempted with and without applying the ICU correction factor with the prediction equation used in Santana et al., (2025), yet our team observed it to be unsuitable to determine CWR in this case. This protocol has since been updated to a sex-specific equation for Canadian adult (40-year-olds) (Lewthwaite et al., 2020) to be tested in future research. However, in terms of this thesis, CWR was prescribed directly by the attending physician (20 W for the female in both sessions, and 40 W for the male), limiting the ability to compare estimated vs. actual CWR at 30%  $\dot{V}O_{2reserve}$  after using the ICU correction factor on the estimated  $\dot{V}O_{2peak}$ .

Finally, another limitation was inability to test the second adaptation of the incremental ramp protocol based on self-reported functional status. During pilot testing, physicians opted for a conservative approach, prescribing a ramp of 10 W/min rather than the intended 20 W/min during the incremental phase. Although our team decided to not pilot the ramp prescription, the patients' self-reported functional status was found helpful to guide participant recruitment and exclusion criterion by subjectively assessing exercise capacity during the participant screening process over the phone. Overall, the proposed standardization was not entirely applied, requiring

further testing in future research. However, given its single-session on/off kinetic design with the application of NIRS technology within the ICU survivor population ( $n = 2$ ), sufficient data was generated and it is important to mention that no adverse events were reported during the execution of the ICU-CARE CPET protocol.

## **6.6 Practical Implications and Future Directions**

This thesis presents a foundational framework to support individualized post-ICU care and contribute to the ongoing efforts in understanding and addressing ICU-AW. The proposed CPET-NIRS protocol offers a combined cardiopulmonary and microvascular assessment that can inform personalized rehabilitation strategies beyond ICU stay, offering a streamlined and cost-effective method to monitor ICU-AW. Promoting standardization in ICU follow-up care, with potential for its integration across clinical, research, and rehabilitation settings, which may enable comparative studies across separate cohorts.

Although the objectives of this thesis were achieved, future research should aim to formally test the proposed standardization of the ICU-CARE CPET protocol. Specifically, to implement the sex-specific equation for Canadian adult (40-year-olds) (Lewthwaite et al., 2020) to test estimated vs. actual CWR at 30%  $\dot{V}O_{2reserve}$  using the ICU correction factor within the CWR phase, and follow the individualized ramp (5, 10, 15, or 20W/min) in the incremental phase within this prescribed protocol. Future research should also evaluate intra- and inter-participant reproducibility over repeated sessions to ensure protocol robustness across repeated assessments (Santana et al., 2025) and test its generalizability in broader populations.

This protocol serves as a foundation to for future longitudinal studies to assess utility in tracking rehabilitation outcomes and long-term recovery, in greater depth, across multiple centers. Future results are anticipated to provide a more detailed evaluation of the role of

microvascular-myocyte oxygen exchange site in ICU survivors to identify any causal relationships between microvascular dysfunction and ICU-AW, to enable new avenues of research across the oxygen delivery pathway to better understand ICU-AW pathophysiology.

## CONCLUSIONS

The objectives of this thesis were successfully achieved. Offering a detailed description of the development of the ICU-CARE CPET protocol, to provide a standardized, single-session CPET-NIRS assessment of  $\dot{V}O_{2\text{peak}}$ ,  $\dot{V}O_2$  kinetics and localized skeletal muscle oxygenation for ICU survivors with potential clinical and research implementation. Yes, it's possible to adapt Santana et al. (2025) healthy protocol to develop a standardized protocol for ICU survivors to quantitatively assess  $\dot{V}O_{2\text{peak}}$ ,  $\dot{V}O_2$  on/off-kinetics and localized skeletal muscle oxygenation (TSI and HHb), observed from ICU survivors' preliminary results ( $n = 2$ ), suggesting its utility within patient populations. This thesis provides a 'proof-of-concept' with sufficient data that may now be tested more widely, however, the described limitations must be addressed. Additionally, it is possible to obtain TSI<sub>peak</sub> and HHb on/off kinetics from the retrospective NIRS data using a single-session, combined CPET protocol, as described by Santana et al. (2025). It is anticipated that this research will lay the groundwork for a standardized, single-session CPET-NIRS protocol, providing a framework to enhance individualized and streamlined care to strengthen ICU follow-up practices, while also empowering research to further investigate the integrated pathophysiology underlying ICU-AW.

## REFERENCES

- Adhikari, N. K., Fowler, R. A., Bhagwanjee, S., & Rubenfeld, G. D. (2010). Critical care and the global burden of critical illness in adults. *The Lancet*, 376(9749), 1339–1346.  
[https://doi.org/10.1016/S0140-6736\(10\)60446-1](https://doi.org/10.1016/S0140-6736(10)60446-1)
- Agbanga, N. F., Audiffren, M., & Albinet, C. T. (2017). Assessing Muscular Oxygenation During Incremental Exercise Using Near-Infrared Spectroscopy: Comparison of Three Different Methods. *Physiological Research*, 979–985.  
<https://doi.org/10.33549/physiolres.933612>
- Ainab, I., Van Ochten, N., Suckow, E., Pierce, K., Arent, C., Kay, J., Forbes, L. M., & Cornwell, W. K. (2025). Determinants of cardiac output in health and heart failure. *Experimental Physiology*, 110(5), 637–648. <https://doi.org/10.1113/EP091505>
- Albouaini, K., Egred, M., Alahmar, A., & Wright, D. J. (2007). Cardiopulmonary exercise testing and its application. *Postgraduate Medical Journal*, 83(985), 675–682.  
<https://doi.org/10.1136/hrt.2007.121558>
- Amador, C., Weber, C., & Varacallo, M. A. (2025). Anatomy, Thorax, Bronchial. In *StatPearls*. StatPearls Publishing. <http://www.ncbi.nlm.nih.gov/books/NBK537353/>
- ATS/ACCP Statement on Cardiopulmonary Exercise Testing. (2003). *American Journal of Respiratory and Critical Care Medicine*, 167(2), 211–277.  
<https://doi.org/10.1164/rccm.167.2.211>
- Azevedo, D. D. P., Medeiros, W. M., De Freitas, F. F. M., Ferreira Amorim, C., Gimenes, A. C. O., Neder, J. A., & Chiavegato, L. D. (2016). High oxygen extraction and slow recovery of muscle deoxygenation kinetics after neuromuscular electrical stimulation in COPD

- patients. *European Journal of Applied Physiology*, 116(10), 1899–1910.  
<https://doi.org/10.1007/s00421-016-3442-7>
- Bagher, P., & Segal, S. S. (2011). Regulation of blood flow in the microcirculation: Role of conducted vasodilation. *Acta Physiologica*, 202(3), 271–284.  
<https://doi.org/10.1111/j.1748-1716.2010.02244.x>
- Ballve, L. P. D., Dargains, N., Inchaustegui, J. G. U., Bratos, A., Percaz, M. D. L. M., Ardariz, C. B., Cagide, S., Balestrieri, C., Gamarra, C., Paz, D., Rotela, E., Muller, S., Bustos, F., Castro, R. A., & Settembrino, E. (2017). Weakness acquired in the intensive care unit. Incidence, risk factors and their association with inspiratory weakness. Observational cohort study. *Revista Brasileira de Terapia Intensiva*, 29(4).  
<https://doi.org/10.5935/0103-507X.20170063>
- Barstow, T. J. (2019). Understanding near infrared spectroscopy and its application to skeletal muscle research. *Journal of Applied Physiology*, 126(5), 1360–1376.  
<https://doi.org/10.1152/jappphysiol.00166.2018>
- Batt, J., Herridge, M. S., & Dos Santos, C. C. (2019). From skeletal muscle weakness to functional outcomes following critical illness: A translational biology perspective. *Thorax*, 74(11), 1091–1098. <https://doi.org/10.1136/thoraxjnl-2016-208312>
- Battle, C., James, K., Temblett, P., & Hutchings, H. (2019). Supervised exercise rehabilitation in survivors of critical illness: A randomised controlled trial. *Journal of the Intensive Care Society*, 20(1), 18–26. <https://doi.org/10.1177/1751143718767061>
- Beltrame, T., Villar, R., & Hughson, R. L. (2017). Sex differences in the oxygen delivery, extraction, and uptake during moderate-walking exercise transition. *Applied Physiology, Nutrition, and Metabolism*, 42(9), 994–1000. <https://doi.org/10.1139/apnm-2017-0097>

- Benington, S., McWilliams, D., Eddleston, J., & Atkinson, D. (2012). Exercise testing in survivors of intensive care—Is there a role for cardiopulmonary exercise testing? *Journal of Critical Care*, 27(1), 89–94. <https://doi.org/10.1016/j.jcrc.2011.07.080>
- Berney, S., Haines, K., Skinner, E. H., & Denehy, L. (2012). Safety and Feasibility of an Exercise Prescription Approach to Rehabilitation Across the Continuum of Care for Survivors of Critical Illness. *Physical Therapy*, 92(12), 1524–1535. <https://doi.org/10.2522/ptj.20110406>
- Biernacki, P., & Waldorf, D. (1981). Snowball Sampling: Problems and Techniques of Chain Referral Sampling. *Sociological Methods & Research*, 10(2), 141–163. <https://doi.org/10.1177/004912418101000205>
- Børsheim, E., & Bahr, R. (2003). Effect of Exercise Intensity, Duration and Mode on Post-Exercise Oxygen Consumption: *Sports Medicine*, 33(14), 1037–1060. <https://doi.org/10.2165/00007256-200333140-00002>
- Cameron, J. I., Chu, L. M., Matte, A., Tomlinson, G., Chan, L., Thomas, C., Friedrich, J. O., Mehta, S., Lamontagne, F., Levasseur, M., Ferguson, N. D., Adhikari, N. K. J., Rudkowski, J. C., Meggison, H., Skrobik, Y., Flannery, J., Bayley, M., Batt, J., dos Santos, C., ... Canadian Critical Care Trials Group. (2016). One-Year Outcomes in Caregivers of Critically Ill Patients. *The New England Journal of Medicine*, 374(19), 1831–1841. <https://doi.org/10.1056/NEJMoa1511160>
- Canadian Society for Exercise Physiology. (2021). *CSEP Physical Activity Training For Health (CSEP-PATH). Resource Manual* (K. Lane, Ed.; 3rd ed.). Canadian Society for Exercise Physiology.

- Chalkias, A., Laou, E., Mermiri, M., Michou, A., Ntalarizou, N., Koutsona, S., Chasiotis, G., Garoufalidis, G., Agorogiannis, V., Kyriakaki, A., & Papagiannakis, N. (2022). Microcirculation-guided treatment improves tissue perfusion and hemodynamic coherence in surgical patients with septic shock. *European Journal of Trauma and Emergency Surgery*, 48(6), 4699–4711. <https://doi.org/10.1007/s00068-022-01991-2>
- Chambers, M. A., Moylan, J. S., & Reid, M. B. (2009). Physical inactivity and muscle weakness in the critically ill: *Critical Care Medicine*, 37, S337–S346. <https://doi.org/10.1097/CCM.0b013e3181b6e974>
- Chan, K. S., Mourtzakis, M., Aronson Friedman, L., Dinglas, V. D., Hough, C. L., Ely, E. W., Morris, P. E., Hopkins, R. O., & Needham, D. M. (2018). Evaluating Muscle Mass in Survivors of Acute Respiratory Distress Syndrome: A 1-Year Multicenter Longitudinal Study\*. *Critical Care Medicine*, 46(8), 1238–1246. <https://doi.org/10.1097/CCM.00000000000003183>
- Clavario, P., De Marzo, V., Lotti, R., Barbara, C., Porcile, A., Russo, C., Beccaria, F., Bonavia, M., Bottaro, L. C., Caltabellotta, M., Chioni, F., Santangelo, M., Hautala, A. J., Griffo, R., Parati, G., Corrà, U., & Porto, I. (2021). Cardiopulmonary exercise testing in COVID-19 patients at 3 months follow-up. *International Journal of Cardiology*, 340, 113–118. <https://doi.org/10.1016/j.ijcard.2021.07.033>
- Colbenson, G. A., Johnson, A., & Wilson, M. E. (2019). Post-intensive care syndrome: Impact, prevention, and management. *Breathe*, 15(2), 98–101. <https://doi.org/10.1183/20734735.0013-2019>
- Connolly, B., Thompson, A., Moxham, J., & Hart, N. (2012). Relationship Of Medical Research Council Sum-Score With Physical Function In Patients Post Critical Illness. *B47*.

- INTENSIVE CARE UNIT PHYSIOTHERAPY AND WEANING: MIND OVER MUSCLE?*, A3075. [https://doi.org/10.1164/ajrccm-conference.2012.185.1\\_MeetingAbstracts.A3075](https://doi.org/10.1164/ajrccm-conference.2012.185.1_MeetingAbstracts.A3075)
- Dallaire, F., Wald, R. M., & Marelli, A. (2017). The Role of Cardiopulmonary Exercise Testing for Decision Making in Patients with Repaired Tetralogy of Fallot. *Pediatric Cardiology*, 38(6), 1097–1105. <https://doi.org/10.1007/s00246-017-1656-z>
- DeLorey, D. S., Kowalchuk, J. M., & Paterson, D. H. (2003). Relationship between pulmonary O<sub>2</sub> uptake kinetics and muscle deoxygenation during moderate-intensity exercise. *Journal of Applied Physiology (Bethesda, Md.: 1985)*, 95(1), 113–120. <https://doi.org/10.1152/jappphysiol.00956.2002>
- Denehy, L., Skinner, E. H., Edbrooke, L., Haines, K., Warrillow, S., Hawthorne, G., Gough, K., Hoorn, S., Morris, M. E., & Berney, S. (2013). Exercise rehabilitation for patients with critical illness: A randomized controlled trial with 12 months of follow-up. *Critical Care*, 17(4), R156. <https://doi.org/10.1186/cc12835>
- Dhanireddy, S., Altemeier, W. A., Matute-Bello, G., O'Mahony, D. S., Glenny, R. W., Martin, T. R., & Liles, W. C. (2006). Mechanical ventilation induces inflammation, lung injury, and extra-pulmonary organ dysfunction in experimental pneumonia. *Laboratory Investigation*, 86(8), 790–799. <https://doi.org/10.1038/labinvest.3700440>
- Dominelli, P. B., Wiggins, C. C., Roy, T. K., Secomb, T. W., Curry, T. B., & Joyner, M. J. (2021). The Oxygen Cascade During Exercise in Health and Disease. *Mayo Clinic Proceedings*, 96(4), 1017–1032. <https://doi.org/10.1016/j.mayocp.2020.06.063>
- Dos Santos, C., Hussain, S. N. A., Mathur, S., Picard, M., Herridge, M., Correa, J., Bain, A., Guo, Y., Advani, A., Advani, S. L., Tomlinson, G., Katzberg, H., Streutker, C. J., Cameron, J. I., Schols, A., Gosker, H. R., Batt, J., MEND ICU Group, RECOVER

- Program Investigators, & Canadian Critical Care Translational Biology Group. (2016). Mechanisms of Chronic Muscle Wasting and Dysfunction after an Intensive Care Unit Stay. A Pilot Study. *American Journal of Respiratory and Critical Care Medicine*, 194(7), 821–830. <https://doi.org/10.1164/rccm.201512-2344OC>
- Edul, V., Dubin, A., & Ince, C. (2011). The Microcirculation as a Therapeutic Target in the Treatment of Sepsis and Shock. *Seminars in Respiratory and Critical Care Medicine*, 32(05), 558–568. <https://doi.org/10.1055/s-0031-1287864>
- Ewert, R., Obst, A., Mühle, A., Halank, M., Winkler, J., Trümper, B., Hoheisel, G., Hoheisel, A., Wiersbitzky, M., Heine, A., Maiwald, A., Gläser, S., & Stubbe, B. (2022). Value of Cardiopulmonary Exercise Testing in the Prognosis Assessment of Chronic Obstructive Pulmonary Disease Patients: A Retrospective, Multicentre Cohort Study. *Respiration*, 101(4), 353–366. <https://doi.org/10.1159/000519750>
- Fan, E., Cheek, F., Chlan, L., Gosselink, R., Hart, N., Herridge, M. S., Hopkins, R. O., Hough, C. L., Kress, J. P., Latronico, N., Moss, M., Needham, D. M., Rich, M. M., Stevens, R. D., Wilson, K. C., Winkelman, C., Zochodne, D. W., Ali, N. A., ATS Committee on ICU-acquired Weakness in Adults, & American Thoracic Society. (2014). An official American Thoracic Society Clinical Practice guideline: The diagnosis of intensive care unit-acquired weakness in adults. *American Journal of Respiratory and Critical Care Medicine*, 190(12), 1437–1446. <https://doi.org/10.1164/rccm.201411-2011ST>
- Ferreira, L. F., Koga, S., & Barstow, T. J. (2007). Dynamics of noninvasively estimated microvascular O<sub>2</sub> extraction during ramp exercise. *Journal of Applied Physiology*, 103(6), 1999–2004. <https://doi.org/10.1152/jappphysiol.01414.2006>

- Friedrich, O., Reid, M. B., Van den Berghe, G., Vanhorebeek, I., Hermans, G., Rich, M. M., & Larsson, L. (2015). The Sick and the Weak: Neuropathies/Myopathies in the Critically Ill. *Physiological Reviews*, 95(3), 1025–1109.  
<https://doi.org/10.1152/physrev.00028.2014>
- Gaesser, G. A., & Brooks, G. A. (1984). Metabolic bases of excess post-exercise oxygen consumption: A review. *Medicine & Science in Sports & Exercise*, 16(1), 29-43.  
<https://doi.org/10.1249/00005768-198401000-00008>
- Garber, C. E. (2018). General Principles of Exercise Prescription. In D. Riebe, A. Ep-c, J. K. Ehrman, G. Liguori, & M. Magal (Eds.), *ACSM's guidelines for exercise testing and prescription* (10th ed., pp. 226–269). Wolters Kluwer Health.
- Geroulanos, S., & Douka, E. T. (2006). Historical perspective of the word “sepsis.” *Intensive Care Medicine*, 32(12), 2077–2077. <https://doi.org/10.1007/s00134-006-0392-2>
- Gildea, N., McDermott, A., Rocha, J., O'Shea, D., Green, S., & Egaña, M. (2021). Time-course of  $\dot{V}O_2$  kinetics responses during moderate-intensity exercise subsequent to HIIT versus moderate-intensity continuous training in type 2 diabetes. *Journal of Applied Physiology*, 130(6), 1646–1659. <https://doi.org/10.1152/jappphysiol.00952.2020>
- Glaab, T., & Taube, C. (2022). Practical guide to cardiopulmonary exercise testing in adults. *Respiratory Research*, 23(1), 9. <https://doi.org/10.1186/s12931-021-01895-6>
- Grassi, B., Porcelli, S., Salvadego, D., & Zoladz, J. A. (2011). Slow  $VO_2$  kinetics during moderate-intensity exercise as markers of lower metabolic stability and lower exercise tolerance. *European Journal of Applied Physiology*, 111(3), 345–355.  
<https://doi.org/10.1007/s00421-010-1609-1>

- Grassi, B., & Quaresima, V. (2016). Near-infrared spectroscopy and skeletal muscle oxidative function *in vivo* in health and disease: A review from an exercise physiology perspective. *Journal of Biomedical Optics*, 21(9), 091313. <https://doi.org/10.1117/1.JBO.21.9.091313>
- Griffiths, J. A., Gager, M., & Waldmann, C. (2004). Follow-up after intensive care. *Continuing Education in Anaesthesia Critical Care & Pain*, 4(6), 202–205. <https://doi.org/10.1093/bjaceaccp/mkh054>
- Griffiths, R. D., & Hall, J. B. (2010). Intensive care unit-acquired weakness: *Critical Care Medicine*, 38(3), 779–787. <https://doi.org/10.1097/CCM.0b013e3181cc4b53>
- Grosu, H. B., Lee, Y. I., Lee, J., Eden, E., Eikermann, M., & Rose, K. M. (2012). Diaphragm Muscle Thinning in Patients Who Are Mechanically Ventilated. *Chest*, 142(6), 1455–1460. <https://doi.org/10.1378/chest.11-1638>
- Guo, Y., Shan, W., & Xiang, J. (2024). Predictive modeling of ICU-AW inflammatory factors based on machine learning. *BMC Neurology*, 24(1). <https://doi.org/10.1186/s12883-024-03981-w>
- Guyen, G., Hilty, M. P., & Ince, C. (2020). Microcirculation: Physiology, Pathophysiology, and Clinical Application. *Blood Purification*, 49(1–2), 143–150. <https://doi.org/10.1159/000503775>
- Hamaoka, T., McCully, K. K., Quaresima, V., Yamamoto, K., & Chance, B. (2007). Near-infrared spectroscopy/imaging for monitoring muscle oxygenation and oxidative metabolism in healthy and diseased humans. *Journal of Biomedical Optics*, 12(6), 062105. <https://doi.org/10.1117/1.2805437>

- Harvey, M. A., & Davidson, J. E. (2016). Postintensive Care Syndrome: Right Care, Right Now...and Later. *Critical Care Medicine*, 44(2), 381–385.  
<https://doi.org/10.1097/CCM.0000000000001531>
- Hassan Farhan, Moreno-Duarte, I., Latronico, N., Zafonte, R., & Eikermann, M. (2016). Acquired Muscle Weakness in the Surgical Intensive Care Unit: Nosology, Epidemiology, Diagnosis, and Prevention. *Anesthesiology*, 124(1), 207–234.  
<https://doi.org/10.1097/ALN.0000000000000874>
- Headley, S. A. (2018). Preexercise Evaluation. In D. Riebe, A. Ep-c, J. K. Ehrman, G. Liguori, & M. Magal (Eds.), *ACSM's guidelines for exercise testing and prescription* (10th ed.). Wolters Kluwer Health.
- Hermans, G., & Van Den Berghe, G. (2015). Clinical review: Intensive care unit acquired weakness. *Critical Care*, 19(1), 274. <https://doi.org/10.1186/s13054-015-0993-7>
- Hermans, G., Van Mechelen, H., Clerckx, B., Vanhullebusch, T., Mesotten, D., Wilmer, A., Casaer, M. P., Meersseman, P., Debaveye, Y., Van Cromphaut, S., Wouters, P. J., Gosselink, R., & Van Den Berghe, G. (2014). Acute Outcomes and 1-Year Mortality of Intensive Care Unit–acquired Weakness. A Cohort Study and Propensity-matched Analysis. *American Journal of Respiratory and Critical Care Medicine*, 190(4), 410–420.  
<https://doi.org/10.1164/rccm.201312-2257OC>
- Herridge, M. S., Chu, L. M., Matte, A., Tomlinson, G., Chan, L., Thomas, C., Friedrich, J. O., Mehta, S., Lamontagne, F., Levasseur, M., Ferguson, N. D., Adhikari, N. K. J., Rudkowski, J. C., Meggison, H., Skrobik, Y., Flannery, J., Bayley, M., Batt, J., Santos, C. dos, ... Canadian Critical Care Trials Group. (2016). The RECOVER Program: Disability Risk Groups and 1-Year Outcome after 7 or More Days of Mechanical

- Ventilation. *American Journal of Respiratory and Critical Care Medicine*, 194(7), 831–844. <https://doi.org/10.1164/rccm.201512-2343OC>
- Herridge, M. S., Tansey, C. M., Matté, A., Tomlinson, G., Diaz-Granados, N., Cooper, A., Guest, C. B., Mazer, C. D., Mehta, S., Stewart, T. E., Kudlow, P., Cook, D., Slutsky, A. S., & Cheung, A. M. (2011). Functional Disability 5 Years after Acute Respiratory Distress Syndrome. *New England Journal of Medicine*, 364(14), 1293–1304. <https://doi.org/10.1056/NEJMoa1011802>
- Heyland, D. K., Garland, A., Bagshaw, S. M., Cook, D., Rockwood, K., Stelfox, H. T., Dodek, P., Fowler, R. A., Turgeon, A. F., Burns, K., Muscedere, J., Kutsogiannis, J., Albert, M., Mehta, S., Jiang, X., & Day, A. G. (2015). Recovery after critical illness in patients aged 80 years or older: A multi-center prospective observational cohort study. *Intensive Care Medicine*, 41(11), 1911–1920. <https://doi.org/10.1007/s00134-015-4028-2>
- Hill, A. V., & Lupton, H. (1923). Muscular Exercise, Lactic Acid, and the Supply and Utilization of Oxygen. *QJM, os-16*(62), 135–171. <https://doi.org/10.1093/qjmed/os-16.62.135>
- Hirai, D. M., Colburn, T. D., Craig, J. C., Hotta, K., Kano, Y., Musch, T. I., & Poole, D. C. (2019). Skeletal muscle interstitial O<sub>2</sub> pressures: Bridging the gap between the capillary and myocyte. *Microcirculation*, 26(5), e12497. <https://doi.org/10.1111/micc.12497>
- Hiser, S. L., Fatima, A., Ali, M., & Needham, D. M. (2023). Post-intensive care syndrome (PICS): Recent updates. *Journal of Intensive Care*, 11(1), 23. <https://doi.org/10.1186/s40560-023-00670-7>
- Hughson, R. L. (2009). Oxygen uptake kinetics: Historical perspective and future directions. *Applied Physiology, Nutrition, and Metabolism*, 34(5), 840–850. <https://doi.org/10.1139/H09-088>

- Jaitovich, A., Khan, M. M. H. S., Itty, R., Chieng, H. C., Dumas, C. L., Nadendla, P., Fantauzzi, J. P., Yucel, R. M., Feustel, P. J., & Judson, M. A. (2019). ICU Admission Muscle and Fat Mass, Survival, and Disability at Discharge. *Chest*, 155(2), 322–330.  
<https://doi.org/10.1016/j.chest.2018.10.023>
- Jawa, N. A., Maslove, D. M., Sibley, S., Muscedere, J., Hunt, M., Hanley, M., Boyd, T., Westphal, R., Mathur, S., Fakolade, A., Tryon, M., & Boyd, J. G. (2025). IMPACT-ICU feasibility study: Pragmatic mixed-methods randomised controlled trial of a follow-up care intervention for survivors of critical illness and caregivers. *BMJ Open*, 15(1), e086799. <https://doi.org/10.1136/bmjopen-2024-086799>
- Jones, A. M., & Poole, D. C. (2005). Oxygen Uptake Dynamics: From Muscle to Mouth—An Introduction to the Symposium. *Medicine & Science in Sports & Exercise*, 37(9), 1542–1550. <https://doi.org/10.1249/01.mss.0000177466.01232.7e>
- Joris, M., Minguet, P., Colson, C., Joris, J., Fadeur, M., Minguet, G., Guiot, J., Misset, B., & Rousseau, A.-F. (2021). Cardiopulmonary Exercise Testing in Critically Ill Coronavirus Disease 2019 Survivors: Evidence of a Sustained Exercise Intolerance and Hypermetabolism. *Critical Care Explorations*, 3(7), e0491.  
<https://doi.org/10.1097/CCE.0000000000000491>
- Joyner, M. J., & Limberg, J. K. (2014). Blood pressure regulation: Every adaptation is an integration? *European Journal of Applied Physiology*, 114(3), 445–450.  
<https://doi.org/10.1007/s00421-013-2636-5>
- Jyoti Batra, Ajit Pal Singh, Rahul Saxena, Suyash Saxena, & Komal Goyal. (2022). BLOOD COMPONENTS AND ITS USAGE: A CLINICAL INSIGHT FROM DIAGNOSTIC

- LENS. *Journal of Pharmaceutical Negative Results*, 1747–1750.  
<https://doi.org/10.47750/pnr.2022.13.S06.230>
- Kleyweg, R. P., Van Der Meché, F. G. A., & Schmitz, P. I. M. (1991). Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barré syndrome. *Muscle & Nerve*, 14(11), 1103–1109. <https://doi.org/10.1002/mus.880141111>
- Koga, S., Okushima, D., Barstow, T. J., Rossiter, H. B., Kondo, N., & Poole, D. C. (2017). Near-infrared spectroscopy of superficial and deep rectus femoris reveals markedly different exercise response to superficial vastus lateralis. *Physiological Reports*, 5(17), e13402. <https://doi.org/10.14814/phy2.13402>
- Lad, H., Saumur, T. M., Herridge, M. S., dos Santos, C. C., Mathur, S., Batt, J., & Gilbert, P. M. (2020). Intensive Care Unit-Acquired Weakness: Not Just Another Muscle Atrophying Condition. *International Journal of Molecular Sciences*, 21(21), 7840. <https://doi.org/10.3390/ijms21217840>
- Landsteiner, I., Ikoma, T., & Lewis, G. D. (2025). Cardiopulmonary Exercise Testing in Advanced Heart Failure Management. *Heart Failure Clinics*, 21(1), 35–49. <https://doi.org/10.1016/j.hfc.2024.09.001>
- Lee, M., Kang, J., & Jeong, Y. J. (2020). Risk factors for post-intensive care syndrome: A systematic review and meta-analysis. *Australian Critical Care*, 33(3), 287–294. <https://doi.org/10.1016/j.aucc.2019.10.004>
- Lewthwaite, H., Benedetti, A., Stickland, M. K., Bourbeau, J., Guenette, J. A., Maltais, F., Marciniuk, D. D., O'Donnell, D. E., Smith, B. M., Tan, W. C., Jensen, D., AaronK, S. E., Chapman, R., Hernandez, P., Sin, D. D., & Walker, B. (2020). Normative Peak

- Cardiopulmonary Exercise Test Responses in Canadian Adults Aged  $\geq 40$  Years. *Chest*, 158(6), 2532–2545. <https://doi.org/10.1016/j.chest.2020.06.074>
- Longobardi, I., Prado, D. M. L. D., Goessler, K. F., Meletti, M. M., De Oliveira Júnior, G. N., De Andrade, D. C. O., Gualano, B., & Roschel, H. (2022). Oxygen uptake kinetics and chronotropic responses to exercise are impaired in survivors of severe COVID-19. *American Journal of Physiology-Heart and Circulatory Physiology*, 323(3), H569–H576. <https://doi.org/10.1152/ajpheart.00291.2022>
- Mandsager, K., Harb, S., Cremer, P., Phelan, D., Nissen, S. E., & Jaber, W. (2018). Association of Cardiorespiratory Fitness With Long-term Mortality Among Adults Undergoing Exercise Treadmill Testing. *JAMA Network Open*, 1(6), e183605. <https://doi.org/10.1001/jamanetworkopen.2018.3605>
- Margaria, R., Edwards, H. T., & Dill, D. B. (1933). THE POSSIBLE MECHANISMS OF CONTRACTING AND PAYING THE OXYGEN DEBT AND THE RÔLE OF LACTIC ACID IN MUSCULAR CONTRACTION. *American Journal of Physiology-Legacy Content*, 106(3), 689–715. <https://doi.org/10.1152/ajplegacy.1933.106.3.689>
- Mart, M. F., Ely, E. W., Tolle, J. J., Patel, M. B., & Brummel, N. E. (2022). Physiologic responses to exercise in survivors of critical illness: An exploratory pilot study. *Intensive Care Medicine Experimental*, 10(1), 35. <https://doi.org/10.1186/s40635-022-00461-8>
- Mart, M. F., Gordon, J. I., González-Seguel, F., Mayer, K. P., & Brummel, N. (2025). Muscle Dysfunction and Physical Recovery After Critical Illness. *Journal of Intensive Care Medicine*. <https://doi.org/10.1177/08850666251317467>

- Mazaheri, R., Schmied, C., Niederseer, D., & Guazzi, M. (2021). Cardiopulmonary Exercise Test Parameters in Athletic Population: A Review. *Journal of Clinical Medicine*, 10(21), 5073. <https://doi.org/10.3390/jcm10215073>
- McDonald, A. M., Knight, R. C., Campbell, M. K., Entwistle, V. A., Grant, A. M., Cook, J. A., Elbourne, D. R., Francis, D., Garcia, J., Roberts, I., & Snowdon, C. (2006). What influences recruitment to randomised controlled trials? A review of trials funded by two UK funding agencies. *Trials*, 7(1), 9. <https://doi.org/10.1186/1745-6215-7-9>
- Mendelson, A. A., Erickson, D., & Villar, R. (2023). The role of the microcirculation and integrative cardiovascular physiology in the pathogenesis of ICU-acquired weakness. *Frontiers in Physiology*, 14, 1170429. <https://doi.org/10.3389/fphys.2023.1170429>
- METABOLIC WITH 12 LEAD ECG Ultima™ CardiO2® gas exchange analysis system Two technologies in a singular all-in-one powerful cardiorespiratory diagnostic system. (n.d.). MGC Diagnostics Cooperation. <https://mgcdiagnostics.com/products/ultima-cardio2-gas-exchange-analysis-system>
- Mirsajadi, A., Erickson, D., Alias, S., Froese, L., Singh Sainbhi, A., Gomez, A., Majumdar, R., Herath, I., Wilson, M., Zarychanski, R., Zeiler, F. A., Mendelson, A. A., & on behalf of the Microvasclar Monitoring in Circulatory Shock and Sepsis (MiMICSS) Investigators and the Canadian Critical Care Translational Biology Group. (2024). Microvascular Autoregulation in Skeletal Muscle Using Near-Infrared Spectroscopy and Derivation of Optimal Mean Arterial Pressure in the ICU: Pilot Study and Comparison With Cerebral Near-Infrared Spectroscopy. *Critical Care Explorations*, 6(7), e1111. <https://doi.org/10.1097/CCE.0000000000001111>

- Miyamoto, T., Watanabe, K., Fukuda, K., & Moritani, T. (2020). Near-infrared Spectroscopy of Vastus Lateralis Muscle during Incremental Cycling Exercise in patients with Type 2 Diabetes. *Physical Therapy Research*, 23(1), 23–30. <https://doi.org/10.1298/ptr.E9984>
- Murias, J. M., Spencer, M. D., Keir, D. A., & Paterson, D. H. (2013). Systemic and vastus lateralis muscle blood flow and O<sub>2</sub> extraction during ramp incremental cycle exercise. *American Journal of Physiology-Regulatory, Integrative and Comparative Physiology*, 304(9), R720–R725. <https://doi.org/10.1152/ajpregu.00016.2013>
- Murias, J. M., Spencer, M. D., Kowalchuk, J. M., & Paterson, D. H. (2011). Muscle deoxygenation to VO<sub>2</sub> relationship differs in young subjects with varying  $\tau$ VO<sub>2</sub>. *European Journal of Applied Physiology*, 111(12), 3107–3118. <https://doi.org/10.1007/s00421-011-1937-9>
- Murias, J. M., Spencer, M. D., & Paterson, D. H. (2014). The critical role of O<sub>2</sub> provision in the dynamic adjustment of oxidative phosphorylation. *Exercise and Sport Sciences Reviews*, 42(1), 4–11. <https://doi.org/10.1249/JES.0000000000000005>
- Murrant, C. L., & Sarelius, I. H. (2015). Local control of blood flow during active hyperaemia: What kinds of integration are important? *The Journal of Physiology*, 593(21), 4699–4711. <https://doi.org/10.1113/JP270205>
- Muscedere, J., Bagshaw, S. M., Boyd, G., Sibley, S., Patrick, N., Day, A., Hunt, M., & Rolfson, D. (2022). The frailty, outcomes, recovery and care steps of critically ill patients (FORECAST) study: Pilot study results. *Intensive Care Medicine Experimental*, 10(1), 23. <https://doi.org/10.1186/s40635-022-00446-7>
- Nadruz, W., West, E., Sengeløv, M., Santos, M., Groarke, J. D., Forman, D. E., Claggett, B., Skali, H., & Shah, A. M. (2017). Prognostic Value of Cardiopulmonary Exercise Testing

- in Heart Failure With Reduced, Midrange, and Preserved Ejection Fraction. *Journal of the American Heart Association*, 6(11), e006000.  
<https://doi.org/10.1161/JAHA.117.006000>
- Needham, D. M. (2008). Mobilizing Patients in the Intensive Care Unit: Improving Neuromuscular Weakness and Physical Function. *JAMA*, 300(14), 1685.  
<https://doi.org/10.1001/jama.300.14.1685>
- Needham, D. M., Davidson, J., Cohen, H., Hopkins, R. O., Weinert, C., Wunsch, H., Zawistowski, C., Bemis-Dougherty, A., Berney, S. C., Bienvenu, O. J., Brady, S. L., Brodsky, M. B., Denehy, L., Elliott, D., Flatley, C., Harabin, A. L., Jones, C., Louis, D., Meltzer, W., ... Harvey, M. A. (2012). Improving long-term outcomes after discharge from intensive care unit: Report from a stakeholders' conference\*. *Critical Care Medicine*, 40(2), 502–509. <https://doi.org/10.1097/CCM.0b013e318232da75>
- Osler W. D. (1892). *The Principles and Practice of Medicine, Designed for the Use of Practitioners and Students of Medicine*. <https://archive.org/details/principlespract00osle>
- Østergaard, L., Granfeldt, A., Secher, N., Tietze, A., Iversen, N. K., Jensen, M. S., Andersen, K. K., Nagenthiraja, K., Gutiérrez-Lizardi, P., Mouridsen, K., Jespersen, S. N., & Tønnesen, E. K. (2015). Microcirculatory dysfunction and tissue oxygenation in critical illness. *Acta Anaesthesiologica Scandinavica*, 59(10), 1246–1259. <https://doi.org/10.1111/aas.12581>
- PAFFENBARGER, R. S., BLAIR, S. N., LEE, I.-M., & HYDE, R. T. (1993). Measurement of physical activity to assess health effects in free-living populations. *Medicine & Science in Sports & Exercise*, 25(1), 60–70. <https://doi.org/10.1249/00005768-199301000-00010>

- Perrey, S. (2024). Could near infrared spectroscopy be the new weapon in our understanding of the cerebral and muscle microvascular oxygen demand during exercise? *Journal of Sport and Health Science*, 13(4), 457–458. <https://doi.org/10.1016/j.jshs.2024.03.006>
- Pittman, R. N. (2011). Regulation of Tissue Oxygenation. *Colloquium Series on Integrated Systems Physiology: From Molecule to Function*, 3(3), 1–100. <https://doi.org/10.4199/C00029ED1V01Y201103ISP017>
- Poole, D. C., Behnke, B. J., & Musch, T. I. (2021). The role of vascular function on exercise capacity in health and disease. *The Journal of Physiology*, 599(3), 889–910. <https://doi.org/10.1113/JP278931>
- Poole, D. C., Hirai, D. M., Copp, S. W., & Musch, T. I. (2012). Muscle oxygen transport and utilization in heart failure: Implications for exercise (in)tolerance. *American Journal of Physiology-Heart and Circulatory Physiology*, 302(5), H1050–H1063. <https://doi.org/10.1152/ajpheart.00943.2011>
- Poole, D. C., & Jones, A. M. (2012). Oxygen Uptake Kinetics. In Y. S. Prakash (Ed.), *Comprehensive Physiology* (1st ed., pp. 933–996). Wiley. <https://doi.org/10.1002/cphy.c100072>
- Poole, D. C., & Jones, A. M. (2017). Measurement of the maximum oxygen uptake  $\dot{V}O_{2\max}$ :  $\dot{V}O_{2\text{peak}}$  is no longer acceptable. *Journal of Applied Physiology*, 122(4), 997–1002. <https://doi.org/10.1152/japplphysiol.01063.2016>
- Poole, D. C., & Musch, T. I. (2023). Capillary-Mitochondrial Oxygen Transport in Muscle: Paradigm Shifts. *Function*, 4(3), zqad013. <https://doi.org/10.1093/function/zqad013>

- Poole, D. C., Musch, T. I., & Colburn, T. D. (2022). Oxygen flux from capillary to mitochondria: Integration of contemporary discoveries. *European Journal of Applied Physiology*, 122(1), 7–28. <https://doi.org/10.1007/s00421-021-04854-7>
- Prescott, H. C., Iwashyna, T. J., Blackwood, B., Calandra, T., Chlan, L. L., Choong, K., Connolly, B., Dark, P., Ferrucci, L., Finfer, S., Girard, T. D., Hodgson, C., Hopkins, R. O., Hough, C. L., Jackson, J. C., Machado, F. R., Marshall, J. C., Misak, C., Needham, D. M., ... Angus, D. C. (2019). Understanding and Enhancing Sepsis Survivorship. Priorities for Research and Practice. *American Journal of Respiratory and Critical Care Medicine*, 200(8), 972–981. <https://doi.org/10.1164/rccm.201812-2383CP>
- Puthuchear, Z. A., & Denehy, L. (2015). Exercise Interventions in Critical Illness Survivors: Understanding Inclusion and Stratification Criteria. *American Journal of Respiratory and Critical Care Medicine*, 191(12), 1464–1467. <https://doi.org/10.1164/rccm.201410-1907LE>
- Puthuchear, Z. A., Rawal, J., McPhail, M., Connolly, B., Ratnayake, G., Chan, P., Hopkinson, N. S., Padhke, R., Dew, T., Sidhu, P. S., Velloso, C., Seymour, J., Agley, C. C., Selby, A., Limb, M., Edwards, L. M., Smith, K., Rowlerson, A., Rennie, M. J., ... Montgomery, H. E. (2013). Acute Skeletal Muscle Wasting in Critical Illness. *JAMA*, 310(15), 1591. <https://doi.org/10.1001/jama.2013.278481>
- Rademakers, T., Horvath, J. M., van Blitterswijk, C. A., & LaPointe, V. L. S. (2019). Oxygen and nutrient delivery in tissue engineering: Approaches to graft vascularization. *Journal of Tissue Engineering and Regenerative Medicine*, 13(10), 1815–1829. <https://doi.org/10.1002/term.2932>

- Radtke, T., Crook, S., Kaltsakas, G., Louvaris, Z., Berton, D., Urquhart, D. S., Kampouras, A., Rabinovich, R. A., Verges, S., Kontopidis, D., Boyd, J., Tonia, T., Langer, D., De Brandt, J., Goërtz, Y. M. J., Burtin, C., Spruit, M. A., Braeken, D. C. W., Dacha, S., ... Hebestreit, H. (2019). ERS statement on standardisation of cardiopulmonary exercise testing in chronic lung diseases. *European Respiratory Review*, 28(154), 180101. <https://doi.org/10.1183/16000617.0101-2018>
- Reuveny, R., Luboshitz, J., Wilkerson, D., Bar-Dayana, A., DiMenna, F. J., Jones, A. M., & Segel, M. J. (2022). Oxygen uptake kinetics during exercise reveal central and peripheral limitation in patients with iliofemoral venous obstruction. *Journal of Vascular Surgery: Venous and Lymphatic Disorders*, 10(3), 697-704.e4. <https://doi.org/10.1016/j.jvsv.2021.12.006>
- Ross, R., Blair, S. N., Arena, R., Church, T. S., Després, J.-P., Franklin, B. A., Haskell, W. L., Kaminsky, L. A., Levine, B. D., Lavie, C. J., Myers, J., Niebauer, J., Sallis, R., Sawada, S. S., Sui, X., & Wisløff, U. (2016). Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. *Circulation*, 134(24). <https://doi.org/10.1161/CIR.0000000000000461>
- Roy, T. K., & Secomb, T. W. (2021). Effects of impaired microvascular flow regulation on metabolism-perfusion matching and organ function. *Microcirculation*, 28(3), e12673. <https://doi.org/10.1111/micc.12673>
- Rozenberg, D., Mathur, S., & Batt, J. (2023). Editorial: Muscle dysfunction of critical illness. *Frontiers in Physiology*, 14. <https://doi.org/10.3389/fphys.2023.1336150>

- Rudd, K. E., Johnson, S. C., Agesa, K. M., Shackelford, K. A., Tsoi, D., Kievlan, D. R., Colombara, D. V., Ikuta, K. S., Kissoon, N., Finfer, S., Fleischmann-Struzek, C., Machado, F. R., Reinhart, K. K., Rowan, K., Seymour, C. W., Watson, R. S., West, T. E., Marinho, F., Hay, S. I., ... Naghavi, M. (2020). Global, regional, and national sepsis incidence and mortality, 1990–2017: Analysis for the Global Burden of Disease Study. *The Lancet*, 395(10219), 200–211. [https://doi.org/10.1016/S0140-6736\(19\)32989-7](https://doi.org/10.1016/S0140-6736(19)32989-7)
- Salluh, J. I. F., Wang, H., Schneider, E. B., Nagaraja, N., Yenokyan, G., Damluji, A., Serafim, R. B., & Stevens, R. D. (2015). Outcome of delirium in critically ill patients: Systematic review and meta-analysis. *BMJ*, 350(may19 3), h2538–h2538. <https://doi.org/10.1136/bmj.h2538>
- Santana, J. L., Enzner, T., Blunderfield, B., Mendelson, A. A., & Villar, R. (2025). Development of a standardized single-session cardiopulmonary exercise test for combined assessment of peak oxygen uptake and on/off-kinetics. *Experimental Physiology*, EP092337. <https://doi.org/10.1113/EP092337>
- Sayde, G. E. (2024). The Evolving Field of ICU Survivorship[s]. *CHEST*, 166(6), 1291–1292. <https://doi.org/10.1016/j.chest.2024.07.146>
- Schefold, J. C., Bierbrauer, J., & Weber-Carstens, S. (2010). Intensive care unit—Acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock. *Journal of Cachexia, Sarcopenia and Muscle*, 1(2), 147–157. <https://doi.org/10.1007/s13539-010-0010-6>
- Schwaiblmair, M., Reichensperner, H., Müller, C., Briegel, J., Fürst, H., Groh, J., Reichart, B., & Vogelmeier, C. (1999). Cardiopulmonary Exercise Testing Before and After Lung and

- Heart–Lung Transplantation. *American Journal of Respiratory and Critical Care Medicine*, 159(4), 1277–1283. <https://doi.org/10.1164/ajrccm.159.4.9805113>
- Segreti, A., Verolino, G., Crispino, S. P., & Agostoni, P. (2021). Listing Criteria for Heart Transplant. *Heart Failure Clinics*, 17(4), 635–646. <https://doi.org/10.1016/j.hfc.2021.05.008>
- Singer, M., Deutschman, C. S., Seymour, C., Shankar-Hari, M., Annane, D., Bauer, M., Bellomo, R., Bernard, G. R., Chiche, J. D., Coopersmith, C. M., Hotchkiss, R. S., Levy, M. M., Marshall, J. C., Martin, G. S., Opal, S. M., Rubenfeld, G. D., Poll, T. Der, Vincent, J. L., & Angus, D. C. (2016). The third international consensus definitions for sepsis and septic shock (sepsis-3). *JAMA - Journal of the American Medical Association*, 315(8), 801–810. <https://doi.org/10.1001/jama.2016.0287>
- Smith, S., & Rahman, O. (2025). Postintensive Care Syndrome. In *StatPearls*. StatPearls Publishing. <http://www.ncbi.nlm.nih.gov/books/NBK558964/>
- Song, L., Qu, H., Luo, J., Wang, W., Zheng, L., Xue, M., & Shi, D. (2022). Cardiopulmonary exercise test: A 20-year (2002-2021) bibliometric analysis. *Frontiers in Cardiovascular Medicine*, 9, 982351. <https://doi.org/10.3389/fcvm.2022.982351>
- Strasser, B. (2018). Survival of the fittest VO sub 2 sub max a key predictor of longevity. *Frontiers in Bioscience*, 23(8), 1505–1516. <https://doi.org/10.2741/4657>
- Talha, K. M., Pandey, A., Fudim, M., Butler, J., Anker, S. D., & Khan, M. S. (2023). Frailty and heart failure: State-of-the-art review. *Journal of Cachexia, Sarcopenia and Muscle*, 14(5), 1959–1972. <https://doi.org/10.1002/jcsm.13306>
- Tandirerung, F. J., Jamieson, A., Hendrick, E., Hughes, A. D., & Jones, S. (2024). Near-infrared spectroscopy (NIRS) in vivo assessment of skeletal muscle oxidative capacity: A

- comparison of results from short versus long exercise protocols and reproducibility in non-athletic adults. *Frontiers in Physiology*, *15*, 1429673.  
<https://doi.org/10.3389/fphys.2024.1429673>
- Tiru, B., DiNino, E. K., Orenstein, A., Mailloux, P. T., Pesaturo, A., Gupta, A., & McGee, W. T. (2015). The Economic and Humanistic Burden of Severe Sepsis. *PharmacoEconomics*, *33*(9), 925–937. <https://doi.org/10.1007/s40273-015-0282-y>
- Tschakovsky, M. E., Saunders, N. R., Webb, K. A., & O'Donnell, D. E. (2006). Muscle Blood-Flow Dynamics at Exercise Onset: Do The Limbs Differ? *Medicine & Science in Sports & Exercise*, *38*(10), 1811–1818. <https://doi.org/10.1249/01.mss.0000230341.86870.4f>
- Tuesta, M., Yáñez-Sepúlveda, R., Verdugo-Marchese, H., Mateluna, C., & Alvear-Ordenes, I. (2022). Near-Infrared Spectroscopy Used to Assess Physiological Muscle Adaptations in Exercise Clinical Trials: A Systematic Review. *Biology*, *11*(7), 1073.  
<https://doi.org/10.3390/biology11071073>
- Turnbull, A. E., Rabiee, A., Davis, W. E., Nasser, M. F., Venna, V. R., Lolitha, R., Hopkins, R. O., Bienvenu, O. J., Robinson, K. A., & Needham, D. M. (2016). Outcome Measurement in ICU Survivorship Research From 1970 to 2013: A Scoping Review of 425 Publications\*. *Critical Care Medicine*, *44*(7), 1267–1277.  
<https://doi.org/10.1097/CCM.0000000000001651>
- Van Aerde, N., Meersseman, P., Debaveye, Y., Wilmer, A., Casaer, M. P., Gunst, J., Wauters, J., Wouters, P. J., Goetschalckx, K., Gosselink, R., Van Den Berghe, G., & Hermans, G. (2021). Aerobic exercise capacity in long-term survivors of critical illness: Secondary analysis of the post-EPaNIC follow-up study. *Intensive Care Medicine*, *47*(12), 1462–1471. <https://doi.org/10.1007/s00134-021-06541-9>

- Van Der Zwaard, S., Jaspers, R. T., Blokland, I. J., Achterberg, C., Visser, J. M., Den Uil, A. R., Hofmijster, M. J., Levels, K., Noordhof, D. A., De Haan, A., De Koning, J. J., Van Der Laarse, W. J., & De Ruiter, C. J. (2016). Oxygenation Threshold Derived from Near-Infrared Spectroscopy: Reliability and Its Relationship with the First Ventilatory Threshold. *PLOS ONE*, 11(9), e0162914. <https://doi.org/10.1371/journal.pone.0162914>
- Van Hooff, M., Meijer, E. J., Scheltinga, M. R. M., Savelberg, H. H. C. M., & Schep, G. (2022). Test–retest reliability of skeletal muscle oxygenation measurement using near-infrared spectroscopy during exercise in patients with sport-related iliac artery flow limitation. *Clinical Physiology and Functional Imaging*, 42(2), 114–126. <https://doi.org/10.1111/cpf.12738>
- Vanhorebeek, I., Latronico, N., & Van Den Berghe, G. (2020). ICU-acquired weakness. *Intensive Care Medicine*, 46(4), 637–653. <https://doi.org/10.1007/s00134-020-05944-4>
- Vianna, J. M., Werneck, F. Z., Coelho, E. F., Damasceno, V. O., & Reis, V. M. (2014). Oxygen uptake and heart rate kinetics after different types of resistance exercise. *Journal of Human Kinetics*, 42, 235–244. <https://doi.org/10.2478/hukin-2014-0077>
- Wagner, J., Knaier, R., Infanger, D., Königstein, K., Klenk, C., Carrard, J., Hanssen, H., Hinrichs, T., Seals, D., & Schmidt-Trucksäss, A. (2021). Novel CPET Reference Values in Healthy Adults: Associations with Physical Activity. *Medicine & Science in Sports & Exercise*, 53(1), 26–37. <https://doi.org/10.1249/MSS.00000000000002454>
- Wang, W., Xu, C., Ma, X., Zhang, X., & Xie, P. (2020). Intensive Care Unit-Acquired Weakness: A Review of Recent Progress With a Look Toward the Future. *Frontiers in Medicine*, 7. <https://doi.org/10.3389/fmed.2020.559789>

- Wasserman. (2012). *Principles of exercise testing and interpretation: Including pathophysiology and clinical applications*: (Fifth edition (5th ed.)). Lippincott Williams & Wilkins.
- Wenceslau, C. F., McCarthy, C. G., Earley, S., England, S. K., Filosa, J. A., Goulopoulou, S., Gutterman, D. D., Isakson, B. E., Kanagy, N. L., Martinez-Lemus, L. A., Sonkusare, S. K., Thakore, P., Trask, A. J., Watts, S. W., & Webb, R. C. (2021). Guidelines for the measurement of vascular function and structure in isolated arteries and veins. *American Journal of Physiology. Heart and Circulatory Physiology*, 321(1), H77–H111. <https://doi.org/10.1152/ajpheart.01021.2020>
- West, J. B. (2005). The physiological challenges of the 1952 Copenhagen poliomyelitis epidemic and a renaissance in clinical respiratory physiology. *Journal of Applied Physiology*, 99(2), 424–432. <https://doi.org/10.1152/jappphysiol.00184.2005>
- Xin, C., Gai, Y., Wei, L., Wang, Y., Luo, Y., & Han, B. (2025). Potential diagnostic tools for intensive care unit acquired weakness: A systematic review. *International Journal of Nursing Studies Advances*, 8, 100301. <https://doi.org/10.1016/j.ijnsa.2025.100301>
- Xu, F., & Rhodes, E. C. (1999). Oxygen Uptake Kinetics During Exercise: *Sports Medicine*, 27(5), 313–327. <https://doi.org/10.2165/00007256-199927050-00003>
- Yang, T., Li, Z., Jiang, L., Wang, Y., & Xi, X. (2018). Risk factors for intensive care unit-acquired weakness: A systematic review and meta-analysis. *Acta Neurologica Scandinavica*, 138(2), 104–114. <https://doi.org/10.1111/ane.12964>
- Yang, T., Li, Z., Jiang, L., & Xi, X. (2018). Corticosteroid use and intensive care unit-acquired weakness: A systematic review and meta-analysis. *Critical Care*, 22(1). <https://doi.org/10.1186/s13054-018-2111-0>

Yorke, J., Khan, N., Garrow, A., Tyson, S., Singh, D., Vestbo, J., & Jones, P. W. (2022).

Evaluation of the Individual Activity Descriptors of the mMRC Breathlessness Scale: A Mixed Method Study. *International Journal of Chronic Obstructive Pulmonary Disease*, Volume 17, 2289–2299. <https://doi.org/10.2147/COPD.S372318>

Zuccarelli, L., Do Nascimento Salvador, P. C., Del Torto, A., Fiorentino, R., & Grassi, B.

(2020). Skeletal muscle  $\dot{V} O_2$  kinetics by the NIRS repeated occlusions method during the recovery from cycle ergometer exercise. *Journal of Applied Physiology*, 128(3), 534–544. <https://doi.org/10.1152/jappphysiol.00580.2019>

## Appendix A – Ethics Certificate of Approval



### CHIPER BIOMEDICAL RESEARCH ETHICS BOARD (BREB) CERTIFICATE OF ANNUAL APPROVAL

|                                                                                                                                                                                                                |                                                                                                                                |                                         |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <b>PRINCIPAL INVESTIGATOR:</b><br>[REDACTED]                                                                                                                                                                   | <b>AFFILIATED INSTITUTION/DEPARTMENT:</b><br>University of Manitoba, HSC, WHRA and Shared Health/Internal Medicine             | <b>ETHICS #:</b><br>HS25592 (B2022:067) |
| <b>MEETING DATE (if applicable):</b><br>NA                                                                                                                                                                     | <b>APPROVAL DATE:</b><br>August 11, 2025                                                                                       | <b>EXPIRY DATE:</b><br>August 22, 2026  |
| <b>STUDENT PRINCIPAL INVESTIGATOR SUPERVISOR (if applicable):</b><br>NA                                                                                                                                        |                                                                                                                                |                                         |
| <b>PROTOCOL NUMBER:</b><br>NA                                                                                                                                                                                  | <b>PROJECT OR PROTOCOL TITLE:</b><br>Exercise testing in ICU survivors to evaluate ICU-acquired weakness (Linked to B2021:063) |                                         |
| <b>SPONSORING AGENCIES, FUNDING AGENCIES AND/OR COORDINATING GROUPS:</b><br>Investigator Initiated - Sponsor<br>Health Sciences Centre Foundation; Thorlakson Foundation and MMSF DuVal Grant-in-aid (Funders) |                                                                                                                                |                                         |
| <b>Submission Date of Investigator Documents:</b><br>July 31, 2025                                                                                                                                             | <b>REB Receipt Date of Documents:</b><br>July 31, 2025                                                                         |                                         |

**REVIEW CATEGORY OF ANNUAL REVIEW:** Full Board Review ☐ Delegated Review ☒

**THE FOLLOWING AMENDMENT(S) and DOCUMENTS ARE APPROVED FOR USE:**

| Document Name (if applicable) | Version (if applicable) | Date |
|-------------------------------|-------------------------|------|
|                               |                         |      |

**Annual approval**

Annual approval implies that the most recent **REB-approved** versions of the protocol, Investigator Brochures, advertisements, letters of initial contact or questionnaires, and recruitment methods, etc. are approved.

**Consent and Assent Form(s):**

|                                                                                   |        |           |
|-----------------------------------------------------------------------------------|--------|-----------|
| Information and Consent Form for Participation in a Research Study (HSC)          | V. 3.2 | 21Oct2024 |
| Information and Consent Form for Participation in a Research Study (St. Boniface) | V. 3.2 | 21Oct2024 |

**CERTIFICATION**

CHIPER BREB has reviewed the annual study status report for the research study/project named on this **Certificate of Annual Approval** as per the category of review listed above and was found to be acceptable on ethical grounds for research involving human participants. Annual approval was granted by the Chair or Acting Chair, CHIPER BREB per the response to the conditions of approval outlined during the initial review (full board or delegated) of the annual study status report.

**ATTESTATION**

CHIPER is organized and operates according to Health Canada/ICH Good Clinical Practices, Tri-Council Policy Statement 2, and the applicable laws and regulations of Manitoba. In respect to clinical trials, CHIPER complies with the membership requirements for Research Ethics Boards defined in Division 5 of the Food and Drug Regulations of Canada or with the definition in the Interim Order Respecting Clinical Trials for Medical Devices and Drugs Relating to COVID-19.

**QUALITY ASSURANCE**

The University of Manitoba Research Compliance Office may request to review research documentation from this research study/project to demonstrate compliance with this approved protocol and the University of Manitoba Policy on the Ethics of Research Involving Humans.

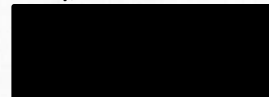
**CONFLICT OF INTEREST**

No Principal or Co-Investigators of this study who are members of CHIPER BREB participated in the review or approval of this study.

**CONDITIONS OF APPROVAL:**

1. The study is acceptable on scientific and ethical grounds for the ethics of human use only. *For logistics of performing the study, approval must be sought from the relevant institution(s).*
2. This research study/project is to be conducted by the local principal investigator listed on this certificate of approval.
3. The principal investigator has responsibility for any other administrative or regulatory approvals that may pertain to the research study/project, and for ensuring that the authorized research is carried out according to governing law.
4. **This approval is valid until the expiry date noted on this certificate of annual approval. An Annual Study Status Report** must be submitted to CHIPER within 15-30 days of this expiry date.
5. Any changes to the protocol (including recruitment procedures, etc.), informed consent form(s) or documents must be reported to CHIPER for consideration in advance of implementation of such changes on the **Research Amendment Form**.
6. Adverse events and unanticipated problems must be reported to CHIPER in accordance with its Standard Operating Procedures.
7. CHIPER must be notified regarding discontinuation or study/project closure on the **Final Study Status Report**.

Sincerely,



Chair, Biomedical Research Ethics Board  
CHIPER BREB

## Appendix B – Consent Form for Participation in Research Study



Hôpital St-Boniface Hospital

### Information and Consent Form for Participation in a Research Study

**Title:** **EXERCISE TESTING IN ICU SURVIVORS TO EVALUATE ICU-ACQUIRED WEAKNESS**

**Short Title:** Exercise after ICU

**Investigator:**



#### INTRODUCTION

You are invited to participate in trial because you have been discharged from the Intensive Care Unit (ICU), during which time your breathing was assisted by a mechanical ventilator for 7 days or more, or were enrolled in the **MiMICSS study** under direction of Dr. Mendelson and his research team. This information and consent form provides you with information to help you make an informed decision about whether or not to participate in an additional long-term study.

- Please read this document carefully.
- Ask any questions you may have. All your questions should be answered to your satisfaction.
- Take your time in making your decision. The study staff will tell you about the study timeline for making your decision.
- You may find it helpful to discuss it with your friends and family.
- Taking part in this study is voluntary.
- You have the option to not participate at all or you may choose to leave the study at any time.
- Whatever you choose, it will not affect the usual medical care that you receive outside the study.

No member of the research team will receive a personal financial benefit from your involvement in this research study (other than their ordinary wages). Health Sciences Centre/St. Boniface Hospital will receive payments for undertaking this research study.

#### ARE THERE CONFLICTS OF INTEREST?

There are no conflicts of interest to declare related to this study. At the present time, no financial or intellectual property content is currently held or in development by the investigators. It is possible that future intellectual property may be developed from the results of this study. By signing this consent form, you agree that data from this study can be used in the future for the application of intellectual property.

#### WHAT IS THE PURPOSE OF THIS STUDY?

You are being asked to take part in this study because you were admitted to the ICU and either participated in the **MiMICSS study** looking at microvascular monitoring in the ICU, or required mechanical ventilation for 7 or more days in the ICU. In this current study, we

#### Exercise testing in ICU survivors to evaluate ICU-acquired weakness

would like to follow your recovery for up to 12 months to see whether you regain strength in your muscles, and to understand how skeletal muscle blood flow affects your strength and function. A total of 20-40 participants will participate in this study from the ICU, and 20 healthy public members, although this number may change depending on success of recruitment.

#### WHAT OTHER CHOICES ARE THERE?

If you decide NOT to participate in this study, there are no consequences for your ongoing medical care. You are under no obligation to participate in this study

#### WHAT WILL HAPPEN IN THIS STUDY?

- A member of the research team will review your medical information to ensure you are an appropriate candidate to join the study.
- There will be up to four timepoints for follow-up after your ICU discharge: **7 days, 3 months, 6 months, and 12 months. You may decide to participate in 1 or more follow-ups without need to complete all four.**
- **You could be contacted for any of the timepoints within 12 months after ICU discharge, and some of these timepoints may not apply to you.**
- **At 7 days:** You will likely be in hospital for this visit. We will be testing your skeletal muscle blood flow with near-infrared spectroscopy (a monitoring system that uses harmless light outside your body) and blocking blood flow to your arm with a blood pressure cuff. We will also be asking you to complete a series of questionnaires related to your health and strength. *This should take no more than 90 minutes*
- **At 3 months, 6 months, and 12 months:** Questionnaires will be asked ahead of time when your appointment is being scheduled; *this should take up to 1 hour on the phone*. Upon arrival for your study session, we will finish the questionnaires, and be testing skeletal muscle blood flow with near-infrared spectroscopy, using the blood pressure cuff. In addition, we will be asking you to perform a number of physical activities including lying down, standing up, walking, and exercising on a bicycle. During these activities, you will be monitored with near-infrared spectroscopy, blood pressure, ECG, and breathing. *These activities together should take up to 6 hours throughout the day.*

#### HOW LONG WILL I BE IN THE STUDY?

The study period lasts for up to 12 months after discharge from the ICU. In total, this will require up to four (4) additional sessions for the research study.

A member of our research team will contact you ahead of each visit to confirm your desire for ongoing participation and schedule and appointment session.

#### CAN I CHOOSE TO LEAVE THE STUDY?

Your decision to take part in this study is voluntary. You can choose to end your participation in this study (called withdrawal) at any time without having to provide a reason.

## Appendix B – Continued

### Exercise testing in ICU survivors to evaluate ICU-acquired weakness

Your decision to not participate or to withdraw from the study will not affect your other medical care.

The study team will ask you if information that was recorded before you withdrew can be used by the researchers for the purposes of the study. You may request that your data be removed from our research program; this is totally acceptable, as long as it has not already been submitted for publication.

#### WHAT ARE THE RISKS OR DISCOMFORTS OF PARTICIPATING IN THIS STUDY?

Using the blood pressure cuff may cause discomfort, because it is being inflated for a period of 5 minutes. If you experience any symptoms, you can notify the research staff and they will discontinue the test.

Answering the questionnaires may produce feelings of anxiety related to your health and well-being. If you feel these questions are psychologically difficult, please notify the research staff and we will accommodate your concerns.

During the activity session, you may experience dizziness during the lying, standing, and walking portions of study. We will be following you carefully to ensure that there are no accidents during this period of testing.

**The exercise session is known to be safe**, with only a very small (less than 0.1%) chance of serious medical problems reported. The exercise session requires a certain degree of physical strength. Before they are started, we will follow standard safety guidelines to make sure it is appropriate to perform the testing; if your health is not strong, then we will not be proceeding exercise testing. This exercise session is performed in the Pulmonary Function Lab at Health Sciences Centre, Pulmonary Function Lab at St. Boniface Hospital or in our adjacent research facility with trained personnel who will be supervising your physical activity. If any changes to your health occur during the test, it will be stopped. If you require any medical attention (very rare) you will be sent quickly to the hospital emergency department.

#### WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Your participation in this study may allow the Study Doctor and their team to discover new information about how best to provide care to patients you are recovering from the ICU. You may not receive any direct benefit from taking part in this study.

#### WILL I BE PAID TO BE IN THIS STUDY?

You will receive compensation for parking during the day that you attend the exercise session.

#### WILL THERE BE EXTRA COSTS IF I PARTICIPATE?

### Exercise testing in ICU survivors to evaluate ICU-acquired weakness

All clinical and professional fees, diagnostic and laboratory tests that will be performed as part of this study are provided at no cost to you. There will be no cost for the study treatment that you will receive.

#### HOW WILL MY INFORMATION BE KEPT CONFIDENTIAL?

Information gathered in this research study may be published or presented in public forums, however your name and other identifying information will not be used or revealed and will be treated as confidential in accordance with the Personal Health Information Act of Manitoba. Despite efforts to keep your personal information confidential, absolute confidentiality cannot be guaranteed. Your personal information may be disclosed if required by law.

All personal health information will be kept confidential, unless release is required by law. By signing this form, you allow the Study Doctor and his team to collect, view and reproduce your health information to carry out this study. This may include contacting Health Record Departments at other hospitals or clinics and / or contacting community doctors to collect your health information related to this study. By signing the Informed Consent Form, you consent to direct access to your medical records for the purpose of this study only. Your contact information will also be stored so that study personnel can contact you to schedule follow-up sessions during the study period

ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on <http://ClinicalTrials.gov>. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

Regulatory authorities such as Health Canada may also review / copy your medical records in accordance with the applicable laws and regulatory requirements. The Biomedical Research Ethics Board at the University of Manitoba and the hospital at which you are receiving treatment may also review your medical and research-related records for quality assurance purposes. You have the right to access, review and request changes to your personal health information if the information is not correct. However, to ensure the scientific integrity of the study, some of your records related to the study may not be available for you review until after the study has been completed.

You will be assigned a unique study number. The link between your name and the unique study number will only be accessible by the study doctor and his staff. The link and study files will be stored separately and securely. Your contact information will be stored so that study personnel can contact you to schedule follow-up sessions during the study period. All files will be kept for a period of 7 years after the study is finished. All paper records will be stored in a locked office, and research data will also be stored in the REDCap research system which is a secure encrypted online database system used for medical research; no personal identifying information will be stored in the database. All electronic records will be stored at Health Sciences Centre and protected by a username and password, accessible

## Appendix B – Continued

### Exercise testing in ICU survivors to evaluate ICU-acquired weakness

only to Dr. Mendelson and the research staff. The University of Manitoba Biomedical Research Ethics Board may review research-related records for quality assurance purposes. At the end of the 7 years, all paper records will be disposed of in confidential waste and then shredded, and all of the electronic records will be erased.

#### WHAT ARE MY RIGHTS AS A PARTICIPANT IN A RESEARCH STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

In the event of an injury that occurs to you as a result of undergoing study procedures, you will receive the necessary medical treatment. You are not waiving any of your legal rights by signing this consent form nor releasing the investigator from their legal and professional responsibilities.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form, you do not give up any of your legal rights against the study doctor, sponsor or involved hospitals for compensation, nor does this form relieve the study doctor, sponsor or their agents of their legal and professional responsibilities. You will be given a copy of this consent form prior to participating in this study.

#### Questions

You are free to ask any questions that you may have about your treatment and your rights as a research participant. If any questions come up during or after the study or if you have a research-related injury, contact the study doctor and the study staff.

Investigator:

Research Coordinator:

For questions about your rights as a research participant, you may contact: The Biomedical Research Ethics Board, University of Manitoba at [REDACTED]

Do not sign this consent form unless you have had a chance to ask questions and have received satisfactory answers to all of your questions.

### Exercise testing in ICU survivors to evaluate ICU-acquired weakness

#### SIGNATURES

- All of my questions have been answered,
- I understand the information within this information and consent form,
- I allow direct access to my medical records and related personal health information as explained in this consent form,
- I do not give up any legal rights by signing this consent form,
- I freely agree, or agree to allow the person I am responsible for, to take part in this study.

\_\_\_\_\_  
Signature of Participant

\_\_\_\_\_  
Printed name of Participant

\_\_\_\_\_  
Date & Time

#### If consent is provided by Authorized 3<sup>rd</sup> Party:

\_\_\_\_\_  
PRINTED NAME of 3<sup>rd</sup> Party

\_\_\_\_\_  
Signature of 3<sup>rd</sup> Party

\_\_\_\_\_  
Relationship to participant

I confirm that I have explained in detail the above referenced study including the purpose, the potential risks and benefits, confidentiality and voluntary participation. All questions about the study have been answered. I confirm that I believe the participant/Authorized 3<sup>rd</sup> party has understood and has knowingly given their consent to participate.

\_\_\_\_\_  
Signature of Person Conducting  
the Consent Discussion

\_\_\_\_\_  
PRINTED NAME & ROLE

\_\_\_\_\_  
Date & Time

## Appendix B – Continued

Exercise testing in ICU survivors to evaluate ICU-acquired weakness

**The following attestation must be provided if the participant is unable to read or requires an oral translation:**

If the participant is assisted during the consent process, please check the relevant box and complete the signature space below:

- ☐ The person signing below acted as an interpreter, and attests that the study as set out in the consent form was accurately sight translated and/or interpreted, and that interpretation was provided on questions, responses and additional discussion arising from this process.

|                                       |                    |               |
|---------------------------------------|--------------------|---------------|
| _____<br>PRINT NAME<br>of Interpreter | _____<br>Signature | _____<br>Date |
| Language: _____                       |                    |               |

**Witness to the informed consent process** (If applicable): The informed consent form was accurately explained to, and apparently understood by, the participant/authorized 3<sup>rd</sup> party, AND Informed consent was freely given by the Participant/Authorized 3<sup>rd</sup> Party

- ☐ The consent form was read to the participant. I attest that the study as set out in this form was accurately explained to the participant, and any questions have been answered.

|                                   |                    |               |
|-----------------------------------|--------------------|---------------|
| _____<br>PRINT NAME<br>of witness | _____<br>Signature | _____<br>Date |
|-----------------------------------|--------------------|---------------|

\_\_\_\_\_  
Relationship to Participant