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# Impact of Graded Passive Cycling on Hemodynamics, Cerebral Blood Flow, and Heart Function in Healthy Adults and Septic ICU Patients

Jennifer Chen, *The University of Western Ontario*

Supervisor: McIntyre, Christopher W, *The University of Western Ontario*
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# Abstract

Sepsis is a life-threatening dysregulation of host response to an infectious insult, which often leads to multi-organ failure. Sepsis survivors suffer from post-intensive care syndrome in part due to their prolonged bed rest and lack of mobility. Although early mobilization has been championed as a mechanism to counter the adverse effects associated with ICU immobility, due to sedation and mechanical ventilation, active early mobilization is not often administered in septic patients due to worries of hemodynamic instability and potential for inducing adverse events. Passive exercise is a mobilization modality that circumvents the need for patients to be conscious and participatory in their mobilization sessions, and thus allows for mobilization of critically ill patients during the acute stages of their ICU stay.

This thesis addresses the safety and feasibility of a graded passive mobilization procedure in septic patients to better understand the effects that passive cycling intensity has on patient hemodynamic status, along with organ perfusion status in key organ systems that are at risk of organ dysfunction as a result of the systemic effects of sepsis.

Keywords: passive exercise, passive mobilization, passive cycling, sepsis, intensive care unit, hemodynamics, cerebral blood flow, transcranial Doppler, echocardiography

# Summary for Lay Audience

Sepsis is a life-threatening syndrome that often results in organ dysfunction and failure. Even following successful stabilization following an initial septic event, sepsis survivors often suffer long-lasting injuries due to prolonged physiologic changes from both the septic event and from their stay in the critical care unit. Early mobilization has been used as a method to reduce immobility in intensive care units (ICU) and has been a deemed safe and feasible mechanism in improving patient outcomes following ICU stay. However, this early mobilization is often active and requires patient alertness and participation, which is not feasible for septic patients that are sedated and unconscious in the early stages of their ICU stay. Passive mobilization is a method of mobilizing patients and reducing immobility even when they are unconscious and unable to participate in physical exercise and is used to bridge the early phases of ICU stay with transition into early active exercise. However, little is known regarding the appropriate amount of passive exercise to administer these sedated, critically ill patients. Thus, this thesis aims to elucidate the impact of passive cycling intensity on a variety of patient safety parameters during early passive exercise.

# Co-authorship statement

A version of a section in the first chapter (Chapter 1.3.2.1. Passive exercise in the intensive care unit) titled "Passive lower limb exercise in critically ill patients: A scoping review and comparison to healthy adults." has been submitted to Critical Care. This article was co-authored by Kyle Fiorini, Shijie Zhou, Ian Ball, Claudio Martin, Christopher William McIntyre and Marat Slessarev.

A version of the second chapter titled "Impact of graded passive cycling on hemodynamics, brain and heart perfusion in healthy adults" was submitted and published in Frontiers in Medicine. This article was co-authored by Claudio Martin, Christopher William McIntyre, Ian Ball, James Duffin, and Marat Slessarev.

A version of the third chapter titled "Impact of graded passive cycling on hemodynamics, cerebral blood flow, and cardiac function in septic ICU patients" was accepted and is being prepared for publication by Frontiers in Medicine. This article was co-authored by Claudio Martin, Ian Ball, Christopher William McIntyre and Marat Slessarev.

*'It does not do to dwell on dreams and forget to live.' – Dumbledore*

- J. K. Rowling, Harry Potter and the Sorcerer's Stone, 1998

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# List of Abbreviations and Symbols Used

2D: 2 Dimensional
3D: 3 Dimensional
BBB: Blood brain barrier
BP: Blood pressure
BOLD fMRI: blood oxygenation level dependent functional magnetic resonance imaging
CBF: Cerebral blood flow
CBFv: Cerebral blood flow velocity
CVP: Central venous pressure
CNS: Central nervous system
CO: Cardiac output
EEG: Electroencephalogram
GMP: Guanosine monophosphate
HR: Heart rate
ICA: Internal carotid artery
ICP: Intracranial pressure
ICU: Intensive care unit
ICU-AW: Intensive care unit acquired weakness
LBF: Leg blood flow
LOS: Length of stay
LV: Left ventricle
MAP: Mean arterial pressure
MCA: Middle cerebral artery
MCAv: Middle cerebral artery velocity
MFV: Mean flow velocity
MV: Mechanical ventilation
NO: Nitric oxide
NOS: Nitric oxide synthase
MODS: Multi-organ Dysfunction Syndrome
PAC: Pulmonary artery catheter
PET: Positron emission tomography
QoL: Quality of life
RPM: Rotations per minute
RAAS: Renin-angiotensin-aldosterone system
SOFA: Sequential Organ Failure Assessment
SV: Stroke volume
TCD: Transcranial doppler
TEE: Transesophageal echocardiography
TTE: Transthoracic echocardiography
TPR: Total peripheral resistance
$VCO_2$: Minute carbon dioxide production
$VO_2$: Minute oxygen consumption

# CHAPTER 1: Introduction and historical review

## 1.1. Thesis Outline

This thesis was motivated by the growing interest of early passive exercise use in the intensive care unit (ICU) by physicians and patient care providers. Thus, this thesis was developed to identify the impact of passive cycling intensity on patient hemodynamic stability and critical organ function. There has been recent interest in applying passive exercise in critically ill patients, as a method of early mobilization in sedated, critically ill patients to address the functional deterioration and loss in muscle mass that ICU patients face due to prolonged bed rest. However, many early mobilization studies have primarily used passive cycling as an intermediary physiotherapy tool until patients are capable of participating in active mobilization. Furthermore, these early mobilization studies utilize a range of cycling intensities across patients and identify safety and feasibility using metrics such as hemodynamic stability and low rates of adverse events during mobilization. The individual impact of passive exercise and its effects on organ function in patients with increased risk of multi-organ failure, such as sepsis, has yet to be identified. The aims of this study are to provide information regarding the response of septic patient responses to passive cycling early on in their ICU stay, and to further identify the impact of graded increases in passive cycling on organ function of two key perfusion-dependent organs: the brain and heart. Sepsis is a complex, multifactorial syndrome, and the findings from this research can provide a glimpse into the care that must be taken when introducing early mobilization interventions into this patient population.

This thesis is divided into four chapters. The first chapter provides an overview of the current knowledge regarding sepsis, including the burden of sepsis, the pathophysiological mechanisms of sepsis and consequences of sepsis. It also provides an overview of the benefits of exercise, particularly as a paradigm to improve cardiac and cognitive function, as well as exercise dosage in adults. Additionally, this chapter includes a review of continuous hemodynamic monitoring (including invasive intra-arterial monitoring and pulse wave analysis) and ultrasound techniques (including transcranial Doppler and echocardiography). Lastly, this chapter ends with a comprehensive outline of the shared methodology used in both Chapter 2 and Chapter 3.

The second chapter describes the development of a graded passive cycling protocol, and its application in a cohort of health adults. A graded passive cycling protocol, previously outlined in Chapter 1, was designed to identify the impact of cycling intensity on hemodynamic, cardiac, and cerebral outcomes. This protocol was applied in a cohort of healthy adults and  was carried out in an ICU setting to mimic the environment and setup of passive mobilization in septic ICU patients. This chapter includes analysis of group-wide and individual responses to increased passive cycling intensity and highlighted the existence of heterogeneity amongst participant responses. Outcomes in this healthy cohort demonstrated safety and feasibility of the protocol, which encouraged next steps for its application in a septic cohort.

The third chapter describes the application of the graded passive cycling protocol in a cohort of septic patients early in their ICU admission. Early mobilization occurs in intensive care units to mitigate muscle loss and decline in functional ability associated with prolonged bed-rest, but the delivery of early passive cycling is poorly understood. This experiment aimed to identify the safety and feasibility of graded increases of passive cycling intensity in a cohort of septic patients by assessment of successful completion of the protocol without adverse incidents, hemodynamic stability, and absence of adverse changes in either cerebral perfusion or cardiac function. The protocol used was one previously outlined in Chapter 1, with additional adjustments given the critical status of these patients. This chapter describes responses from a cohort of septic patients, and confirms the heterogeneity of patient response to graded passive cycling. Furthermore, this chapter highlights potential risks that may occur as a result of early passive cycling, and postulates mechanisms that may be responsible for the decline in cerebral blood flow velocity seen in these patients.

The last chapter summarizes the work throughout this thesis and outlines the contributions that these findings bring to the field of knowledge, as well as their application to current practices and further research. Lastly, this chapter will provide a critique of limitations of this thesis, and identification further areas of research, that will allow us to better understand this field of research.

## 1.2. Sepsis

Sepsis is a syndrome of life-threatening organ dysfunction caused by a dysregulated host response to infection (1), and is a major global healthcare burden (2). Sepsis is important for clinicians to recognize because of its rapid course of action, poor patient outcomes, and lethality. Sepsis is defined as a non-hemostatic host response to infection and it poses a risk of higher lethality in excess of a normal infection, and thus requires urgent recognition and care. Sepsis pathogenesis is multifaceted and is due to the variations in host response to infecting pathogens (1). Clinical manifestation of sepsis is highly variable, and the resultant organ dysfunction can occur in multiple organ systems. However, the pathophysiology of sepsis has been identified by an initial hyper-inflammatory phase followed by a subsequent and sometimes profound immunosuppressive phase, that can lead to T-cell exhaustion (3). The clinical progression of sepsis is fast, and due to variability in clinical manifestations and patient symptoms, the swift identification and diagnosis of sepsis is crucial to guide rapid, targeted therapy and improve patient survivability. However, due to the nuances of the syndrome and symptom presentations (4), as well as variations in historical diagnostic terminology and criteria (1), sepsis mortality rates still remain high and remains a global healthcare challenge.

### 1.2.1.    Burden of sepsis

Sepsis is a major contributor to the global burden of disease (2), with an annual estimate of 49 million cases and 11 million sepsis-related deaths (5). Although the majority of these deaths occur in low and middle-income countries (2,6), sepsis remains a major problem in the Western world where it remains the most common cause of in-hospital deaths in the United State (6), accounting for more than 50% of all hospital deaths (7), and 11% of all hospital deaths in Canada (8). Globally, sepsis remains a leading cause of mortality, with a mortality rate of 30-50% (8) and is a prominent cause of death in intensive care units worldwide. Over the years, there has been a global decrease in the number of sepsis cases a 19% decrease from 1990 to 2017 (5), with decreases reported worldwide (2). However, despite global decreases in sepsis cases, and increased understanding of sepsis pathophysiology, sepsis still remains a major cause of mortality and critical incidence worldwide (1,5) that afflicts all age groups. The high mortality associated with sepsis has been attributed to the heterogeneous patient presentation, rapid clinical progression, and variability in the definition and diagnoses of sepsis. Even in patients that recover from sepsis, these patients

have increased likelihood of re-hospitalization and suffer from both acute and long-term sepsis-related morbidities (9). Early recognition and diagnosis are critical to reduce sepsis-associated microcirculatory and organ dysfunction, and early interventions are necessary to reduce subsequent patient mortality and morbidity

## 1.2.2.  Pathophysiology of sepsis

Sepsis can arise from any infection, but is most commonly caused by pneumonia, abdominal infections, and urinary tract infections (9). The outcomes of sepsis have been studied at both a microvascular level, as well as a systemic, hemodynamic level.

The definition and diagnosis of sepsis have changed over time, and there has been a shift in understanding of the pathophysiology, pathobiology, and immunology of sepsis (10).  An update to the definition of sepsis made during Sepsis-3 from 2015 (1) to mitigate the use of redundant terminology for interchangeable terms indicating the same pathobiology, as well as eliminating the use of terms with narrow scopes of definition (1). With these updates to the definition and diagnosis of sepsis, the disease focus has shifted away from previous definitions which fixated on hyper-inflammatory host responses, and instead now focus on the collection of dysregulated host response to infection. It is now understood that the variations in interactions between the infectious agent and the host are what contribute to the variable manifestations of sepsis (10) on a local, regional, and systemic level (4).

### 1.2.2.1.  Hemodynamic changes in sepsis

Systemically, sepsis causes increased vascular permeability that results in an initial acute pro-inflammatory phase which consists of systemic hypertension, increased cardiac output, and reflexive peripheral vasodilation that decreases both total peripheral resistance and blood pressure (11). This phase is followed by a prolonged immunosuppressive phase (10), which is hallmarked by lowered cardiac output and persistently low total peripheral resistance (11) and can result in impaired tissue oxygenation, tissue edema, organ hypoxia, and multi-organ failure (4). The heterogenous presentation of patient deterioration and rapid disease progression make sepsis challenging to identify and treat. Furthermore, septic presentation varies depending on the pathogen, host characteristics, and host-pathogen interactions (4).

Sepsis results in the dysregulation of homeostasis by simultaneously increasing the activity of both inflammatory and coagulation cascades, and it can result in a spectrum of coagulopathies ranging from mild thrombocytopenia to fulminant disseminated intravascular coagulation (10). The cause of sepsis-induced coagulopathy is multifactorial, and can involve increased pro-coagulant activity, excessive fibrin deposition due to increased tissue factor activity by disrupted endothelial cells, impairments in anticoagulation mechanisms (e.g. protein C and antithrombin), and decreased fibrinolysis and fibrin removal (4), all which lead to unregulated activation of the coagulation cascade and the production of microvascular thromboses (10). The production of microthrombi can lead to impair local tissue perfusion and result in tissue hypoxia and organ dysfunction.

In the absence of inflammatory insult, pro-inflammatory and anti-inflammatory mechanisms are at homeostasis. With activation of an inflammatory cascade, the body aims to remove infection and stimulate tissue recovery; however, in the case of a dysregulated host response to an infectious agent, there is a loss of balance between these opposing mechanisms (4), which gives rise to organ injury and secondary infections. Evidence of immunosuppression is seen in patients that survive early sepsis but remain dependent on intensive care (e.g. recurring infections despite antimicrobial therapy, reactivation of latent viral infection) (4).

Mechanistically, sepsis results in tissue and organ dysfunction due to hypoperfusion of tissues and organs which leads to decreased cellular oxygen delivery and uptake. Systemic hypoperfusion stems from sepsis-associated cardiovascular dysfunction (12), and cardiomyopathy which is thought to occur due depression of cardiac myocytes caused by circulating inflammatory cytokines (e.g. TNFα and IL-1β). Additionally, sepsis has been found to be associated with low left ventricular ejection fraction with either normal or low left ventricular filling pressures as well as increased left ventricular compliance (13). As a result, sepsis can elicit both systolic and/or diastolic dysfunction and is associated with decreased stroke volume and increases in end-diastolic and end-systolic volume (14,15). Circulating inflammatory mediators induce arterial and venous vasodilation (10), which decrease venous return, ultimately decreasing left-ventricular preload. Venodilation leads to increased blood sequestration in venous vasculature and promotes hypotension and distributive shock, which are often seen during sepsis (10).

### 1.2.2.2. Microvascular changes in sepsis

Pathophysiological mechanisms of sepsis are characterized by microcirculatory blood flow abnormalities which arise as a result of alterations in local microcirculatory perfusion pressures due to distributive shock, endothelial cell dysfunction, and activation of both inflammatory and coagulation cascades (16).

Decreased systemic blood flow results in inadequate oxygenation and ventilation of cells and tissue, which drives an increased dependency toward cellular anaerobic glycolysis and increased lactic acid production (10). Activation of the immune system and the inflammatory cascade produces reactive oxygen species (ROS) which enter cells and facilitate mitochondria dysfunction, thus impairing cellular energy production (10). Mitochondrial damage leads to release of alarmins (e.g. mitochondrial DNA and formyl peptides) into the extracellular environment where they interact with neutrophils, exacerbate immune system contributions, and further cause tissue damage (17).

Vasodilation seen at arteries and veins is also observed at all three microvascular components: the arterioles, venules, and capillaries. This vasodilation is further exacerbated by the pathologic movement of intravascular fluid into interstitial space due to deterioration of endothelial barrier stability as a result of alterations in endothelial cellular cadherin and tight junctions (10). The alterations in systemic hemodynamics and microvascular thrombosis caused by sepsis-associated coagulopathies culminate in hypoperfusion of tissues and organs.

During sepsis, on a microcirculatory level, the vascular endothelium is disrupted due to activation of the inflammatory cascade which promotes vasodilation and leukocyte adhesion, as well as increased actions of the coagulation cascade (10). The proinflammatory and procoagulant states that arise with onset of sepsis, along with disruption of the vascular endothelium promote fluid leakage of intravascular fluid into the interstitial space and subcutaneous tissue, which ultimately contribute to tissue edema. In experimental models of sepsis, sepsis is associated with an increased number of dysfunctional capillaries and decreased capillary density (18,19), both of which impair tissue oxygen delivery. In rat models of sepsis, endothelial cell swelling, leukocyte adhesion and extravasation, loss of red blood cell malleability, and microvasculature clot formation have been

observed and indicated in the impairment of tissue perfusion, oxygenation, and function (20,21). These pathologic disturbances at a microvascular level affect tissues and organs and largely contribute to sepsis morbidity and mortality (10).

### 1.2.2.3.    Impact of sepsis on end-organs

The hemodynamic and microcirculatory alterations that result from aberrant interactions between the offending pathogen and patient host responses play a key role in sepsis organ dysfunction and organ failure. Systemic hypotension, red blood cell stiffness, and microvascular thromboses impair adequate tissue perfusion and decrease oxygen delivery (4). Inflammation associated with sepsis results in vascular endothelium damage and dysfunction, promotes cellular death, and impairs tissue perfusion resulting in dysfunction to a slew of organ systems, termed multi-organ dysfunction, which includes but is not limited to: the nervous system, the respiratory system, the cardiovascular system, coagulation system, the hepatic system, and renal system.

Although the impact on end organs is varied, the impact of sepsis on organ function is clinically measured by various scoring systems (e.g. Sequential Organ Failure Assessment (SOFA) score, and Multi-organ Dysfunction Syndrome (MODS) score), which assess the six tissue and organ systems listed previously. With Sepsis-3 updates, recommendations for the preliminary assessment and diagnosis of sepsis-associated organ function are conducted via qSOFA (quick SOFA) and SOFA (1).

Of the organ systems impacted, mental state alterations in septic patients are commonly observed and are an indicator of central nervous system dysfunction (22). Changes in cerebral vascular endothelium impair the integrity of the blood brain barrier (BBB), and allow entry of circulating inflammatory cells, inflammatory mediators, and toxins from into cerebral tissue (10). These changes result in cerebral edema, cerebral hypoperfusion, disruption of neurotransmitters, and damage to white matter tracts. The spectrum of septic encephalopathy that arises can range from mild confusion and delirium to more severe clinical presentations, such as coma (10). The lungs are also impacted to due impairments of the alveolar-endothelial barrier which causes fluid accumulation in both the interstitial lung spaces and alveoli. Lung edema impairs oxygenation and ventilation across the alveolar-capillary barrier, and results in ventilation-perfusion mismatch and

systemic hypoxia (10). It also results in decreased lung compliance which can lead to acute respiratory distress syndrome in severe cases. Cardiac dysfunction is observed in septic patients, with evidence of myocardial depression, impaired cardiac contractility, diastolic dysfunction, as well as decreased cardiac index and ejection fraction. Although the mechanism governing myocardial depression are not fully understood, it is thought to involve altered nitric oxide production, altered calcium homeostasis, impaired β-adrenergic signaling, and impairments in cardiomyocyte metabolism and energy production (23). Furthermore, impairments to the hepatic system involve inadequate bilirubin clearance that can lead to cholestasis, while decreased renal perfusion, nephron and renal microvasculature damage can result in acute tubular necrosis and varying severity of acute kidney injury (10).

## 1.2.2.3.1.    Sepsis and the brain

Adequate cerebral microcirculation and a functional and intact BBB are both crucial to regulate normal cerebral function, and aberrations can result in impairment of BBB integrity that causes septic encephalopathy. Septic encephalopathy is a common neurological complication associated with sepsis, that is characterized by diffuse central nervous system (CNS) dysfunction that occurs secondary to a non-CNS infection (22). The pathophysiology of septic encephalopathy is poorly understood but is most likely multifactorial and a result of the combination of vascular endothelium damage, cellular apoptosis, BBB dysfunction, alterations in neuronal signalling, and cerebral inflammation (23). These changes likely involve direct neuronal damage, mitochondrial dysfunction, endothelial damage, loss of calcium homeostasis, and impairments in neurotransmission (22). In the acute phase of sepsis, endothelial production of nitric oxide acts as a proinflammatory agent and contributes to cerebrovascular endothelial cell dysfunction (24). Lipopolysaccharides and cytokines have also been implicated in contributing to breakdown of the BBB through induction expression of adhesion molecules on cerebral microvascular endothelium (25).

Following autopsies of septic shock patients, cerebral ischemia was identified, which indicate potential alterations in cerebral microcirculation during sepsis (26,27).  Decreased blood flow (28) and loss of cerebral autoregulation (29,30) have also been observed in septic patients. These alterations are likely due to both micro- and macro-hemodynamic alterations. On a macrodynamic level, alterations in septic cerebral blood flow are thought to be related to hypotension, low cardiac

output, and myocardial depression seen in septic patients, which may provide insufficient blood flow (26) to organ systems, particularly the brain which is a perfusion-sensitive organ that is typically exposed to tightly regulated perfusion flows and pressures. Loss of cerebral autoregulation and impaired cerebral vasoreactivity to carbon dioxide content and extracellular pH (30) in sepsis further heightens risk of cerebral damage as cerebral vasculature is more susceptible to changes in systemic mean arterial blood pressure. Micro-hemodynamic alterations are due to changes in BBB permeability and local, production of nitric oxide and free radicals in response to cerebral inflammation. Animal models of sepsis have discovered that microcirculation in a sheep model of sepsis demonstrate profound microvascular impairments (31), as seen by a decrease in both functional capillary density and proportion of perfused cerebral capillaries.

The BBB normally regulates cerebral capillary blood flow and creates a tightly regulated environment for neural cells to prevent systemic insults from interacting with the central nervous system. The BBB is comprised of astrocytes, pericytes, and endothelial cells which form a tight barrier to prevent systemic and cerebral interactions. During sepsis, the BBB is impaired, through endotoxin disruption of tight junctions, and detachment of pericytes from neuronal cells in the hippocampus (32). Dysfunction of the BBB allows for entry of inflammatory cells and mediators that promote microvascular and cerebral edema, disruption of astrocyte attachment, and passage of neurotoxic molecules to the CNS system which contribute to septic encephalopathy (27). Further damage is caused by cerebral hypoperfusion, disruption of neurotransmitter signalling, and white matter tract damage.

The BBB prevents cerebral exposure to systemic inflammation with the exception of two pathways that allow neuroimmune communication: circumventricular organs (CVOs) and the vagus nerve (33). The CVOs are situated near neuroendocrine structures and brainstem autonomic centers and lack a BBB. They express constituents of both the innate and adaptive immune systems, and cytokine receptors for IL-1β, IL-6, and TNFα. The vagus nerve detects systemic inflammation through axonal cytokine receptors, and in turn modulates activation of behavioral and neuroendocrine centres to increase production of cytokines such as TNFα, IL-1β, and transforming growth factor beta (TGFβ) (22). This uptake in cytokine production leads to microglial activation, which imparts them with neurotoxic properties, such as increased production of nitric oxide,

cytokines, reactive oxygen species, and glutamate, all of which contribute to causing cellular death within the brain (34). Although these brain signalling pathways are inherently supposed to serve as protective and anti-inflammatory mechanisms, but due to input from systemic inflammation, these signalling mechanisms become pathogenic. Neuropathological changes of the blood brain barrier and brain cells result in persistent neuropsychiatric defects and cognitive impairment seen in sepsis survivors (35).

Diagnosis of septic encephalopathy requires two elements: extracranial infection and an impaired mental state (22), with the primary clinical feature being a change in mental status. However, clinical manifestation of septic encephalopathy can range from mild (e.g. malaise, mild confusion, concentration deficits) to severe (e.g. coma). Septic encephalopathy is often the first manifestation of sepsis, and patients with septic encephalopathy have a higher mortality rate than those without (32).

### 1.2.2.3.2. Sepsis and the heart

Cardiac dysfunction is common in sepsis and greatly affects patient mortality. Septic cardiac dysfunction is characterized by impairments in cardiac contractility, systolic and diastolic dysfunction, decreased cardiac output and ejection fraction, and increased arrhythmogenesis (36). The mechanisms of development of septic cardiac dysfunction are multifactorial in nature and causes of septis have been attributed to inflammation as well as ATP depletion caused by suppression of fatty acid and glucose oxidation (23). Following initial impairments in cardiac function due to sepsis, deficiencies in cardiac adrenergic signalling further exacerbate the decline of cardiac function (23). Both left and right ventricular performance can be compromised during sepsis, with decreased left ventricular contractility that is worsened by systemic vasodilation, and pulmonary hypertension that increases right ventricular afterload (36).

Impaired β-Adrenergic signalling is an aspect of impaired septic cardiac dysfunction that leads to compromised cardiac contractility (37) seen in septic patients. Cardiac $\beta_1$ and $\beta_2$ adrenergic receptors (βARs) are key receptors that modulate cardiac function. The early stages of sepsis coincide with increased catecholamine levels (23) that are likely produced to promote an adrenergic response to increase cardiac chronotropy and inotropy. Although this initial adaptive

response is initiated to counteract the drop in peripheral resistance and blood pressure, the excessive stimulation of cardiac βARs can result in myocardial damage by increasing intracellular calcium levels (36), which subsequently activate intracellular apoptotic signalling cascades (23). In septic patients, continuous sympathetic over-stimulation that further increases catecholamine production can lead to diastolic dysfunction, tachycardia, arrhythmias, myocardial ischemia, myocardial stunning, and apoptosis and necrosis of cardiac cells (38).

The left ventricle ensures adequate systemic circulation and is responsible for the perfusion and oxygenation of vital organs. During early sepsis, patients exhibit decreased systemic vascular resistance and impaired cardiac contractility, however, the heart compensates for the compromised cardiac contractility by an increase in heart rate, which maintains a normal or increase cardiac output (36). Despite maintenance of cardiac output and stroke volume, the decreased cardiac contractility and increased heart rate prevent the left ventricle from fully emptying at each contraction. As a result, an increase in both left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) can be observed. Alterations in left ventricular function and compliance lead to a rise in left ventricular end-diastolic pressure (LVEDP), with further exacerbates cardiac dysfunction seen in sepsis (23).

Diastolic dysfunction in sepsis arises due to changes in myocardial relaxation and ventricular geometry (36). Furthermore, during sepsis, increased activity of inducible cellular nitric oxide synthase (iNOS) results in excess production of NO that decreases calcium release during systole which decreases contractility, and decreases calcium removal during diastole which results in abnormal cardiac filling, both of which compromise cardiac force due to abnormal modulation of myocardial fibre length which ultimately result in diastolic dysfunction, which is seen as an increase in LVEDP (36). Excess NO production also decreases myocardial sensitivity to adrenergic stimulation via alteration of the secondary messenger pathways of both protein kinase and cyclic guanosine monophosphate (GMP). These mechanisms that unfold due to excess NO production all contribute to overall decline in ventricular dysfunction.

Nitric oxide further contributes to cardiovascular dysfunction during sepsis through its role in vascular dysfunction. During its normal physiologic activity, NO is responsible for myogenic

changes of vascular resistance in response to detected changes in peripheral and local blood pressure and blood flow. Production of endothelial NO is followed by NO diffusion into vascular smooth muscle cells, where it activates guanylyl cyclase, an enzyme that is responsible for production of the intracellular secondary messenger cyclic GMP. Production of cyclic GMP results in a signalling cascade that results in the reduction of intracellular calcium and increased activity and hyperpolarization of potassium channels (36), both of which contribute to increased vascular smooth muscle relaxation. Due to increased endothelial production of NO, persistent smooth muscle relaxation and peripheral vasodilation occur thus leading to decreased systemic vascular resistance along with patient hypotension.

The initial decline in arterial pressure stimulates cardiovascular reflexes (36) to counteract the shock via sympathetic and neuroendocrine mechanisms in efforts to increase systemic blood pressure. These responses are also achieved via G-protein and second messenger system activity. However, due to increased NO production, both sympathetic activity and neuroendocrine activity from secretion of hormones from the hypophyseal-pituitary-adrenal axis and activity via the renin-angiotensin-aldosterone system (RAAS) effects are dampened (36) due to NO decreasing cellular activity of intracellular signal transduction pathways.

Hypotension is sensed by pressure receptors in the aortic arch and carotid bodies which activate the baroreceptor reflex, by transmitting signals of decreased blood pressure to the medulla oblongata which organises efferent responses (36). Secretion of norepinephrine increases heart rate, cardiac contractility, and peripheral vasoconstriction. However, in sepsis, increased nitric oxide activity dampens baroreflex activity at both the heart and the peripheral vasculature. This results in an abnormal reflex response which struggles to maintain homeostasis in the presence of worsening disease. Although sympathetic activity maintains cardiac output during early sepsis, prolonged activation causes compensatory pathways to become overwhelmed. Extended sympathetic activation and nitric oxide release contribute to peripheral vasculature desensitization to vasoconstrictors secreted from RAAS activity (i.e. vasopressin and angiotensin II) (39).

## 1.2.3. Consequences of sepsis for patients

Sepsis is associated with markedly high rates of mortality (8) and long-term patient morbidity even after sepsis has resolved. Post-sepsis morbidity is frequently debilitating and decreases patient independence and quality of life. Morbidity resulting from sepsis is due to alterations in systemic perfusion that results in long lasting organ modifications and includes functional disability, cognitive impairments, prolonged patient pain, increased likelihood rates of hospital readmission which can persist for long after sepsis has resolved.

### 1.2.3.1.    Mortality

Sepsis is associated with high rates of mortality, and although global sepsis incidence and mortality have both declined with improvements in understanding of septic pathophysiology and advancements in critical care, current sepsis mortality continues to remain high (5). Compared to ICU patients without sepsis, patients with sepsis have higher mortality in the ICU, as well as higher rates of hospital readmissions and functional decline two years after discharge (40). The incidence and mortality rates of sepsis vary greatly around the globe, with the highest burden of sepsis in sub-Saharan Africa, Oceania, south Asia, east Asia, and southeast Asia (5). Despite having lower rates of sepsis mortality than these regions, mortality rates for sepsis are still high in Canada and the US, with sepsis deaths accounting for 10.9% of all Canadian hospital deaths between 2008-2009 and a crude mortality of 30.5% for patients with sepsis (8). In the US, recent retrospective studies have reported septic mortality rates ranging from 12.5 to 17.2% (12,41). A 2019 study by Rhee and coworkers report that recent sepsis mortality in US acute care hospitals is largely influenced by presence of chronic comorbidities, with only 4% of sepsis-associated deaths judged as moderately or definitely preventable (42).

### 1.2.3.2.    Morbidity

Initial treatment of sepsis aims to treat the causal infection while maintaining support for organs experiencing organ dysfunction (9). Despite this, even after sepsis has been resolved, some patients experience long-term morbidities which consist of new medical problems or new symptoms after surviving sepsis. Some patients even experience new onset of chronic critical illness after their initial sepsis injury (43). Common post-sepsis impairments include muscle weakness, concentration and memory deficits, difficulty sleeping, sleeping, and anxiety. Sepsis survivors are also at increased risk of subsequent infections following recovery from sepsis (9). Patients that overcome early sepsis but still remain dependent on intensive care demonstrate post-sepsis

immunosuppression (3); however, the mechanisms for this immunosuppression are poorly understood. The average 30-day rehospitalization rate of sepsis survivors range between 19.9% to 32% (44), and repeat hospitalization in these patients increases risk of death. Rehospitalization rates increase with increased follow-up time (44), thus demonstrating persistent health risks in sepsis survivors. In approximately one-third of patients discharged from the hospital following sepsis, re-hospitalization occurs within the first 3 months after sepsis, most commonly due to repeat sepsis or infection (45) but may also occur due to heart failure and kidney failure. These morbidities are postulated to be a result of sepsis multi-organ injury.

### 1.2.3.2.1.  Functional outcomes

Sepsis has been associated with new functional disability and increased care required at discharge (46). Compared to a general hospital population, patients with sepsis are less commonly discharged to home, have higher mortality rates, and are more likely to require increased home care and post-hospitalization skilled care (46). Sepsis survivors are also at a greater risk of developing additional functional limitations as measured via instrumental activities of daily living limitations following hospital discharge, and the decline in functional independence is worse than projected decline prior to sepsis (47). The effects of functional decline have larger negative impacts in patients with better baseline physical functioning and functional limitations were reported to develop faster (47). Sepsis was found to be independently associated with an increase of 1.5 functional limitations in patients with no, mild or moderate previous functional limitations, and these disabilities were well in excess to those seen following non-sepsis, general hospital admissions (47). In a long term observational study of quality of life (QoL) in septic shock survivors, they were reported to have decreased QoL compared to general populations (48). These QoL impairments were found to last as long as 5-years after ICU admission (49). However, the QoL reported in both sepsis and non-sepsis critically ill survivors appears to be similar (44). Sepsis often occurs in frail and elderly patients, who often encounter worse outcomes, likely due to reduced baseline functional status. Furthermore, septic patients also often present with comorbid conditions, thus decline of functional outcomes and QoL may be impacted due to these co-existing conditions (50). The decline in functional independence and quality of life in sepsis survivors points to sepsis as a substantial public health problem, due to the burden that sepsis survivorship has on patients, families and the healthcare system.

## 1.2.3.2.2.   Cognitive outcomes

Regardless of etiology, hospitalization is associated with cognitive decline (51), and this decline is frequently documented in critical illness survivors (52,53). Cognitive impairments in sepsis is likely a complex and bidirectional interaction. Cognitive decline presents as a risk factor for other diseases, including sepsis and pneumonia, while sepsis has been identified as an risk factor for cognitive decline, and is independently associated with tripling the odds of moderate/severe cognitive impairments in elderly sepsis survivors in comparison to non-sepsis, general hospital admission patients (47). However, the rate of increase in cognitive impairments in sepsis survivors has been found to be similar to rates of cognitive decline pre-sepsis (47). In animal models of sepsis, common forms of cognitive and psychological impairments that have been identified include: impairment of learning, short-term and long-term memory, aversive memory, depressive-like behavior, and anxiety-like behavior (50). Sepsis survivors demonstrated cognitive damage in verbal learning and memory, as well as a decrease in left hippocampal volume, in comparison the healthy controls (35). In the same study, sepsis survivors also presented low-frequency EEG activity, indicative of cerebral impairment. Mechanisms that contribute to cognitive decline in sepsis survivors include brain dysfunctions including delirium, white matter disruption, neuro-inflammation, microvascular brain injury, decreased cerebral blood flow index, increased BBB permeability, abnormal cerebral perfusion, and others (50).

Sepsis is associated with both delirium and pre-sepsis cognitive decline, which demonstrate central nervous system involvement in sepsis. Delirium is an acute cognitive impairment and is characterized by decline in attention and awareness (47). Delirium is common in critically ill patients and is associated with white matter disruption and worsened cognitive scores up to 12 months following critical illness (54). Although delirium is both preventable and treatable (47), sepsis-associated delirium is postulated to occur in approximately 50% of septic patients (50). Incidence of delirium and contributes to prolonged hospitalization and prolonged cognitive impairment such as dementia and memory deficits in critically ill survivors. In addition to cognitive impairments, acute delirium is also associated with psychological disorders such as depression and anxiety (55). Depressive symptoms are associated with post-sepsis cognitive impairment (50). Furthermore, decreased mental health-related QoL are not only limited to sepsis

survivors themselves; impairments in these parameters and increased anxiety are also observed in spouses of sepsis survivors (56).

### 1.2.3.2.3.    Survivorship burden on caregivers and society

As a result of the myriad of functional and cognitive impairments that arise in sepsis survivors, these patients present a large burden on both caregivers and society. Sepsis survivors experience increased functional disability at discharge, and require increased care following discharge. Severe cognitive impairment that develops in septic survivors has been associated with an additional 40 hours per week of care provided by patient families (47); however, unlike many forms of dementia, with sepsis, the onset of cognitive impairment and subsequent cognitive decline are potentially preventable in patients with increased standard of care for septic patients (47). Potential routes to decrease patient, familial, and healthcare burden associated with sepsis-associated cognitive impairment include early physical and cognitive rehabilitation, and improved management of patient sedation.

Sepsis is associated with increased use of hospital resources and prolonged ICU stays (8). With recent global estimates of sepsis reporting 48.9 million incidents and 11 million sepsis deaths (5), sepsis poses an enormous burden on caregivers and society across the world. In the US alone, sepsis results in the most in-hospital deaths and costs more than $24 billion USD annually (6). Beyond the costs of sepsis treatment alone, surviving sepsis also poses a large economic burden due to the slew of post-sepsis impairments that arise, and high rates of rehospitalization in sepsis survivors; with hospital readmission rates ranging from 10-16% (41).

Poor clinical outcomes, mortality, healthcare resource use, and associated costs increase with increased sepsis severity. However, the highest burden of sepsis incidence, hospital LOS, and total aggregate costs are associated with the lowest severity sepsis cohort (sepsis without organ dysfunction; 10.4 million days, $22 billion USD) due to the higher prevalence of sepsis without organ dysfunction compared to either sepsis with organ dysfunction (4.1 million days, $10.2 billion USD) or septic shock (6.5 million days, $19.8 million USD) (41). Furthermore, sepsis cases that are not diagnosed until after hospital admission are associated with increased sepsis severity, higher mortality, and a greater economic burden on an individual basis (41). Improvements to

better identify sepsis earlier, and improvements in early treatment may benefit in reducing the societal and economic burden of sepsis.

## 1.3. Exercise as a paradigm to improve outcomes in the critically ill

Exercise is a ubiquitous, non-invasive, and non-pharmaceutical intervention that is able to improve patient health outcomes and quality of life. It is well known that exercise confers benefits to overall physical health and fitness, cognition, and psychological wellbeing. The benefits of exercise have been demonstrated across many populations, including the general public, patients with cardiovascular disease, and patients rehabilitating from physical injuries (57). The benefits of exercise also appear to be essential in prevention of chronic diseases and premature death (58). Although much of the benefits of physical activity in healthy adults are studied in the context of chronic adaptions due to routine physical activity (57), acute changes from single bouts of dynamic exercise have also been found to result in transient, beneficial changes in lipid levels, and reduced blood pressure (59). The mechanisms for the multitude of benefits that exercise confers are similarly multi-faceted, including activation of the sympathetic nervous system and evidence of changes in cellular and molecular processes including increased capillary density, alterations in endothelial function, and changes in mRNA and proteins responsible for glucose and glycogen regulation (60).

In ICU patients, exercise has become increasingly more utilized as the benefits of mobilization have been recognized to improve patient outcomes at discharge, and beyond. Although exercise has been linked with promising improvements in patient outcomes, and early exercise has been reported to be safe and feasible by many studies, there remains apprehension in its implementation due to barriers regarding its cost, manpower and skill for implementation, perception that exercise is unfeasible in patients that are too sick, lack of comprehensive understanding regarding the mechanisms of its effects on patient outcomes, and lack of knowledge regarding the appropriate exercise dosage for patients.

## 1.3.1. Physiology of exercise

Physical inactivity is a modifiable risk factor for cardiovascular disease, chronic diseases (e.g. obesity, type II Diabetes mellitus (T2D), colon and breast cancer, hypertension, bone and joint diseases, depression and premature death) (57). Lack of exercise exacerbates risk associated with cardiovascular disease (hypercholesterolemia, hypertension, diabetes, obesity, and smoking). Participation in routine physical activity and higher levels of fitness are associated with reduced risk of premature death particularly from cardiovascular disease in asymptomatic men and women (57). Furthermore, reductions in relative risk of death ranged between 20-35% in asymptomatic men and women that reported increases of physical activity and fitness (57). Determinants of health-related physical fitness include current cardiovascular and musculoskeletal fitness, body composition, and metabolism (61). The benefits of physical fitness associated with risk of premature death appear to be graded (58), with increased improvements given further increases in physical fitness; even small improvements in physical fitness are associated with a significant reduction in risk (58). Additionally, there appears to be an inverse dose-response association between physical activity and risk of premature death (62), with subjects that have the highest level of physical activity and fitness presenting the lowest risk of premature death (57). However, although intensity of physical activity is inversely associated with mortality (63), the benefit of incremental increases in physical activity do not appear to be equal across subjects of varying pre-existing fitness levels. Benefits of increased physical activity appear to be most beneficial in patients in previously sedentary subjects, with modest enhancements in participation of physical fitness associated with large improvements in overall health (64). With improved baseline participant fitness, additional increases in physical fitness appear to promote diminishing returns on improvements in participant outcomes.

The benefits of exercise are both preventative and protective by reducing likelihood of worsening existing cardiovascular disease, developing new cardiovascular disease, and premature death. Beyond the common, well-known benefits of exercise on improved cardiovascular health and muscle strength, exercise has also been associated with improved mood and cognition, increased bone density, improved flexibility and mobility, improvements in glucose control and insulin sensitivity, and lowered risk of colon and breast cancer (57). Routine physical activity has been associated with prevention of loss of bone density and osteoporosis in postmenopausal women,

and these benefits have been deemed to outweigh potential risks of exercise particularly in the elderly (57). Exercise is associated with improvements in psychological wellbeing, including reductions in stress, anxiety, and depression (65). Furthermore, psychological wellness plays a role in prevention and management of cardiovascular diseases, and other chronic diseases. Exercise training favourably improves cognitive function, through improvements in learning and memory, improved sleep quality, counteracts cognitive decline associated with aging, and assists in functional recovery from depression (66).

With increased public knowledge regarding the benefits of exercise on overall health and well-being, there is much interest on determining the optimal amount of exercise to benefit; however, the optimal and minimum dosage of exercise (intensity, duration, and frequency of exercise) to confer health benefits remains unknown, and likely differs on an individual basis. It appears that even lower levels of weekly exercise and increased energy expenditure may be associated with improvements in indicators of health (57). Measures of physical activity are estimated through measurements of energy of expenditure, with more practical measures achieved via heart rate monitors and motion sensors (pedometers and accelerometers), that measure surrogates of energy use.

Several biological mechanisms have been implicated in the role of exercise to reduce the risk of chronic disease and premature death. These include improvements in body composition through decreased abdominal adiposity and weight control, improvements in lipoprotein profiles through decreased serum triglycerides, increases in high-density lipoprotein cholesterol levels and decreases in low-density lipoprotein (60). Further methods of action include effects on glycemic control and insulin sensitivity, reduced blood pression, improvements in autonomic tone, reduced systemic inflammation, reduced coagulation, improvements in coronary blood flow and cardiac function, and improved endothelial function (60).

Exercise activates the sympathetic nervous system, which results in a systemic response through multiple organ systems to maintain homeostasis following sympathetic stimulation to meet increased physical, metabolic, and cardiovascular demand. The combined efforts of cellular changes, musculoskeletal, circulatory, respiratory, and endocrine systems contribute to the acute

bodily response to exercise (60). Improvements in the musculoskeletal system include increased muscle capillary perfusion, muscle hypertrophy and increased strength, increased endurance as a result of increased mitochondria in muscle cells, and increased bone mineral density (57). Improvements in cardiovascular heath include improved heart contractility, improvement in blood vessel responsivity and vasodilation, and decreased blood pressure at rest (60).

The impact of exercise on endothelial function is thought to play a large role in the multiple benefits that exercise confers. Endothelial damage and dysfunction have been observed with aging, chronic disease states (e.g. coronary artery disease, T2D, hypertension, and obesity), and smoking. In contrast, regular aerobic physical activity has been reported to improve vascular function in adults, likely due improvements in endothelial function mediated by shear-stress. Exercise has also been shown to alter cellular functions, including alterations of metabolite concentrations, adjustments in cellular ATP:ADP ratios, changes in intracellular calcium ion concentrations, intracellular pH, and stimulation of oxidative stress-sensitive cellular MAPK signalling pathways (e.g. ERK1/2, p38, and JNK) and AMPK pathways (60). Increased, low-level production of free radicals induces expression of antioxidant enzymes, with decreased oxidative damage in animals that have been exposed to chronic exercise in comparison to untrained ones (67). Endothelial adaptions to chronic exercise lead to the improvements in endothelial function in the face of chronic disease states. Physical activity has been demonstrated to increase glycogen synthase and hexokinase activity, and also increases both GLUT-4 protein receptor production and mRNA expression and increased muscle capillary density (57), both which illustrate changes in glucose homeostasis that are beneficial to patients with type 2DM. Although, much of the literature surrounding health benefits following physical exercise have been in the context of chronic adaptions following routine physical activity, acute bouts of exercise have also been demonstrated to produce transient, beneficial changes in triglyceride levels, cholesterol levels, blood pressure, insulin resistance, and glucose regulation.

## 1.3.1.1.  Benefits of exercise in critically ill patients

Exercise has routinely been used as a technique for rehabilitation in patients suffering muscular injuries (68), stroke (69), and prolonged bedrest (70). Exercise in elderly adults is associated with improved endothelial function, increased endothelial nitric oxide synthase (eNOS) production, and

improved microcirculatory responsivity (71). These factors are important, given the prevalence of elderly patients in the ICU. The negative consequences of bed-rest are well documented and include decline in function of the cardiovascular (e.g. decreased functional capacity), respiratory (e.g. difficulties weaning from MV), and neuromuscular systems (e.g. ICU-acquired weakness) (72). Due to the benefits associated with exercise and its non-invasive and non-pharmaceutical nature, exercise has increasingly been employed in intensive care units to improve cardiovascular function, respiration (increased tidal volume and oxygen transport capacity), and skeletal muscle function to combat immobility and post-intensive care syndrome. Post-intensive care syndrome describes problems experienced by critical illness survivors, including cognitive impairments (e.g. altered memory, executive function, and attention), psychological changes (e.g. depression, anxiety, and physical function) and physical impairments (e.g. physical, pulmonary, and neuromuscular function) (73).

Immobility leads to muscle dysfunction, ICU delirium, impaired exercise capacity, ICU-acquired weakness (ICU-AW), and decreases in functional outcomes and quality of life. Muscle dysfunction arises due to inactivity, inflammation, presence of neuromuscular syndromes, and use of pharmacologic agents (74). ICU-acquired weakness is associated with increased mortality and includes disorders caused by polyneuropathy and myopathy after ICU admission (75). It is also associated with axonal nerve degeneration, myosin loss, and has been postulated to be the result of multifactorial combination of systemic inflammation, medication, electrolyte disturbances, and immobility. Factors that impact the severity of ICU-AW include increased age, presence of comorbidities, and ICU length of stay (76). Muscle wasting begins within the first 48 hours of onset of critical illness or injury and is highest during the first 2-3 weeks of ICU stay (77), with up to 40% loss in muscle strength following the first week of immobilization that increases patient mortality rates (78). ICU-AW is aggravated by muscular hypercatabolic, prolonged bed rest caused by sedation and immobility, and prolonged ICU stay is associated with muscle wasting, exercise intolerance, and decreases of both functional status and quality of life following discharge, which persist even after 1 year following discharge (72). Long-term weakness following ICU-AW arises due to muscular pathophysiology involving muscle atrophy and decreased contractile capacity (79). Progressive worsening of ICU-AW can prolong the duration of mechanical ventilation, length of ICU stay, length of hospital stay (80,81). Furthermore, ICU-AW is associated with sepsis,

multi-organ failure, and increased functional impairments at hospital discharge (82). Thus, mobilization, particularly early mobilization in the ICU is crucial in preventing or reducing the amount of muscle wasting as early as possible in patients with prolonged bed-rest. Early mobilization is a promising intervention to counter ICU-AW because it attenuates critical illness-associated muscle weakness (83). Mobilization in the ICU has been reported by multiple studies to be safe and feasible in critically ill patients (74,84,85) and can be delivered via a variety of modalities including passive stretch and range of motion movement, continuous passive motion, and bed-side cycle-ergometry.

Even amongst ICU patients, sepsis survivors have worsened functional impairment when compared to critically ill patients without sepsis (86). Furthermore, sepsis patients demonstrate more aggressive decline in muscle mass and force (87), likely due to systemic inflammatory responses and immobility (88), which may further present difficulties in weaning patients from mechanical ventilation. Particularly in sepsis, with its many endothelial changes, mobilization may provide benefit through low-grade ROS production which may improve endothelial functioning (89). Animal models of sepsis have demonstrated that exercise is an effective preconditioning mechanism against the development of sepsis-induced systemic inflammation and coagulation, with observed decreases in inflammatory chemoattractant molecules, and lowered pro-coagulant responses in active septic mice compared to sedentary mice (90), and these differences were attributed to potential upregulation of eNOS in exercised mice. As a potent vasodilator, and modulator of neutrophil and platelet adherence to endothelial surfaces, it has been implicated in many of the negative outcomes associated with systemic effects of sepsis (71). In a subgroup of patients with initially high sepsis severity scores, exercise rehabilitation was found to be associated with significant improvements in measures of functional recovery and functional independence during hospitalization (86). Although early mobilization in critically ill patients has been questioned, due to induction of systemic, exercise-induced inflammation which has at times been postulated to share a similar model as the systemic inflammation seen in sepsis (91), non-exhaustive exercise has been reported to perpetuate antioxidant effects through increase activation of antioxidant pathways through low-grade production of ROS, and has also been found to influence levels of inflammatory cytokines (60). Overall, both active and passive mobilization have been demonstrated to improved functional exercise capacity, perceived functional status,

quadriceps muscle force, and decreased pain scores (72). Furthermore, increases in regional limb blood flow of mobilized limbs have been reported, and are likely associated to changes in intramuscular pressure and muscle stretch (92).

### 1.3.1.2. Exercise dosing

Due to the improved understanding across different disciplines of the need for individualized prescriptions of exercise, similar to prescriptions of pharmaceutical drugs, there has been increased interest in determining the impact of various aspects of exercise dosing and prescription. Personalization and individualization of exercise aims to maximize the efficiency and benefits of exercise through an understanding of the factors that influence heterogeneity of personal responses to exercise. Due to the uniqueness of each human, there is both between-individual and within-individual (93) physiologic heterogeneity that influences variations in both acute and chronic psychological and physiological responses to the same exercise. Heterogeneity in patient responses is observed across various modes of exercise including endurance/cardiovascular training, resistance/strength training, and combined training (93). To address variations in individual responses, exercise physiologists have introduced the concepts of responders (individuals with high sensitivity to exercise stimuli in a variable of interest above a pre-determined threshold), and non-responders (individuals with low sensitivity, or did not respond to exercise stimuli/changes in a variable of interest below a pre-determined threshold) (93). Further analysis of responders groups subjects into "adverse or negative responders" to define and identify subjects that demonstrated unfavourable responses.

Between-individual heterogeneity in response to physical exercise are deemed to be due to both non-modifiable, endogenous factors (e.g. sex, age, and genotypes) and modifiable, exogenous factors (e.g. nutrition, social and cognitive activities, and exercise prescription) (94). Approximately half of interindividual heterogeneity observed in physical and cognitive outcomes in response to exercise have been attributed to differences in genetics (95). The remaining heterogeneity is likely due to variations in modifiable factors. It has further been reported that global non-responders do not exist, and non-responsiveness can be addressed by modifying dose of physical training (93), suggesting that dosage of physical interventions play a large role in observed interindividual heterogeneity.

Quantification of the summation of exercise exposure in the context of acute bouts of physical exercise is usually accomplished through exercise dosage, which is a product of exercise and training variables, including: exercise intensity, exercise duration, and frequency of exercise (96). Given the ability to modulate dosage of exercise, measurements of doses are required to determine changes in dosage of exercise delivery. In active exercise, common markers of internal load to describe exercise intensity during acute exercise include hemodynamic and metabolic parameters, including: heart rate, heart rate variability, and oxygen uptake (oxygen consumption VO2) (93).

Ultimately due to individual heterogeneity in psychophysiological responses to both acute exercise and long-term training, aspects of exercise dosing to tailor physical exercise prescription on an individual basis to achieve maximal efficiency in psychophysiological responses, and to avoid negative consequences associated with excess exercise. Exercise intensity that is too high may result in harm through oxidative stress (97) or injury (98), while low intensity may confer no or reduced benefits (99). In order to best determine proper exercise prescription, graded exercise tests are necessary as exercise intensity cannot be accurately predicted (93), thus responses to changes in exercise intensity are also incapable of being adequately assessed. The true impact of various variables of exercise dosage are difficult to adequately isolate given their overlap during the course of exercise delivery.

When approaching physical activity as a mechanism to improve patient health and wellbeing, healthcare practitioners have been recommended to deliver exercise dosing as a form of medicine (100). However, unlike chemical drugs, the dose-response, minimum dose to elicit a response, and maximum safe dose of exercise are poorly understood. The optimal exercise dose that elicits the greatest benefit differs based on the clinical parameter studied, thus exercise prescription is best achieved by identifying specific therapeutic targets for individual patients (96). However, regardless of the outcome of interest, the administration of exercise in patients follows a similar format as the prescription of pharmacological agents, with an initial introduction of the minimum effective dose of low intensity exercise, and gradual increases in exercise intensity based on patient physical fitness and response to exercise (100). Additional consideration in exercise dosage should be made based on particular needs and comorbidities of patients, due to heterogeneity across

patients, and increased potential risks when caring for patients that are elderly, overweight or obese, and patients with chronic diseases or severe illnesses (57).

It is unclear whether vigorous, long-endurance exercise may have potentially detrimental impacts on individual wellbeing, through acceleration of atherosclerosis or adverse cardiac remodelling (96). Intense, exhaustive exercise has been reported to cause sudden cardiac death (SCD) in young athletes (101), while animal studies have demonstrated adverse cardiac remodelling, and predisposition for cardiac arrythmias in rats that have been exposed to chronic vigorous, endurance exercise training (102). However, SCD is now understood to be due to genetic inheritance or acquired conditions that predispose cardiac disease (60). These conditions emphasize the necessity of exercise dosage based on patient characteristics, and the importance of conservative exercise dosing in patients with predisposition for adverse response to exhaustive exercise. Overall, the prescription of regular aerobic exercise has been demonstrated to impart a dose-response relationship on improvements in the health and longevity of the general population.

## 1.3.2. Exercise in the intensive care unit

Mobilization in the ICU, particularly early mobilization, has been of much interest lately, and has been associated with improvements in a multitude of patient outcomes. Recent guidelines for care of critical patients have included early mobilization as facets of patient care plans. The Pain, Agitation/Sedation, Delirium, Immobility, and Sleep disruption guideline (2018) recommends safe mobilization and rehabilitation of critically ill adults when cardiovascular, respiratory, and neurologic statues are stable (103), while early mobilization has also been recommended as part of the Awakening and Breathing Coordination, Delirium management, and Early mobility (ABCDE) bundle which combines reports from evidence-based patient care research to improve patient outcomes through decreasing dependence on mechanical ventilation, decrease ICU and hospital length of stay, restore pre-ICU brain function, improve patient functional status, and improve patient survival (54). The majority of early mobilization research has been focused on active therapies, rather than passive mobilization (72). Active mobilization relies on patient participation in the mobilization therapies, and includes active or resistive exercises, patient self-ambulation and mobilization. Depending on patient status, early active mobilization can be safely administered on the first day of ICU admission, and even during mechanical ventilation or

administration of vasopressors (72), with minimal adverse events, that are usually categorized as non-serious adverse events (104).

In contrast, passive exercises are utilized in patients that are either unable to participate in active mobilization due do sedation, or are unable to cooperate with instruction required for active mobilization. Passive mobilization is similarly also achieved through a variety of modalities including manual passive patient mobilization, cycle ergometers, or continuous passive motion machines. Due to the overlap early clinical course, and occurrence of more patient sedation, the safety of early mobilization has been questioned (105). However, studies of early passive mobilization in septic patients was found to be safe and feasible, and early mobilization overall was similarly found to be safe and feasible in multiple studies (74,84,85) with minimal adverse events. Furthermore, both continuous passive motion and passive stretch have been demonstrated to beneficially decrease or prevent muscle atrophy from prolonged bed-rest. Bed-side cycle ergometry has been identified as a particularly beneficial method of delivering mobilization in patients that are confined to the bed (e.g. severe chronic obstructive pulmonary disease). Furthermore, in-bed cycle ergometry provides additional benefits by allowing for prolonged mobilization sessions, and for adjustment of training intensity to deliver a wide range of training intensities based on patient needs (72), and adjustment of these intensities during a mobilization session based on patient response to exercise. During mobilization, patients physiologic and hemodynamic statuses are carefully assessed to ensure patient cooperation and safety.

A combination of early passive exercises, and early introduction of active exercises are conducted through progressive exercise and mobility. In unconscious patients, early passive exercise is introduced and implemented until patients become responsive and interactive during the course of their ICU stay, allowing for progressive increases in passive mobilization intensity, with gradual transition from passive to active mobilization to improve mobility (72). The exercises range from fully passive (e.g. passive range of motion) to more interactive (e.g. active range of motion, resistance physical therapy, bed mobility exercise, activities of daily living, and walking). As patients become increasingly responsive, they are able to better participate in active mobilization, and mobilize out of the bed even when mechanically ventilated. Critically ill patients that underwent early progressive therapy were found to mobilize from their beds earlier, have shorter

ICU and hospital lengths of stay, have shorter duration of delirium, and demonstrated better functional status at hospital discharge (106).

Early mobilization is defined as mobilization that occurs within the first 2-5 days of ICU admission (107), however, ICU-AW has been demonstrated to occur within the first 48 hours of ICU admission (77). Thus, mobilization may need to be introduced to ICU patients earlier than 2 days of ICU stay. With swift implementation of early mobilization in critically ill patients, increased caution must be taken to prevent and minimize adverse events. Factors that limit mobilization of patients include hemodynamic instability, altered sleep patterns, vascular attachments, and dependency on mechanical ventilation. A key barrier to early mobilization is patient safety, particularly in more vulnerable patients with severe critical states, coma, or delirium. Thus, it is paramount for clinicians and healthcare workers to appropriately assess patient exercise tolerance. Current parameters monitored include assessments of hemodynamic stability and metabolic activity including heart rate, blood pressure, and respiratory rate (72). Although there is hesitancy in implementation of exercise programs in ICU patients with various clinical presentations, and comorbidities, early mobilization has thus far been found to be safe and feasible in adult ICU patients receiving mechanical ventilation (108), vasopressor infusions (74,84) or chronic renal replacement therapy (109).

Additional barriers to mobilization exist when attempting to implement early active mobilization include the sedated, unconscious state of patients (77). This can be overcome by starting patients on early passive mobilization, however, there is limited knowledge regarding the isolated impact of passive mobilization on patient outcomes. Furthermore, patients that are sedated and unable to participate in active mobilization often have greater illness severity (87), thus requiring more care. Furthermore, given the attenuated hemodynamic and metabolic responses of patients receiving sedatives (110), there is further dependence on monitors of hemodynamic and metabolic responses to determine adequacy of passive exercise, and exercise tolerance. However, these measures are restricted given their global monitoring status, with limited information regarding regional impact passive cycling has on organ systems that are most at risk of suffering from impaired perfusion.

Overall, current literature surrounding early mobilization in critically ill patients demonstrates its safety, feasibility, and effectiveness, and it has been associated with benefits on patient outcomes including decreased ICU and hospital LOS, decreased duration of delirium, decreased dependence on mechanical ventilation, improved ambulation, and better functional status at hospital discharge (72). Furthermore, early mobilization also demonstrated decreases in patient pain, swelling, stiffness, and improvements in patient satisfaction and motivation (111). Questions that remain to be addressed include the lack of a standardized mobility protocol, due to institutional differences in equipment and mobilization standards, which makes it difficult to compare outcomes from different researchers. Given the severe critical status of patients early in their ICU admission, clinical practice of early mobilization is increasingly recommended as a standard of care (103,112), but still requires research-based exploration of exercise prescription within the first 48 hours of ICU admission to optimize improvements in patient outcomes. To do so, aspects of exercise prescription including exercise intensity, frequency, duration, and timing of exercise initiation must first be addressed. Furthermore, differences in exercise modalities used, variations in mobilization provider techniques, resources available at varying institutions all play a role in heterogeneity of delivery of early mobilization, in already diverse critically ill patient populations.

## 1.3.2.1.   Passive exercise in the intensive care unit

Passive exercise is a promising intervention that may improve patient-centered outcomes in critically ill patients, but there is paucity of data in the critically ill. Passive exercise in ICU patients does not appear to adversely affect hemodynamic variables (e.g. blood pressure, heart rate, stroke volume) (85,92,113–115), and may increase blood flow to exercising limbs (115,116). However, the relationship between increased limb blood flow and perfusion of ischemia-prone organs (e.g. the heart and the brain) remain unknown. Furthermore, there is a lack of agreement regarding an established standard for appropriate passive exercise dose as well as best the modality for passive exercise delivery in the critically ill.

### 1.3.2.1.1.   Delivery of passive exercise in the ICU

Delivery in the critically ill appears to be limited to three modalities of passive leg movement (92,113–117), passive cycling (85,113,118) and continuous motion machines (105). Furthermore, the delivery of passive exercise in the ICU differed with respect to patient posture during passive

exercise delivery. Most ICU studies delivered these interventions in semi-recumbent (85,92,117) or supine (113–115,118) positions and report no changes in hemodynamic or metabolic variables with passive cycling.

Currently, choices of passive exercise modalities and patient positioning in ICU studies are likely dictated by patient's ability to participate (84), availability of appropriate exercise tools (e.g. in-bed cycle ergometer) human power (e.g. physiotherapists) (107), and practical consideration of integrating passive exercise sessions within other patient care activities (119).

The two most common passive exercise modalities used in the ICU thus far include passive leg movement (92,113–117) and passive cycling (85,113,118). Both modalities appear to be safe in critically ill patients with respect to patient hemodynamic stability, but there are no studies comparing these two modalities with respect to their cost of delivery and impact on metabolic parameters, organ perfusion, and patient outcomes following ICU discharge. Both passive leg movement and passive cycling can be delivered at a prescribed, reproducible RPM, but passive cycling may provide a more consistent and less labor-intensive means of delivering passive exercise in the critically ill. However, the benefits of passive cycling require increased costs associated with purchasing and maintaining in-bed cycling ergometers, thus, further studies are needed to determine whether these additional costs can be offset by improved patient-centered outcomes. Large-scale randomized controlled trials of in-bed cycling are underway and will provide much needed high-quality evidence in the near future (120).

## 1.3.2.1.2. Dosage of passive exercise in the ICU

Dosage of passive exercise in critically ill adults is complicated by the severity of critical illness, as inappropriately dosed exercise may worsen patient's clinical status (e.g. by inducing organ ischemia through vascular steal). The optimal dose of passive exercise in the critically ill patients remains unknown and largely unexplored. Intensity of passive exercise in the ICU varied from 20 to 60 RPM (105,116) , duration from 2 to 20 minutes (85,105,116,118), and the frequency was mostly limited to a one-time intervention. While availability of equipment, human power and time for exercise interventions are important practical limitations that merit consideration when developing passive exercise protocols in the ICU, the actual exercise dose prescription should be

based on exercise science and should consider patient specific factors that may potentially influence response to exercise (e.g. age, sex, comorbidities, illness severity and pre-existing fitness levels). To highlight the variation within ICU patients, in one study, ICU patients with pre-existing cardiac disease had no change in cardiac output during passive leg movement, while those without cardiac disease had a 12% increase in their cardiac output (92). Furthermore, it is also important to consider that although some participants that do not respond or respond negatively to a certain exercise paradigm, they may respond positively to alternative exercise protocols (121).

### 1.3.2.1.3.    Safety of passive exercise in critically ill patients

Patient safety is an important consideration when introducing new interventions into critical care. Current studies demonstrate that passive exercise was well tolerated from the global hemodynamics perspective and with minimal adverse events (85), however, it remains unknown whether it can negatively impact organ perfusion, particularly in sicker patients. Although passive exercise should not impact metabolic parameters, two studies in ICU cohorts showed that passive cycling can elicit increases in $VO_2$ (92,117), cardiac output (92,115), and heart rate (92). While this may be tolerated in some critically ill patients, it may negatively impact sicker patients. Given that passive cycling has no impact on metabolic or hemodynamic parameters, and it can be standardized using settings on cycling ergometer, it may be the safest and most practical modality for use in critically ill patients. However, future studies should ensure that increase in limb blood flow with passive exercise does not result in vascular steal and impaired perfusion of ischemia prone organs, including the heart and the brain. This is especially important given that protective mechanisms such as cerebral autoregulation are commonly impaired in the critically ill (30,122).

### 1.3.2.1.4.    Outcome measures of importance

Passive exercise does not appear to impact traditional ICU outcomes such as duration of mechanical ventilation, ICU and hospital length of stay. In fact, as shown in the only randomized control study, passive cycling did not shorten hospital and ICU length of stay, and duration of mechanical ventilation, compared to the standard care physiotherapy group (118). However, in the same study, passive cycling in the ICU in addition to regular physiotherapy increased peripheral strength at hospital discharge (118). Given that weakness and functional impairment are common (123) and costly (73) complications of critical illness, improvement in peripheral strength

represents an important patient-centered outcome. Other well-known benefits of exercise include improvements in mood and cognition (124,125). Given the high prevalence of delirium in the critically ill (126), as well as mood and cognitive impairment in ICU survivors (53,127,128), future studies should explore whether passive exercise can reduce delirium and improve cognitive outcomes in the critically ill. The plausibility of this hypothesis is supported by the observation that passive exercise appears to increase cerebral blood flow in healthy adults (129–131). Whether the same is true in the critically ill is unknown.

# 1.4. Hemodynamic monitoring

Hemodynamic monitoring in critically ill patients is required to monitor patient status due to increased risk of hemodynamic instability and subsequent impact on systemic physiologic function. Monitoring during sepsis is importance given the variable hemodynamic changes that patients go through as they progress from early to later stages of sepsis, with increased risk of organ dysfunction, deterioration into multi-organ failure, and death (132). Information obtained through hemodynamic monitoring is essential in guiding treatment measures including fluid resuscitation, use of vasopressors, or inotropes. Many techniques can be used to perform hemodynamic monitoring, and selection of monitoring techniques depends on the level of monitoring required by individual patients, the patient disease, devices, and expertise available at the institution of use.

ICU patients usually either suffer from organ failure or are at increased risk of sustaining organ failure. In these patients, hemodynamic instability that leads to mismatch between oxygen delivery and demand contributes to shock and risk of organ failure (132). Critically ill patients often demonstrate hemodynamic instability caused by adaptive and pathologic changes in circulating volume, cardiac function, and/or vascular tone. In these patients, basic vital parameters are monitored, including heart rate (HR), blood pressure (BP), central venous pressure (CVP), peripheral and central O2 saturation, respiratory variables, and urine output (133); however, BP provides limited ability in aiding the identification of tissue hypoperfusion in septic patients, particularly given that patients with sepsis-associated hypoperfusion can still demonstrate normal blood pressures (134). Ultimately, it is key to assess parameters that provide better indications of hemodynamic instability and tissue hypoperfusion. Thus, functional hemodynamic monitoring (e.g. CO, pulmonary arterial wedge pressure (PAWP), pulmonary arterial pressure (PAP), and mixed venous oxygen saturation (SvO2)) are required under circumstances where basic vital parameters are not sufficient to guide fluid management, vasopressor and/or inotropic support, and during cardiovascular system challenge (132). Hemodynamic monitoring can be achieved by a wide array of techniques and devices which can be categorized based on calibration versus non-calibrated techniques and degree of invasiveness. Although all patients admitted to the ICU require hemodynamic monitoring, the degree of monitoring varies. Increased monitoring is required in those with hemodynamic instability, increased risk of instability, and is usually accomplished via

an arterial line for continuous invasive blood pressure measurement, and a route for drawing arterial blood samples for arterial blood gas evaluations (132). Patients receiving vasopressors/inotropes require a central venous line for drug administration, which also serves as a method for acquiring CVP and central venous O2 saturation (ScvO2) measurements (134). There is a preference to use less-invasive and non-invasive techniques for hemodynamic monitoring, if there is little benefit in way of the information obtained (134).

Invasive techniques include pulmonary artery catheter (PAC), the gold standard of hemodynamic monitoring which involves the insertion of a flow-directed catheter through the jugular or subclavian vein to the right atrium and ventricle where it rests at the pulmonary artery (132). PAC allows for direct measurement of CVP PAP, and PAWP. However, the invasive nature of this monitoring technique has resulted in a decline of its use. Currently PAC is implemented when there is right ventricular heart failure or pulmonary hypertension, because remaining techniques are unable to measure the right heart and pulmonary circulation (132). Less invasive and non-invasive techniques are preferred for hemodynamic monitoring to reduce risks associated with PAC use. Less-invasive techniques include transpulmonary thermodilution, transpulmonary dye dilution, ultrasound flow dilution, pulse contour and pulse pressure analysis, respiratory derived cardiac output monitoring, transesophageal echocardiography, and esophageal doppler ultrasound (132). Non-invasive techniques include transthoracic echocardiography, non-invasive pulse contour systems, bioimpedance, estimated continuous cardiac output, and ultrasonic cardiac output monitoring (132). Of the less-invasive and non-invasive hemodynamic monitoring techniques, intermittent thermodilution is deemed the reference standard, but still presents risks of the invasive nature, albeit much less than that of PAC (135). Overall, hemodynamic measurements via less-invasive and non-invasive methods are preferable if the their techniques are more quickly and easily administered, in lieu of being less accurate. In particularly, there is a shift towards continuous hemodynamic monitoring in favour of intermittent monitoring, with continuous measurements of many variables including HR, BP, and CVP (135).

However, despite the increased information that continuous hemodynamic monitoring provides, these modalities are still lacking in the ability to provide information on microcirculation and individual organ function. This is especially detrimental in monitoring the status of sepsis patients

that demonstrate persistent tissue hypoperfusion even after restoration of adequate blood pressure and cardiac output (134). In sepsis, impairments in blood flow can impair perfusion at regional areas (e.g. cerebral, cardiac, renal, splanchnic, and mesenteric) through microvascular and cellular disturbances in oxygen use despite adequate oxygen delivery (cytopathic hypoxia) (136). Treatment of sepsis involve early recognition of sepsis, and early antibiotic therapy. Assessment of hemodynamic status and its management are crucial components in adequate care of septic patients to outline therapeutic interventions which improve intravascular volume, blood flow, perfusion pressure, and tissue perfusion. Hemodynamic targets, particularly cardiac output should be assessed based on clinical examination, and individualized on a per-patient basis.

## 1.4.1. Continuous arterial monitoring

In ICU patients with increased risk of hemodynamic instability, continuous arterial monitoring is frequently used and is the gold standard of blood pressure measurement (132). Arterial monitoring provides continuous, beat-to-beat information regarding heart rate and arterial blood pressure. Usage of continuous arterial monitoring is useful when rapid changes in patient blood pressure is expected (e.g. cardiovascular instability, massive fluid shifts, response to pharmacologic interventions) or when non-invasive blood pressure monitoring is not possible or likely to be inaccurate (137). Furthermore, invasive, intra-arterial blood pressure monitoring is also recommended in patients that are expected to require long-term measurement (137) because it negates local tissue damage caused by repeated cuff inflation of non-invasive blood pressure monitors while also allowing a route for blood sampling to conduct blood gas and laboratory analyses.

## 1.4.2. Pulse wave analysis

Non-invasive options of continuous hemodynamic monitoring allow researchers to circumvent any invasive techniques needed to obtain HD measurements. This opens up avenues of hemodynamic assessment in subjects who have little need or justification for use of invasive, intra-arterial blood pressure monitoring, which is often associated with discomfort and risks associated with arterial cannulation. A non-invasive hemodynamic assessment is a photoplethysmorgraphic arterial pressure monitor such as the Finapres (137), which continuously and noninvasively measures beat-to-beat blood pressure at the finger.

The Finapres (FINger Arterial PRESsure) was first introduced in 1982 (138), and is clinically used technology that is based on the volume-clamp Penaz principle of pulsatile unloading of arterial walls, and the "Physiocal" Wesseling procedure which describes a dynamic servo-setpoint adjuster that allows for automated identification and periodic adjustment of arterial unloaded volume (139). The combined methodology of both techniques is well accepted and has been validated (140). The Finapres equipment consists of a small finger cuff (sized for the subject's finger size, and contains an infrared light-emitting diode (LED)), a plethysmograph, a wrist-box that contains a rapid servo-controlled pressure system for continuous adjustment of finger cuff pressure in response to plethysmographic output (137) The cuff and box are connected to the main unit that encompasses the air pump, and console (141).

Infrared light shines through the finger, which is detected on the other side of the cuff. The light absorbed is proportional to the volume of blood and tissue through which the light passes. Thus, each cardiac cycle exists fluctuations in the amount of blood flowing through a finger, and subsequent variations in the amount of light absorbed by tissues. These changes in arterial pulsation are detected by a photoplethysmograph which is located above a pressure cuff that adjusts pressure applied to the finger. To maintain constant light absorption, volume within the cuff must also be kept constant, in a partially open state (139). This is achieved by applying to the finger within the cuff in response to output from the plethysmograph. Changes in arterial unloading are detected by a fast pneumatic servo system and a dynamic servo setpoint adjuster that maintain arterial unloading at zero transmural pressure to allow for full transmission of finger arterial blood pressure to cuff air pressure (141). Thus, the waveform of pressure applied to the finger corresponds to the pressure waveform of arterial blood supply to the finger within the cuff and resembles intra-arterial pressure in most subjects (139).

The finger cuff measures finger arterial blood pressure, which differs from blood pressure observed at the brachial artery (as typically measured by a non-invasive, inflatable blood pressure cuff) (139). The shape of pressure waves at peripheral arteries differ from more central arteries as a result of reflection and alterations in pressure gradients from the arterial tree (141), but several methods exist to correct for physiologic differences between finger and brachial pressure, which

allow for reconstruction of brachial pressure from finger measurements. Ultimately, the Finapres system requires calibration via an arm cuff. The Finapres system additionally takes its beat-to-beat finger arterial pressures and reconstructs brachial artery pressure based on calibration (142), as well as input values regarding subject weight, height, sex, and age. Finapres signals are deemed acceptable if signal is large in size, with a sharp shape and distinct dicrotic notch, and is reasonably in line with brachial artery measurements (141). Accurate cuff sizing is paramount in ensuring that Finapres signals are representative of true finger pressure (141). Finger cuff sizing recommend the cuff be applied snugly, determined via a finger cuff sizer, and placed on either the middle or annular finger. Furthermore, the relative level of the cuffed finger and the heart impact the mean BP measured at the finger (141). Thus, the finger and finger cuff must be maintained at heart level. When done so, the Finapres allows for continuous, non-invasive blood pressure monitoring, and allows for measurement and recording of BP variables during assessments which are anticipated to elicit transient changes in circulation.

## 1.5.    Ultrasound

Ultrasound is a ubiquitous technique that is non-invasive, portable, and less expensive in comparison to other imaging and monitoring equipment (143). It allows for assessment of visualization of tissue structures, and assessment of blood flow velocities. The ability to easily and rapidly obtain evaluations of organs, tissue, and vasculature aids in improvement of speed and safety of procedures for which these measurements are required. Additional benefits of ultrasound as an assessment modality include its low risk of use for both patients and health practitioners (144).

Ultrasound is based upon the use of soundwaves, which are transmitted to tissue, reflected and recorded by the ultrasound device (143) to display the desired information (e.g. image, or blood flow tracings). The application of ultrasound is achieved through application of the piezoelectric effect, by which certain crystals are able to transform electrical oscillations to mechanical oscillations. (145) Sound waves used can differ from low-frequency to high-frequency of emitted sound waves based on the required penetration and resolution desired. High frequency (10-15 MHz) and midrange frequency probes (5-10MHz) offer better resolution but have lower penetration, thus they are used for superficial and slightly deeper structures, respectively (143). In

contrast, low frequency probes (2-5Mhz) are able to image deeper tissue structures, at the cost of poorer image quality.

There are many imaging ultrasound modes, including: A-mode, B-mode, M-mode, real-time mode, pulsed wave Doppler, continuous wave Doppler and colour Doppler (145). The mode used depends on the intended application of the ultrasound equipment. Visualization of ultrasound structures depend on operator factors and tissue factors. Operator factors include angle of incidence (141) which impacts the way structures appear, and clarity of tissues visualized due to variations in reflected ultrasound waves. Perpendicular angles of incidence result in less scatter, and better ultrasound images. Tissue factors include tissue echogenicity and anisotropy. Echogenicity describes tissue's ability to reflect and transmit ultrasound waves when compared to surrounding tissues. Visualization of structural differences can be observed when examining neighbouring structures with different echogenicity. Hyperechoic structures appear white (strong reflection of sound waves), hypoechoic structures appear grey (weak reflection echoes), and anechoic structures appear black (no reflection due to absorption of sound waves). Anisotropy is another quality of tissues, which describes the tissue property that results in dramatic changes of ultrasound reflections, even with minor changes in angle of incidence. Different tissues vary in their degrees of anisotropy. Lastly, ultrasound artefacts may occur, and result in the product of false images that don't exist in real life. These artefacts are acknowledged as fabrications due to physics of ultrasound echo interactions including reverberations, mirror imaging, and acoustic enhancements (143), along with other relationships that are not fully understood.

## 1.5.1.    Transcranial Doppler

Transcranial doppler (TCD) is a non-invasive measurement of real-time, continuous assessment of cerebral blood flow characteristics and cerebrovascular hemodynamics within basal cerebral arteries. TCD is a portable, convenient technique to assess cerebrovascular changes at the bed-side and allows point-of-care monitoring of acute cerebrovascular events that may occur (146). Due to its convenience of use, and as a diagnostic modality, there is widespread use of TCD as both a clinical and research tool.

Transcranial doppler ultrasonography is an ultrasound technique, that utilizes pulsed, low frequency (≤2 MHz) transducer probes (147) to penetrate the skull and insonate intracranial vasculature, most commonly the basal cerebral arteries (147). Its technology is based on the Doppler effect principle, which describes the phenomena that occurs when a sound wave encounters a moving object and results in a change in frequency proportional to the speed of the moving object. The difference in frequency between emitted and reflected waves is termed the doppler shift frequency. Echoes returned to the probe generate an electrical impulse and are used to produce spectral waveforms. In the context of cerebral blood flow, ultrasound waves emitted from the probe are transmitted through the skull and insonate red blood cells inside cerebral vessels (146). The doppler shift frequency both arises from and is proportional to the speed that the RBCs move at, which is measured as the cerebral blood flow velocity. However, due to the laminar nature of blood flow within vasculature, the Doppler signal observed at the probe describes a spectrum of varying Doppler frequency shifts, and thus, a distribution of individual RBC velocities spanning peak systolic velocity and end diastolic velocity values (148). Further spectral analysis can be used to determine measurers of blood flow velocity and other flow characteristics within the insonated blood vessel. Overall, TCD allows real-time, dynamic monitoring of cerebral blood flow velocity over time with high temporal resolution (148).

Blood flow velocity as measured by TCD is dependent on a variety of factors. Measurements of blood flow velocity include peak systolic velocity (PSV), end diastolic velocity (EDV), and mean flow velocity. Mean flow velocity is calculated from PSV and EDV and is a useful parameter to assess clinical conditions. Physiologic variables that influence blood flow velocity include age, sex, hematocrit, viscosity, carbon dioxide, temperature, blood pressure, mental activity, and motor activity (149). Furthermore, blood flow velocity is highly impacted by the changes in vessel radius, with modulations in vessel radius resulting in a fourth power change in blood flow velocity (146). Cerebral blood flow through a vessel is the product of mean flow velocity (MFV) and the cross-sectional area of the vessel. However, a main assumption of TCD use is that the diameter of the insonated vessel does not change during an assessment, if cerebral vasculature is normal and constant. With this assumption, MFV is considered a surrogate of CBF, and increases in MFV may clinically indicate stenosis, vasospasm, or hypodynamic flow, while decreases of MFV may

indicate decreased CBF and/or intracranial pressure (ICP), cerebral hypotension, or brain-stem death (148).

Two types of TCD equipment exist and include non-duplex/non-imaging, as well as duplex/imaging devices. Non-duplex devices identify cerebral arteries based on audible Doppler shifts and a spectral display (146). Flows moving toward or away from the transducer are shown as positive or negative channels, respectively. Use of colour or colour M-mode Doppler further identifies flow toward the transducer as red and flow away from the transducer as blue. Identification of specific arteries is done through evaluation of standard criteria which includes: cranial window used, orientation of probe, depth of sample volume, and direction of blood flow. Unlike non-duplex devices, duplex TCD allows for imaging of cerebral vasculature (149). It combines pulsed Doppler ultrasound with a cross-sectional imaging of the area of insonation, which allows imaging of cerebral arteries in relation to cerebral anatomic structures.

Insonation is done across acoustic windows, which are skull regions that best transmit ultrasound waves to basal cerebral arteries. The skull has four main acoustic windows, the transtemporal, transorbital, submandibular, and suboccipital windows. The most relevant insonation is the transtemporal window which is located above the zygomatic arch, anterior to and above the tragus of the ear. The transtemporal window is capable of insonating the middle cerebral artery (MCA), anterior cerebral artery (ACA), posterior cerebral artery (PCA), and internal carotid artery (ICA) (147,149). The ICA is a commonly landmark to locate other cerebral arteries, and is located at depts of 55-65mm (146). However, the MCA is the most regularly clinically insonated vessel because it is easily accessed through the transtemporal window, and can be detected at depths of 45-60mm with blood flow directed towards the transducer (147). Furthermore, the MCA collects 60-70% of ICA blood flow, and insonation of one MCA vessel is mostly representative of global cerebral blood flow to a single brain hemisphere (149).

Clinical applications of TCD include identification and diagnosis of many clinical conditions including, but not limited to subarachnoid hemorrhage, intra- and extra- cranial stenosis and occlusion, increased intracranial pressure, acute ischemic stroke, collateral flow, detection of

microemboli, cerebral circulatory arrest, and for intraoperative monitoring (146). Furthermore, TCD has also been used to study cerebral pressure autoregulation and used as an aspect to identify increased cerebrovascular resistance, vasospasm, and hyperdynamic flow states which are altered in aspects of clinical conditions (148).

TCD is a portable, repeatable, and relatively inexpensive method of continuously, non-noninvasively measuring intracranial cerebral artery blood flow velocity with high temporal resolution. These characteristics make it particularly useful as a technique for inferring cerebral perfusion at patient bedsides, particularly in critically ill patients, in intensive care units. However, limitations and inconsistencies in its use are due to operator dependency and long learning curve to obtain a competent understanding of 3-dimensional cerebrovascular anatomy and use TCD to achieve desired measurements (148). Furthermore, TCD requires patients to have adequate transtemporal acoustic windows, which 10-20% of patients do not have (148). These drawbacks limit the utility of TCD, despite its many benefits. Given variability in TCD findings based on patient physiology and user adequacy, interpretation of these findings must be performed with caution, and trends observed in cerebral blood flow parameters are more important than isolated values in the guidance of diagnoses (146).

## 1.5.2. Echocardiography

Echocardiography is a commonly clinically used cardiac imaging modality that uses Doppler ultrasound to create cardiac images. Echocardiography is often the first modality to assess patients suspected to have cardiovascular disease (150). Echocardiography employs frequencies with range from 1.5-7.5 MHz (145) and is most commonly used to assess left ventricular function. Echocardiography can be categorized in many ways but is broadly grouped into two main categories: transthoracic versus transesophageal echocardiography, and 2D versus 3D echocardiography. Thus, echocardiography can differ in route used to acquire images from the patient, and in the creation of the ultrasound image within the echocardiographic device itself. Clinical applications of echocardiography include the assessment of systolic and diastolic function, chamber size and myocardium thickness, identification of wall-motion abnormalities, visualizing valvular abnormalities (e.g. aortic stenosis, aortic regurgitation, mitral stenosis, mitral regurgitation), and infectious endocarditis (150).

Transthoracic echocardiography (TTE) is the most commonly performed echocardiogram, and cardiac investigation. It is a portable, non-invasive method and consists of the application of the ultrasound transducer on the subject chest or abdomen to obtain ultrasound cardiac images. TTE allows for assessment of cardiac structure and function, and it is able to obtain images of all four cardiac chambers, valves, and certain cardiac pathologies that result in morphologic changes (150). The image quality and visibility of these structure differs from person to person and is reliant on both operator skill and subject cardiac physiology and overall physiology (151). TTE aids in the visualization of cardiac structure and function, and is critical in assisting establishing diagnosis of some cardiac pathologies, as well as guiding therapy planning. Hemodynamic information acquired from TTE can be paramount in critically ill patients, as the technique allows for point-of-care use and visualization of cardiac physiology throughout the assessment of cardiac hemodynamic parameters. Hemodynamic information that can be acquire from a TTE are but not limited to: cardiac output, stroke volume, and heart rate. Transesophageal echocardiography (TEE) is similar in theory to TTE but differs because it requires the insertion of a probe through the esophagus to the level of the heart. TEE is a more invasive cardiac imaging modality, and often requires mild sedation to allow for smooth probe insertion.

Two dimensional, transthoracic echocardiography is the most used cardiac imaging modality (145). Two-dimensional Doppler ultrasound echocardiography is built on previously discussed ultrasound principles, but further converts information from sound waves in the form of an image. It uses either a pulsed or continuous electric current, with a firing time and listening time, to assess the time taken for the signal to be delivered, and reflected back to the transducer (145). From this information, the device determines the depth that a data point should be projected, and its intensity. Through these mechanisms, a 2D image in the plane of the probe is obtained. 3D echocardiography takes 2D echocardiography further and reconstructs 2D planes into a 3D visualization (152).

Due to limits that 2D echocardiography has with respect to alignment of Doppler signal and sensitivity to signal noise, speckle-tracking echocardiography techniques are increasingly employed to provide additional information on strain and strain-rate that can be calculated through use of ultrasound speckles that function as tags in the myocardium. This offline technique can be

applied to previously acquired 2D echocardiograms, and produces data regarding myocardial deformation comparable to information obtained through tagged cardiac magnetic resonance imaging (150). Clinical use of speckle tracking echocardiography mainly encompasses quantitative assessment of myocardial function. Speckles generated from 2D echocardiogram images result from the meeting of constructive and destructive interference of sound waves that are backscattered by structures smaller than the ultrasound wavelength (152). These speckles can be tracked from frame-to-frame of echocardiogram acquisition, and used to determine strain (tissue deformation), and strain rate (time course of tissue deformation). Assessment of strain are particularly useful in the assessment of regional myocardial infarction, ischemia, and stunning.

## 1.6. Objectives

Despite advancements in understanding the benefits of early mobilization in critically ill patients, there still remain several knowledge gaps regarding this topic regarding the administration of the mobilization itself. Although it is commonly acknowledged that early passive exercise can still be achieved when early active exercise is not feasible in patients due to limitations impacting patient participation (72,85,105), there still remains a poor understanding of early passive exercise dosage in intensive care patients. Furthermore, given the critical status of these patients, particularly those with increased susceptibility to developing multi-organ dysfunction, such as septic patients, there is a further dire need to understand the impact of early passive exercise on patient outcomes, as identified by prior literature (72,153–155). We studied the relationship between intensity of passive mobilization on hemodynamic outcomes and organ perfusion. We hypothesized that there is a dose-response relationship between intensity of early passive mobilization on both hemodynamic outcomes and organ perfusion in critically ill septic patients.

As a currently used method of mobilizing critically ill patients with dependable delivery of passive cycling at adjustable intensities to critically ill patients (85,118), an in-bed cycling ergometer was determined to be a good modality to explore potential dose-dependent relationships between passive cycling and acute patient responses on both a systemic and organ-specific scale. Thus, using this modality to address existing knowledge gaps, this thesis consisted of two main objectives:

1) To develop a passive cycling protocol that can be used in septic patients and test for its safety and feasibility in healthy adults. This will also provide a control group for the later septic cohort.

   With guidance and input from critical care physicians, we created a passive cycling protocol with step-wise increases in cycling intensity to identify dose-response relationships between intensity of passive cycling and hemodynamic, cardiac, and cerebral outcomes of interest. During the development of this protocol, we considered the feasibility and ease of translation of its use on septic patients in the ICU. Additional factors we considered include the need for familiarity and a baseline measurement of all parameters for comparison to later stages, the time it would take for physiologic adaption to increased cycling intensity, and the need for post-exercise measurements to identify acute, lasting effects of passive mobilization. We employed the use of various non-invasive techniques to assess cardiac function at each stage, and continuously measure global hemodynamic parameters and cerebral blood flow throughout the exercise protocol. We applied this protocol in a cohort of healthy adults to determine its safety and feasibility in a control population, and to identify the impact of graded increases of passive cycling in a healthy cohort, as it has not been previously studied. *Our goal was to determine the safety and feasibility of the passive protocol in a cohort of healthy adults, and identify its impact on participant hemodynamics, cerebral blood flow, and cardiac function. We hypothesized that this passive protocol would be both feasible and well-tolerated in healthy adults, and that there would not be a significant difference in patient outcomes examined (e.g. hemodynamics, cerebral blood flow, cardiac contractility) with increased passive cycling cadence.*

2) To apply the passive cycling protocol to a cohort of septic patients.

   Upon confirmation of the safety and feasibility of the passive cycling protocol in our previous cohort of healthy subjects, we applied the graded passive cycling protocol to a cohort of septic patients early in their ICU admission. The same passive cycling protocol that incorporated graded increases of cycling intensity that was developed previously was administered in a group of septic patients. The same non-invasive techniques used previously were also used in this patient group, with the addition of supplementary

hemodynamic measurements via invasive, continuous, intra-arterial blood pressure monitoring. Compared to healthy adults, septic patients present higher risk of hemodynamic instability, and also are commonly on vasoactive and sedative medication. Thus, vasoactive and sedative medications were not adjusted during the duration of the passive cycling protocol, to minimize any confounding variables these management medications may create. Patient physicians were consulted prior to initiation of the cycling protocol, and ICU nurses and physiotherapists were present to ensure patient safety throughout the duration of the protocol. *Our goal was to identify the impact of graded passive cycling on hemodynamic, cerebral, and cardiac outcomes in septic patients, to identify potential relationships between passive cycling intensity and patient safety as determined by both hemodynamic stability, and impact on perfusion sensitive organs. We hypothesized that the passive protocol would be feasible in septic patients, and passive mobilization would elicit changes in patient outcomes (e.g. hemodynamics, cerebral blood flow, cardiac contractility).*

# 1.7. General methods

The following methodology was shared between both the healthy cohort and septic cohort. The passive cycling protocol that was developed was initially tested for safety and feasibility in the healthy cohort prior to application in the septic cohort. This methodology has been previously published in an article by the author of this thesis, titled "Impact of graded passive cycling on hemodynamics, brain and heart perfusion in healthy adults" (156).

*Subjects:* Following Institutional Research Ethics Board approval, we obtained informed written consent and prospectively enrolled adult (18-80 years) healthy subjects and septic ICU patients or their surrogate decision maker. We recorded participants' ages, weights, heights as well as resting blood pressures prior to and after the experiment. Subject and equipment setup are illustrated in Figure 1-1.
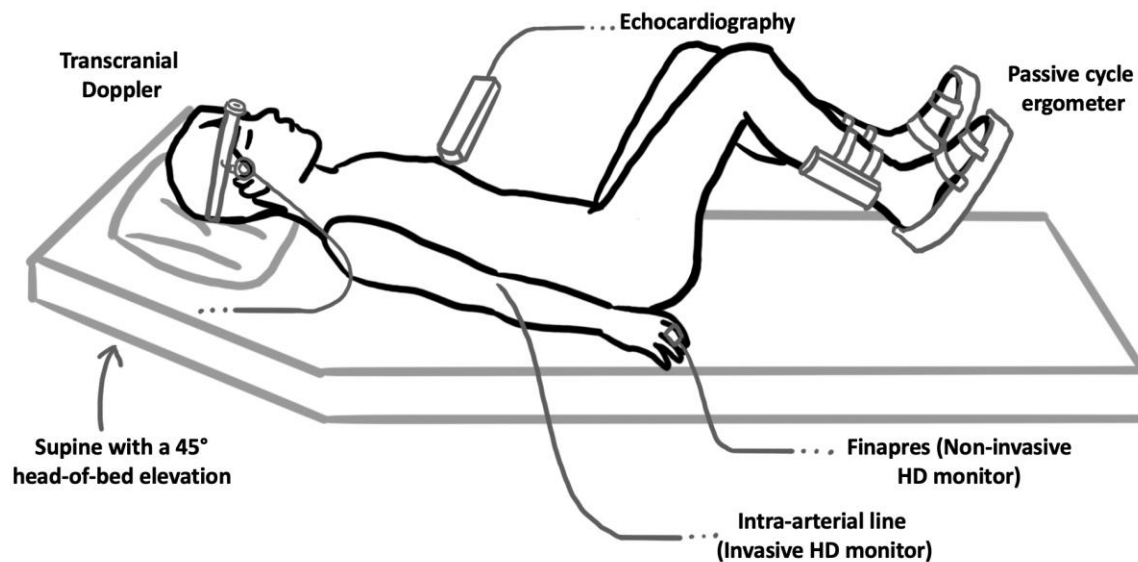


**Figure 1-1.** Subject and experimental setup used. Subjects were positioned supine with a 45 degree head-of-bed elevation and passively cycled using an in-bed cycle ergometer. Transcranial Doppler was used to measure the velocity of blood flow in the middle cerebral arteries (as a surrogate marker of global cerebral blood flow. Grey-scale 2D-echocardiography was used to collect apical 2 and 4-chamber views of the left ventricle at each cycling intensity, which were then used to compute patient ejection fraction and global longitudinal strain at each experimental

stage. We used Finapres® NOVA to measure hemodynamic parameters using pulse wave analysis, with additional mean arterial pressure and heart rate monitoring performed through routine care intra-arterial hemodynamic monitoring.

*Global hemodynamic monitoring:* We used Finapres® NOVA (Finapres Medical Systems, Amsterdam, Netherlands) to measure beat-by-beat arterial blood pressure, stroke volume, cardiac output and total peripheral resistance using pulse wave analysis. The appropriate finger cuff was sized for each subject and applied to the middle finger, with a height correction unit which was placed at the level of the heart. We used participant height and weight to calculate their body surface area, which we used to compute indices of stroke volume (SVI), cardiac output (CI) and total peripheral resistance (TPRI) obtained from Finapres©.

*Cerebral blood flow monitoring:* We used transcranial Doppler (TCD, Spencer Technologies, Redmond, USA) to measure the mean velocity of blood flow in the middle cerebral arteries (MCAv) as a marker of global cerebral blood flow (CBF). Given that we aim to tailor these methods to study patients early in the course of their critical illness, transcranial Doppler provided a safer alternative for monitoring exercise induced changes in CBF with high temporal resolution, and it is an accepted practice for monitoring cerebral hemodynamic in critical care (147). After adequate signals were attained using standard techniques (146), Doppler probes were fixed in place using a head harness (Spencer Technologies, Redmond, USA) to ensure the same angle of insonation and adequate signal power. Data was recorded continuously at 125 Hz using provided software.

*Cardiac function monitoring:* We used standard grey-scale 2D-echocardiography (Vivid I® with 1.5-3.6MHz imaging transducer, GE medical systems, Sonigen, Germany) to collect apical 2-chamber and 4-chamber views of the left ventricle (LV) at each experimental stage. Images were collected with a frame rate of 70-90/second by an experienced and trained echocardiographer and saved digitally for offline analysis. We used speckle tracking software (Echo-PAC Dimension, GE healthcare, Germany) to determine ejection fraction, as well as global longitudinal strain (GLS) as previously described (152). After tracing the endocardial border in both views of the left ventricle at end systole, the software automatically selected stable acoustic objects within the myocardium to track and compute strain throughout the cardiac cycle. The LV was divided into 6 segments per

view (12 in total) with the peak systolic strain values calculated for each segment (segmental strain) and GLS calculated as the mean of all 12 segments. Segments that failed to track were manually adjudicated. Previous studies have demonstrated that healthy individuals have GLS ranging from -16 to -19% (less negative values correspond to reduced contractility (154)).

*Passive cycling protocol:* To deliver passive cycling, we used a clinical in-bed cycling ergometer (RT300 Supine Cycle, Restorative Therapies, Baltimore, USA) that allowed both setting and measurement of cadence to ensure that the subject was not applying any force (exercise intervention remaining passive). Subjects were studied in supine position with 45 degree head-of-bed elevation. After positioning subjects in bed, we secured their legs to the bike using the straps provided as per standard protocol. We ensured that the bike and leg positioning was optimal to enable full passive leg range of motion.

We used TCD probes to identify MCAv in one or both middle cerebral arteries. We applied the Finapres probe to the middle finger of participants' right hands and ensured that we could measure beat-by-beat blood pressure and other hemodynamic parameters. Following subject's acclimatization to the equipment (~10 minutes), we started the experimental protocol. The protocol consisted of 8 stages each lasting 5 minutes. Starting at baseline (0 RPM), the cadence on the bicycle was increased in stages from 5 to 55 RPM in increments of 10 RPM, followed by a 5-minute recovery period at 0 RPM. TCD and Finapres data were acquired continuously, and echocardiography was performed during the last two minutes at each cadence stage and baseline/recovery periods.

*Data Analysis:* Eight parameters were analyzed in healthy subjects: MCAv, mean arterial pressure (MAP), heart rate (HR), CI, SVI and TPRI, left ventricular ejection fraction (EF), and left ventricular GLS. Three additional parameters were analyzed in septic patients: systolic blood pressure (SPB), diastolic blood pressure (DPB), and pulse pressure (PP). For each subject, data collected by the TCD and Finapres were exported to Excel (Microsoft) and sorted by experimental stage (baseline 0 RPM, 5 RPM, 15 RPM, 25 RPM, 35 RPM, 45 RPM, 55 RPM, or recovery 0 RPM). Data from the last 2 minutes of each stage were used to calculate mean and standard deviation for that stage. MCAv values were expressed as the percent change from each subject's

baseline value in order to allow between subject comparisons (absolute MCAv values depend on the angle of insonation, which can differ between subjects). Echocardiographic data (EF and GLS) from each stage also recorded. These metrics were exported to statistical software (Prism 7, GraphPad, San Diego, USA) that was used to construct graphs of measured parameters vs. experimental stage for individual subjects and for the whole group. We inspected the graphs visually for trends. We used descriptive statistics to report demographic data, and repeated measures one-way ANOVA to assess difference in metrics within subjects, and for group differences between subjects. Sphericity was not assumed. Comparisons of group-wide parameters were conducted between baseline and each experimental stage to determine significance of change from baseline values. Statistical significance was assumed when $p < 0.05$.

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# CHAPTER 2: Graded passive biking in healthy subjects

## 2.1 Introduction

Critically ill patients spend 96% of their time inactive in bed (1), which leads to increased cognitive, musculoskeletal, pulmonary and cardiovascular complications (2) that translate into functional disability (3) and decreased quality of life (4). Early mobilization is a therapeutic modality has been demonstrated to reduce these deleterious effects, and is associated with shortened duration of delirium, mechanical ventilation, hospital length of stay, while also improving functional outcomes at hospital discharge (5). However, in the critical care population, early active mobilization is limited in its use due to ventilator dependence and decreased level of consciousness, which often prohibit active exercise in the early stages of a critical illness.

Passive in-bed cycling circumvents these barriers and enables early mobilization (6). However, given tenuous hemodynamics and impaired autoregulation (7–9) in the critically ill, passive in-bed cycling may impair global hemodynamics or organ perfusion of ischemia-prone organs, such as the brain and the heart, with potential dose dependent effects.

Consequently, understanding the effects of graded passive in-bed cycling on hemodynamics, brain blood flow and cardiac function in the critically ill patients is paramount for ensuring that this promising intervention is delivered safely and effectively. However, there is a paucity of such data, even in healthy subjects. Given safety concerns regarding direct implementation of graded protocols in the critically ill, we initially characterized hemodynamic, brain blood flow and cardiac function responses to a graded increase in passive cycling cadence in a cohort of normal healthy volunteers.

## 2.2 Materials, Methods, and Protocol

The materials, methodology, and data analysis used were the same as the general methodology and data analysis previously listed in Chapter 1.5. Healthy adult participants were recruited using flyers distributed around Victoria Hospital, a part of the LHSC, in London, Ontario.

## 2.3  Results

*General:* Eleven healthy subjects (6 females) completed the study protocol. Their median (interquartile range, IQR) age, body mass, and height were 34 (13.5) years, 80 (20.5) kg, and 172 (17) cm respectively. Figure 2-1 illustrates the protocol and data from a representative subject. Data from all subjects are shown in Figure 2-2. Baseline parameters and individual responses to increasing cycling intensity varied between subjects.

*Hemodynamics:* All data are reported as mean ± standard deviation. Across subjects, increase in cadence from 0 to 55 RPMs resulted in a modest 7% increase in MAP (from 94.7±2.7 to 101.2±3.3 mmHg, p=0.024), but had no effect on HR (p=0.128), SVI (p=0.679), CI (p=0.551) or TPRI (p=0.366). During the recovery period, MAP remained elevated compared to baseline at 101.3±3.3 mmHg (p=0.016).

*Cerebral blood flow:* The CBF response to increasing cadence varied between subjects, increasing by a maximum of 6% starting at 5RPMs in one subject, and decreasing by up to 10% at higher RPMs in others. In two subjects, MCAv increased by more than 5% from baseline at higher RPMs, and continued to increase or remained above the baseline during the recovery stage. There were no statistically significant changes in the mean MCAv across subjects with increase in cadence (p=0.711), which may have been due our small sample size and the heterogeneity of responses.

*Cardiac function:* There were no changes in mean contractile function of the left ventricle whether assessed using ejection fraction (p=0.999) or global longitudinal strain (p=0.984). Two subjects showed worsening of cardiac function at higher RPMs (increases ranging from 1-16% GLS from baseline), which recovered to normal with rest during the last protocol stage.

*Heterogeneity of responses:* Although we only studied eleven subjects, we noted that their hemodynamic, CBF and cardiac function responses to graded passive cycling can be grouped into three patterns (Figure 2-3). In response to increased cadence, most subjects (n=6)

demonstrated no changes in any of the measured parameters. However, two subjects showed a dose-dependent reduction in cardiac index due to a decrease in SVI with increasing cadence. This decrease in cardiac index was accompanied by an increase in MAP due to an increase in TPRI, with no change in MCAv. In three subjects, we observed a biphasic trend in the hemodynamic parameters, with an initial, albeit small, decrease in cardiac index due to decreased heart rate at lower RPMs, followed by an increase in HR, SVI and CI at higher RPMs. MAP followed changes in cardiac index due to an absence of change in TPRI. These changes were accompanied by a decrease in mean MCAv by 6% at peak PC intensity in one subject, returning to baseline with recovery.
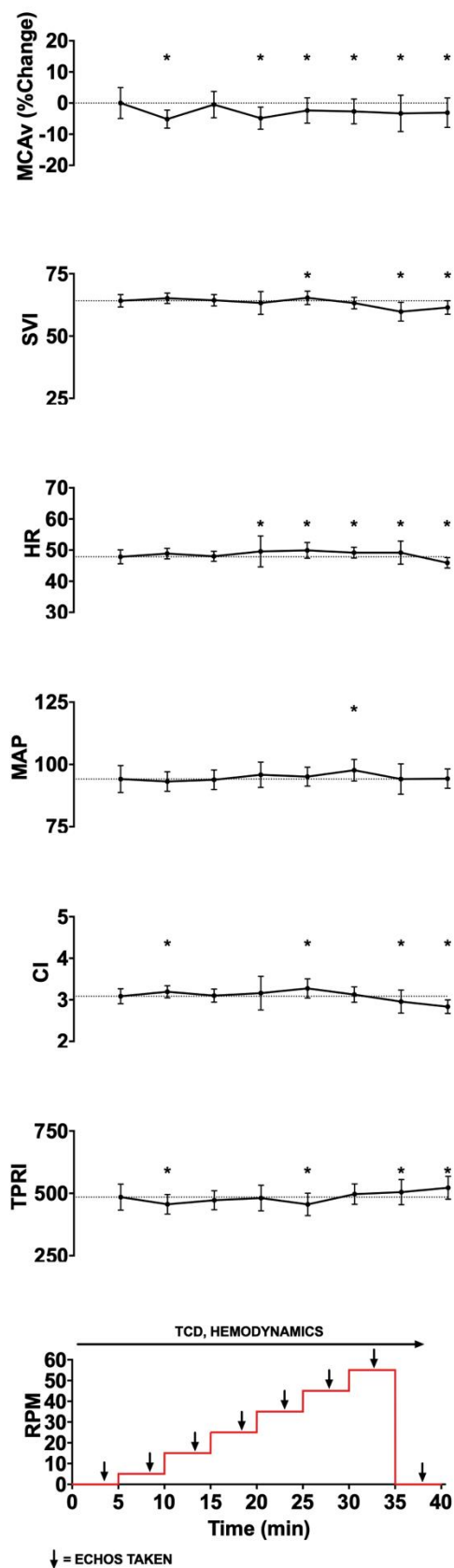
**Figure 2-1.** Experimental data showing changes in middle cerebral artery blood flow velocity (MCAv, % change from baseline, cm/s), stroke volume index (SVI, mL/m$^2$/beat), heart rate (HR, beats per minute), mean arterial pressure (MAP, mmHg), cardiac index (CI, L/min/m$^2$), total peripheral resistance index (TPRI, mmHg /m$^2$·L·min), global longitudinal strain (GLS), and ejection fraction (EF) with increasing cycling cadence from a representative subject. The bottom panel illustrates experimental protocol, with eight 5-minute stages starting from 0 RPM baseline, then increasing from 5 to 55 RPMs in increments of 10 RPM, and followed by 0 RPM recovery stage. Monitoring of cerebral blood flow using transcranial doppler (TCD) and hemodynamics occurred continuously, while cardiac function was assessed using transthoracic 2D-echocardiography during the last 2 minutes of each stage. To allow for stabilization following change in cadence, data from the last 2 minutes of each experimental stage was averaged for continuously monitored variables and is shown as mean and standard deviation. Given that angle of insonation may affect absolute MCAv, and that these angles can vary between subjects, we standardized within subject MCAv values by expressing them as percent change from subject's resting baseline value.
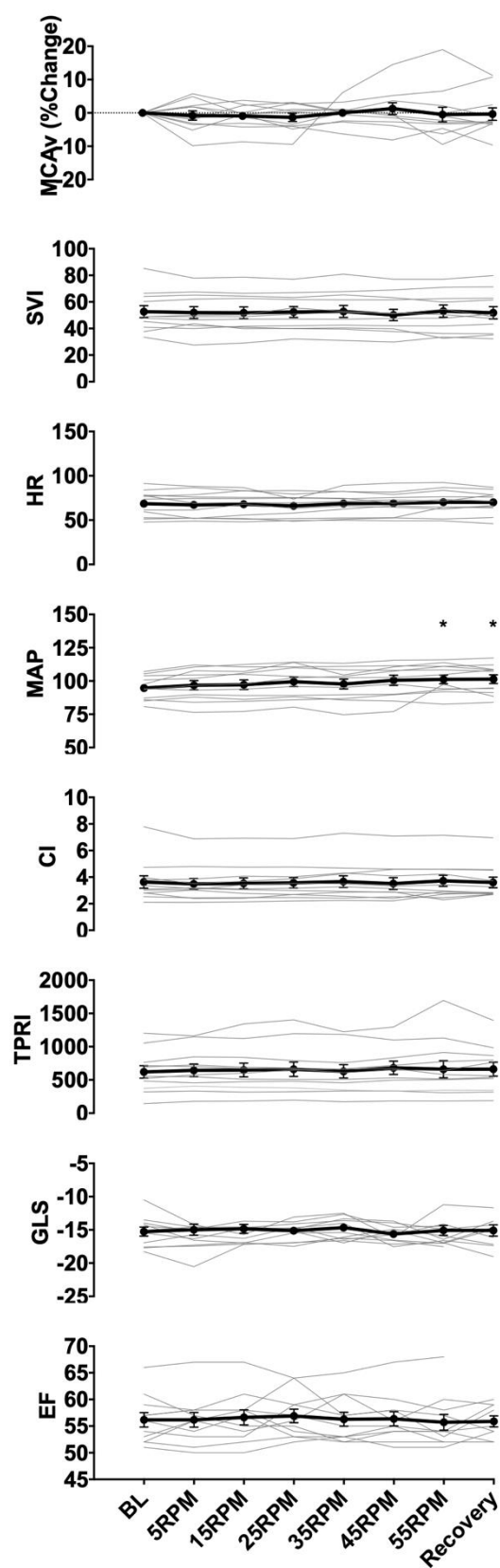
**Figure 2-2.** Group data showing changes in middle cerebral artery blood flow velocity (MCAv), stroke volume index (SVI), heart rate (HR), mean arterial pressure (MAP), cardiac index (CI), total peripheral resistance index (TPRI), global longitudinal strain (GLS), and ejection fraction (EF) with increasing cycling cadence. Average values across all subjects for all measured parameters are illustrated by the data points, with error bars representing the standard error of the mean. No significant changes were seen in MCAv, GLS. EF, and the majority of the hemodynamic parameters (SVI, HR, CI, TPRI), however, there was a significant increase in MAP from baseline at 55RPMs and recovery (0RPM) (p=0.024, and p=0.016, respectively). * indicate $p < 0.05$ as measured with repeated measures ANOVA.
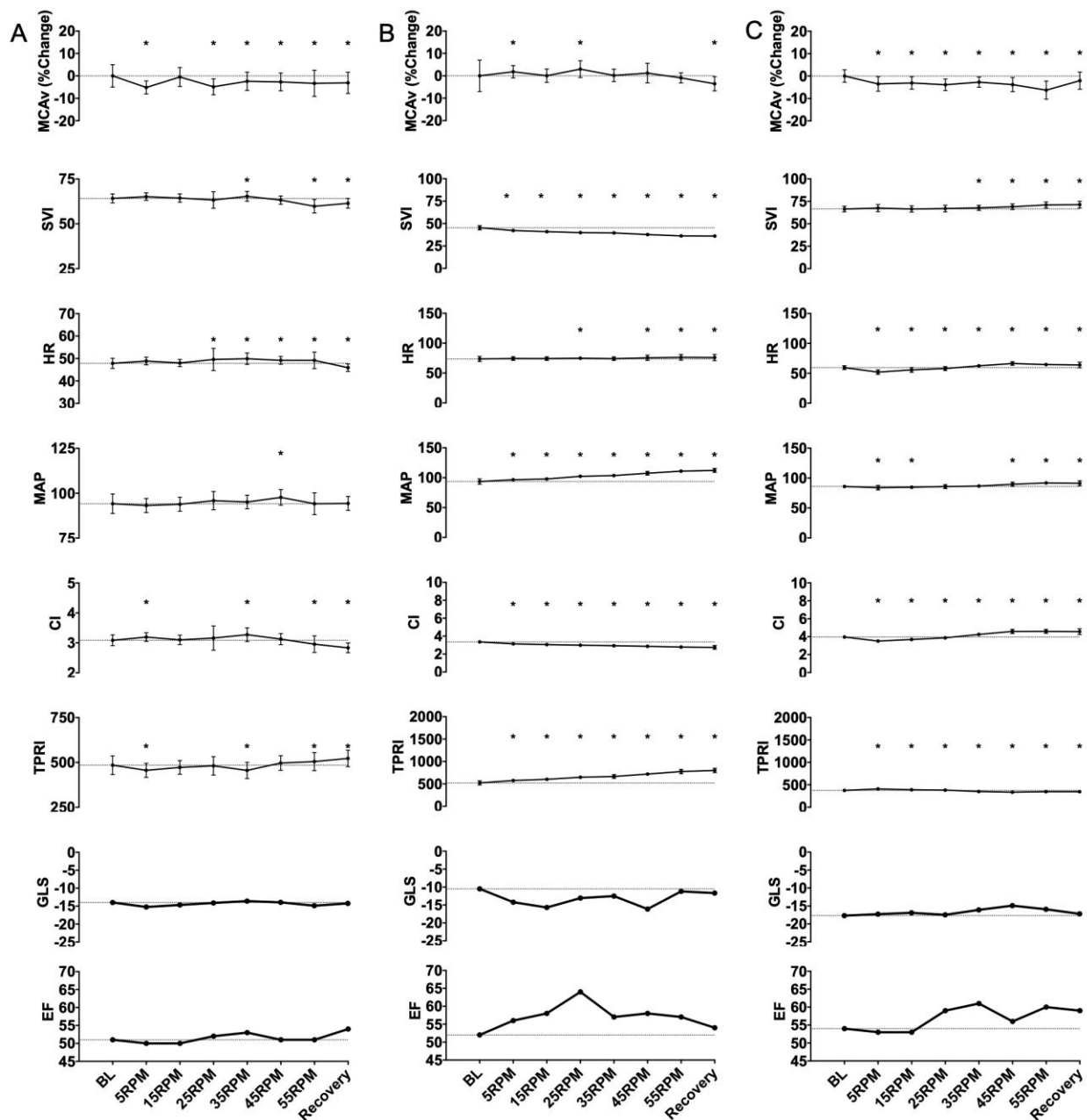
**Figure 2-3.** Representative subject data illustrating three patterns of responses to graded passive cycling. Panel A: Data from a subject with no change in any measured parameters. Panel B: Data from a subject that had decrease in stroke volume index (SVI) and corresponding increase in mean arterial pressure (MAP) and total peripheral index (TPRI), with no change in middle cerebral artery blood flow velocity (MCAv). Panel C: Data from a subject with biphasic response characterized by initial decrease in MAP, heart rate (HR) and cardiac index (CI), followed by increase in these parameters at higher cycling intensities.

## 2.4  Discussion

*Main findings:* This is the first study examining the effect of graded passive in-bed cycling on global hemodynamics, CBF and cardiac function in a group of healthy subjects. We demonstrated that increasing passive cycling cadence had no effect on mean CBF, cardiac function or hemodynamics, apart from a small dose-dependent increase in the mean arterial pressure. However, within individuals we found significant heterogeneity in the responses, with some subjects experiencing a reduction in cardiac index, CBF and cardiac function, especially at higher cadence. Although the magnitude of these changes was small, occurring inconsistently in a few subjects, they raise the concern that such responses may be augmented and more frequent in critically ill patients who have exhausted their hemodynamic reserve and have impaired adaptive mechanisms (e.g. cerebral autoregulation). Furthermore, the dose response varied between subjects, suggesting that it may be necessary to individualize the passive cycling prescription when this intervention is applied in critically ill patients.

*Hemodynamic changes*: Consistent with the results of prior studies, we demonstrated an increase in mean arterial pressure with the increase in cycling cadence. Two studies utilizing a tandem bike (10,11) and one cycle ergometer (12) study showed that upright cycling at 40 and 60 RPMs for five minutes increases mean arterial pressure.  Only one study (11) reported the actual magnitude of the increase in the mean arterial pressure, which was greater than that seen our study (14% vs 7% respectively). However, unlike our study that showed a dose-dependent increase in MAP with higher cadence, mean arterial pressure did not change from 40 to 60 RPMs (11).

Although cardiac index remained constant across our subjects, prior studies using tandem bike (10,11) and cycle ergometer (12) showed increase in cardiac output via increase in either heart rate (10) or stroke volume (11,12). However, in contrast to these prior studies employing one level of cycling intensity in upright posture, we studied supine subjects and used a graded increase in cadence from 0 to 55 RPMs, which may explain the difference from our results. The effects of posture on the observed cardiac output changes is unclear, since passive range of motion studies showed both increases (13–15) and no change (14,16,17) in cardiac output irrespective of posture. In keeping with prior findings, some (n=2) of our subjects showed trends

of dose-dependent reduction in cardiac index with increasing cadence, while others (n=3) showed a small increase in cardiac index at higher RPMs. The reasons for these differences are unclear, but highlight the variability of responses to the same dose of passive cycling across subjects. Another aspect that may modulate the hemodynamics we observed is the ventilatory response to changes in PC cadence (18). Changes in tidal volume may alter the sympathovagal balance affecting cardiac output and systemic blood pressure, and this response is likely to vary between individuals.

*Cerebral blood flow changes*: Increasing cadence of passive supine cycling has no effect on MCAv in healthy subjects; despite increases in mean arterial pressure, suggesting that cerebral autoregulation was intact. In one prior study (19), passive range of motion exercise of the lower and upper limbs resulted in a 3.4% and 4.6% increase in MCAv, respectively, which was attributed to neuronal mechanisms mediated through stimulation of carotid body chemoreceptors (19). Despite the differences between our findings and prior studies, the magnitude of MCAv changes in both studies are small, and the significance of these findings in critically ill patients remains to be determined.

*Cardiac function*: This is the first study that measured left ventricular contractile function during increasing intensity of passive cycling in healthy subjects. Between subjects, there was no change in either left ventricular ejection fraction or global longitudinal strain. At the individual level, however, we observed impairment in contractile function at higher cadence in two subjects using global longitudinal strain and in one subject using ejection fraction. Since longitudinal myocardial fibres are located predominantly in the subendocardium, which is the myocardial wall layer farthest away from epicardial coronary vessels and therefore most susceptible to ischemia, global longitudinal strain may detect ischemia prior to reduction in ejection fraction (20).

The reason for the observed changes in our healthy subjects is unclear, and while myocardial ischemia is one possible explanation, this warrants further investigation. Given the high prevalence of cardiac dysfunction in the critically ill (21), impairment in contractile function

with passive cycling is an important consideration for future studies, especially if higher cycling intensities are utilized.

*Heterogeneity of response*: The observed heterogeneity of hemodynamic, CBF and cardiac responses in our small cohort of healthy subjects has important implications for future studies in the critically ill. First, while our study examined the impact of cycling intensity on outcomes, it did not explore other exercise dose parameters (duration, frequency), as well as their interaction. Second, we did not explicitly study whether the observed responses in our study are affected by subject age, pre-existing comorbidities, or baseline fitness, all of which are likely to be variable in the critically ill. Translation of this work into critical care arena, therefore, should include assessment of the relative impact of exercise dose parameters (intensity, duration and frequency) on observed outcomes, and whether these responses are affected by patient baseline factors including age, comorbidities and fitness. Such approach would allow informed prescription of personalized passive cycling interventions in individual patients, and help identify safe, yet effective, training plans akin to those currently used with active exercise in healthy adults (22).

*Exercise dose:* In the present study, we studied only one parameter of passive exercise dose: cycling intensity, or cadence. This was done intentionally to assess the relative impact of this parameter on observed outcomes. Future dedicated studies should examine the relative impact of other parameters of passive exercise dose (duration and frequency), and their interaction with each other and with exercise intensity.

## 2.5  Conclusion

In healthy subjects, graded increases in PC has heterogeneous effects on cerebral blood flow, cardiac function and global hemodynamics. The only consistent change across subjects was a small increase in MAP with increasing cadence, but its clinical significance is unclear and warrants further study. Reduction in cardiac function with higher cadence in some of our subjects is concerning, and questions the presumed safety of passive in-bed cycling. If this is confirmed in the critically ill patients, it may warrant individualized prescription of exercise dose in these hemodynamically vulnerable patients.

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# CHAPTER 3: Graded passive biking in subjects with sepsis

## 3.1 Introduction

Sepsis is associated with short- and long-term complications including physical and cognitive impairment (1,2). Although early active mobilization is associated with improvement in peripheral strength at hospital discharge (3,4) and shorter delirium duration (5), many patients are unable to participate in active mobilization during earlier stages of critical illness due to decreased level of consciousness and ventilator dependence. In these patients, passive exercise has been reported as a safe and feasible method to incorporate mobilization early in the course of their ICU stay (6), and is also associated with improved patient motivation during recovery following critical illness (7). However, prior studies that assessed the safety and feasibility of early mobilization protocols in critically ill patients have primarily done so by confirming the stability of global hemodynamic variables and minimal adverse events (3,8). The impact of passive exercise on perfusion of ischemia-prone organs, such as the brain and the heart, remains unknown in critically ill patients.

In this study, we assessed the impact of graded passive cycling on global hemodynamics, cerebral blood flow and cardiac function in a cohort of septic patients. Given that early sepsis is associated with hemodynamic instability (9), tenuous organ perfusion (10) and impaired cerebral autoregulation (11), it is important to confirm that graded passive cycling does not result in impaired perfusion and function of ischemia prone organs prior to wide implementation of this promising intervention in critically ill patients.

## 3.2 Materials, Methods, and Protocol

The materials and methodology used were the same as the general methodology previously listed in Chapter 1.5. Septic patients categorized using Sepsis-3 criteria (acute increases in total Sequential Organ Failure Assessment scores of $\geq 2$ points due to an infection (12)) were consecutively recruited at the Critical Care Trauma Centre in Victoria Hospital, a part of the LHSC, in London, Ontario.

## 3.3 Results

*Patient demographics:* Ten septic patients (4 females and 6 males) were enrolled and all patients successfully completed the study protocol. The median (IQR) age, body mass (kg), and sequential organ failure assessment (SOFA) score were 56.5 (7.8), 82 (31), and 7.5 (3.4) respectively. At the time of enrollment, all patients were intubated, 6 (60%) were treated with vasopressors, and 8 (80%) received sedation with propofol, hydromorphone, fentanyl, or a combination of these three sedatives. The median (IQR) duration from patients' ICU admission to participation in passive cycling was 2 (2) days. Patient baseline characteristics are summarized in Table 3-1.

*Hemodynamics:*

Figure 3-1 illustrates the experimental protocol used, which was previously tested for safety and feasibility in a healthy cohort (12), along with data from a representative subject. Averaged group trends are shown in Figure 3-2. All data are reported as mean ± standard deviation. Across patients, increasing cadence from rest (0RPM) to 55RPM did not change the MAP from baseline (p=0.057). There was, however, a 16% TPRI increase from baseline to 55RPM ($567\pm264$ to $658\pm298$ mmHg /$m^2$·L·min, p=0.008), which further increased to 18% ($667\pm308$ mmHg /$m^2$·L·min) during the recovery period. Passive cycling did not elicit changes in SVI, CI, HR, nor PP across experimental stages and patients, although there was substantial variability in the magnitude of hemodynamic responses between patients. At peak cycling intensity, three patients had a 13-19% increase in MAP and five patients had an 11-19% increase in PP compared to baseline. All five patients that had increases in PP also demonstrated increased TPRI.

**Table 3-1.** Patient characteristics of sepsis patients.

| Characteristic | n = 10 patients |
|---|:---:|
| Age in years, median (IQR) | 56.5 (7.8) |
| Males, n (%) | 6 (60) |
| Height in cm, median (IQR) | 170 (11) |
| Body mass in kg, median (IQR) | 82 (31) |
| Comorbidities, n (%) | |
|     Hypertension | 4 (40) |
|     Congestive heart failure | 2 (20) |
|     Atrial fibrillation | 2 (20) |
|     Pneumonia | 1 (10) |
|     COPD | 1 (10) |
|     Stroke | 1 (10) |
| SOFA score, median (IQR) | 7.5 (3.4) |
| Vasopressors, n (%) | 6 (60) |
|     Levophed | 6 (60) |
|     Vasopressin | 3 (30) |
|     Phenylephrine | 1 (10) |
|     Amiodarone | 1 (10) |
| Sedatives, n (%) | 8 (80) |
|     Propofol | 8 (80) |
|     Hydromorphone | 7 (70) |
|     Fentanyl | 1 (10) |
| Duration from ICU admission to conduction of passive cycling protocol in days, median (IQR) | 2 (2) |
| ICU LOS in days, median (IQR) | 16 (8) |
| ICU mortality, n (%) | 4 (40%) |
| Hospital LOS in days, median (IQR) | 22 (14) |
| Hospital mortality, n (%) | 4 (40%) |
| Duration of MV in days, median (IQR) | 10 (11) |

**Table 3-1.** This table summarizes patient demographics, and patient outcomes. Abbreviations: IQR = interquartile range, COPD = chronic obstructive pulmonary disease, SOFA = Sequential Organ Failure Assessment, a 6-item instrument with scores from 0-24, with higher scores indicating more severe organ failure, ICU = intensive care unit, LOS = Length of stay, MV = mechanical ventilation.
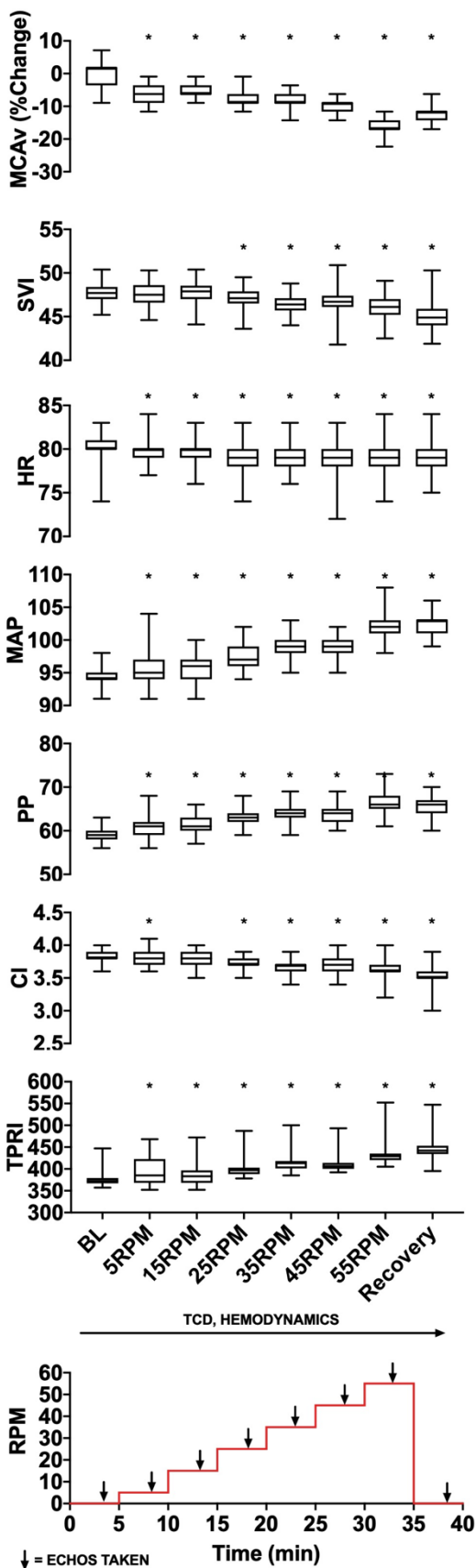
**Figure 3-1.** Experimental data from a representative patient showing changes in middle cerebral artery blood flow velocity (MCAv, % change from baseline, cm/s), stroke volume index (SVI, mL/m$^2$/beat), heart rate (HR, beats per minute), mean arterial pressure (MAP, mmHg), pulse pressure (PP, mmHg) cardiac index (CI, L/min/m$^2$), and total peripheral resistance index (TPRI, mmHg /m$^2$·L·min) with increasing cycling cadence. The bottom panel illustrates the experimental protocol, with eight 5-minute stages starting from 0 RPM baseline, then increasing from 5 to 55 RPMs in increments of 10 RPM and followed by 0 RPM recovery stage. Monitoring of cerebral blood flow using transcranial doppler and hemodynamics occurred continuously, while cardiac function was assessed using transthoracic 2D-echocardiography during the last 2 minutes of each stage. The median, lower quartile, upper quartile, and the min and max are illustrated describing values from a single patient. MCAv values are standardized and expressed as percent change from subject's resting baseline value, because the angle of insonation may affect absolute MCAv and these angles can vary between subjects. * indicates $p < 0.05$ as measured with repeated measures ANOVA.
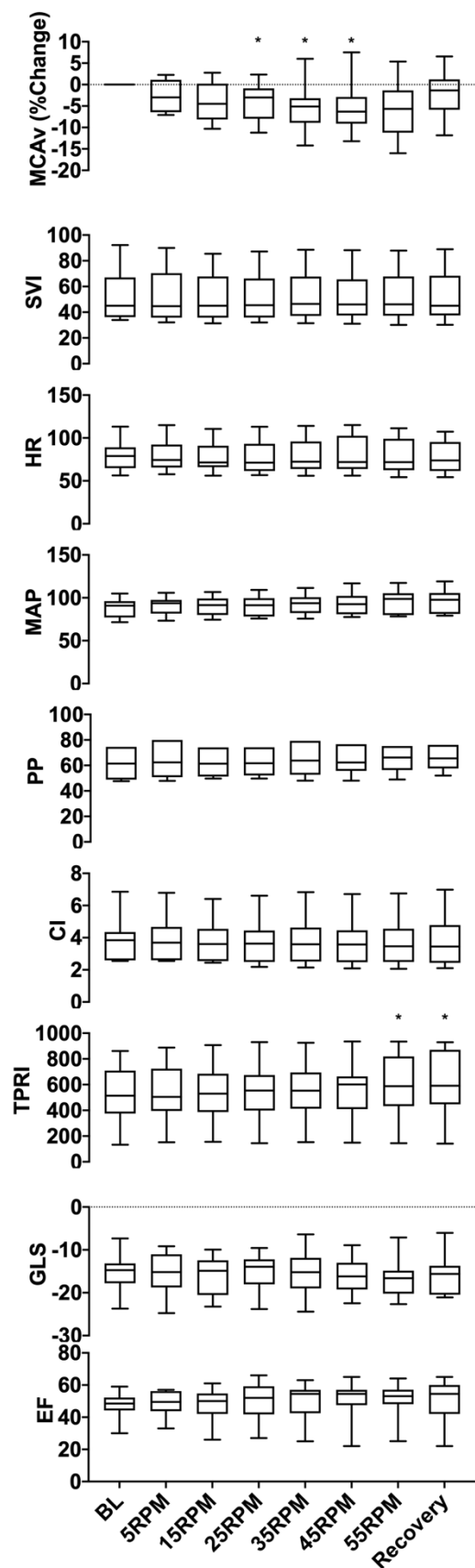
**Figure 3-2.** Group data showing changes in middle cerebral artery blood flow velocity (MCAv), stroke volume index (SVI), heart rate (HR), mean arterial pressure (MAP), pulse pressure (PP), cardiac index (CI), total peripheral resistance index (TPRI), global longitudinal strain (GLS), and ejection fraction (EF) with increasing cycling cadence. The box plots represent values averaged at each passive cycling stage, across all patients. A significant decrease was seen in MCAv between 25-45 RPM(p=0.004), while an increase in TPRI was observed at 55RPM (p=0.008) which persisted throughout the recovery period. No significant changes were seen in the remaining hemodynamic parameters (SVI, HR, MAP, PP, CI, and TPRI), nor in either assessment of cardiac function (GLS and EF). * indicates p<0.05 as measured with repeated measures ANOVA.

*Cerebral blood flow:* Across patients, an increase in cadence was associated with a $5.2 \pm 1.4\%$ reduction in MCAv from baseline between 25-45 RPM (p=0.004). The MCAv increased back towards baseline values during recovery. The magnitude of MCAv response varied across patients. In 8/10 patients, an increase in cadence resulted in a dose-dependent and statistically significant decrease (p<0.005) in MCAv from baseline, and in four of these patients MCAv decreased by 10-16% from baseline at higher cycling intensities (35-55RPM). These reductions in MCAv occurred on the background of stable MAP. In one patient, we observed a dose-dependent increase in MCAv ($7.5 \pm 2.9\%$ at 45RPM) that was associated with a dose-dependent increases in MAP that peaked at 55RPM (P<0.0001, $78 \pm 1$mmHg). In another patient, we observed a biphasic response with the initial reduction ($-2.9 \pm 4.0\%$) in MCAv at lower cycling intensities, followed by increase in MCAv ($2.3 \pm 5.7\%$) at higher intensities of $\geq$ 45RPM. Based on a predetermined clinical importance cutoff of 10% change in MCAv from baseline, 4 (40%) patients had clinically important decreases of 10-16% from baseline, with the mean change of $10 \pm 9\%$ at peak cycling intensity.

*Cardiac function:* We did not observe a statistically significant change in cardiac function across patients in our cohort when using either EF (p=0.99) or GLS (p=0.99). However, upon inspection of individual patient responses, we identified two response patterns. Six patients demonstrated improvements in contractility, with lower (19-51%) GLS versus baseline, while four patients demonstrated worsening cardiac function with increased (12-31%) GLS versus baseline. The cadence at which these changes in GLS occurred varied across patients, ranging from 5 to 45 RPMs.

## 3.4  Discussion

This is the first study examining the effect of graded passive in-bed cycling on global hemodynamics, cerebral blood flow, and cardiac function in septic patients. We demonstrated that increasing passive cycling cadence is associated with a statistically significant reduction in cerebral blood flow from baseline that exceeded 10% in 4 of 10 patients in our cohort. The impact of passive cycling on cardiac function varied across patients, with six patients demonstrating improvement and four patients demonstrating worsening of left ventricular contractile function as measured by GLS. These changes occurred at variable cycling cadence

across patients and were not associated with changes in global hemodynamics except for dose-dependent increase in TPRI. Our data highlight the variability of individual patient responses to the same exercise stimulus and call into question the safety of a one-size fits all approach to passive cycling dose prescription in septic patients.

*Hemodynamics:* We showed that in septic patients graded passive cycling is associated with an increase in peripheral resistance, with no changes in other hemodynamic parameters. This contrasts previous findings from healthy participants which used a similar passive cycling protocol, in which increases of MAP occurred without a change in peripheral resistance (12). Given that sepsis is associated with peripheral vasodilation, the observed increase in peripheral resistance in our septic cohort likely represents improved vasomotor tone as a result of passive cycling intervention. In a previous study of septic patients, 20 minutes of passive cycling at 30 RPM had no effect on peripheral resistance (13). The different result in our patients may reflect the longer duration (35 minutes) or higher cadence (10 minutes at RPM $\geq$ 45) employed in our protocol. While in our study the increase in peripheral resistance was not associated with an immediate decrease in vasopressor requirements, future studies should evaluate if repeated passive cycling leads to lower vasopressor requirements and more vasopressor-free days.

*Cerebral blood flow:* Increasing cadence of passive cycling resulted in a dose-dependent decrease in MCAv in most patients, with a greater than 10% reduction in a subset of patients. These changes in MCAv were not associated with changes in MAP, suggesting that factors other than perfusion pressure may influence CBF in septic patients. These results are in contrast to our findings in healthy participants, where passive cycling using the same protocol did not impact CBF despite a small increase in MAP at peak cadence (12). Our findings also contrast previous studies of healthy participants, where passive exercise has been associated with an increase in cerebral blood flow. Passive leg movement for 20s, followed by 20s of rest, repeated 10 times resulted in a 3% increase in MCAv (14). Passive cycling at 30 and 60 RPM were both associated with increases in regional blood flow. Given that passive cycling is associated with the increase in leg blood flow (15,16), and since cardiac index remained unchanged in our patients, the observed reduction in MCAv may represent vascular steal as a result of redistribution of blood flow from the brain to exercising extremities. While we cannot directly confirm this hypothesis

using our current data as we didn't measure leg blood flow, future studies should explore this relationship by directly comparing the magnitude of changes in leg and cerebral blood flow during passive cycling in septic patients. The clinical importance of the observed reduction in MCAv in our study is unclear. However, given high the prevalence of delirium and cognitive impairment in critically ill patients (2), as well as the high burden of ischemic lesions in septic patients (17,18), the observed reduction in MCAv is concerning and warrants further assessment and correlation with clinically relevant cognitive outcomes (1).

*Cardiac function:* The effect of graded passive cycling on cardiac function was variable across our patient cohort. Six patients showed improvement and four patients showed worsening in left ventricular contractility as measured by the global longitudinal strain. Global longitudinal strain is a more reproducible measure of left ventricular function (19) and offers better prognostic value than standard measurements such as ejection fraction (20), although it can be affected by loading conditions (21), age and sex (22). Since each patient served as their own control, the observed changes in global longitudinal strain are likely due to cycling induced changes in loading conditions, myocardial blood flow, sympathetic tone or neuroendocrine signaling. However, it is not clear why some patients had improvement and others deterioration in strain with increased cadence, and whether these changes are clinically relevant. While it is reassuring is that changes in contractile function resolved during the recovery period, the cumulative effect of these changes over the course of critical illness on clinical and functional outcomes in septic patients warrants further investigation.

*Heterogeneity of responses***:** An important observation in our study is that hemodynamic, cerebral blood flow and cardiac responses to passive cycling varied between individual patients in terms of magnitude, direction of change and the cycling cadence at which these changes occurred. This highlights the fact that, similar to regular exercise in healthy humans (23), a one-size fits all approach to passive cycling in critically ill patients may not be appropriate. Variable magnitude of the responses suggests that some patients may yield greater benefit (or sustain more harm) than other patients. Variable direction of the cardiac function response highlights that the same exercise paradigm may improve or worsen cardiac function in different patients. Finally, the exercise intensity (cadence) threshold for eliciting a given response differs between

patients, which suggest that future clinical trials should individualize exercise dose prescription in each patient. While our study focused on adjusting exercise intensity, future work should assess the impact of changing exercise duration and frequency on measured parameters.

## 3.5 Conclusion

In septic patients, graded passive cycling is associated with dose-dependent decreases in cerebral blood flow, increases in total peripheral resistance, and variable improvement or worsening of left ventricular function. The magnitude and cadence threshold of these responses vary between patients. Future studies should establish whether these changes are associated with clinical outcomes including cognitive impairment, vasopressor use, and functional outcomes.

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# CHAPTER 4: Summary, Contributions, Limitations, and Future directions

The purpose of this chapter is to summarize the findings of this thesis, outline the contributions of the findings from this thesis, address limitations of the research, and identify future directions for the field of research that can further improve the practice of early passive cycling in critically ill patients.

## 4.1   Summary and Conclusions

This thesis was motivated to facilitate a greater understanding of both passive exercise dosage, and impact of passive exercise on organ perfusion in critically ill septic patients as recommended by prior literature (1–3) in order to improve delivery of early passive exercise in critically ill patients. To do so, this thesis was comprised of two studies, the first which was an exploratory study to determine the safety and feasibility of a graded passive cycling protocol developed with intention for application in critically ill patients, and the second which was a pilot study for the application of the passive cycling protocol in a cohort of early admission septic patients.

In order to address our first objective of developing a passive cycling protocol that that would be able to mobilize critically ill septic patients throughout a range of cycling intensities despite barriers to mobilization present including patient sedation, ventilation, and vasopressor use, a graded passive cycling protocol was developed in collaboration between Dr. Christopher McIntyre, Dr. Marat Slessarev, and myself. Afterward, this protocol was applied in a cohort of healthy adults to assess its safety and feasibility in this control cohort. The application of the passive cycling protocol in healthy adults was deemed feasible and was well tolerated in all participants, which was consistent with our hypothesis. Furthermore, we found the graded increase in cycling speed elicited a small increase in mean arterial pressure (MAP) across subjects, despite a lack of group-wide changes in any other hemodynamic parameters, cerebral blood flow, nor cardiac function parameters. Additional inspection of individual subject responses unearthed response patterns between subjects, which demonstrated heterogeneous

response between subjects despite exposure to the same passive cycling protocol. The change in MAP contradicted our hypothesis, but was supported by two studies which used tandem bike mobilization and another which used a cycler ergometer. Ultimately, given the passive nature of the mobilization procedure, the changes in MAP observed highlight the impact of interpersonal heterogeneity on outcomes following passive mobilization, which has been previously observed in healthy adult males stratified by age and fitness (4–6).

To address the second objective of applying the previously developed passive cycling protocol in a cohort of septic patients, ten consecutive septic ICU patients were enrolled to take part in our study. The protocol was used to perform passive mobilization in critically ill septic patients, in which we similarly evaluated hemodynamic, cerebral blood flow, and cardiac function in response to passive cycling. Although evaluation of hemodynamic stability in critically ill patients is commonplace (7), particularly during a hemodynamically challenging event such as mobilization (8), assessment of ischemia-prone organs during early mobilization is infrequent. As we hypothesized, the passive cycling protocol was feasible in our septic cohort, with an 100% completion rate in all patients enrolled. Also in agreement with our hypothesis of change in patient parameters as a result of the passive cycling protocol, in our septic cohort we found we found dose-dependent decreases in cerebral blood flow and increases in total peripheral resistance with variable outcomes on left ventricular function. Similar to prior findings in healthy subjects, individual responses varied between patients, with differing exercise intensity thresholds prior to eliciting changes in measured parameters. As a result of these findings, it is likely insufficient to merely ascertain safety and feasibility of early passive exercise in critically ill patients through monitoring of hemodynamic stability and adverse events (9–11). Our findings of decreased cerebral blood flow, and reduced cardiac contractility in a portion of our septic cohort suggest that early, graded passive cycling may have detrimental consequences on ischemia-prone organs in patients with elevated risk of multi-organ failure (8). The results of this thesis will provide guidance towards the implementation of passive mobilization in critically ill patients, particularly regarding an increased need to evaluated peripheral impact of mobilization procedures used.

## 4.2   Contributions

This thesis is the first study to assess the impact of graded passive cycling on hemodynamics, cerebral blood flow, and cardiac contractility in both healthy subjects, and patients with sepsis. Findings of heterogenous response patterns with respect to cerebral blood flow velocity and hemodynamic measurements in healthy adults raises worry regarding the heterogeneity in response patterns that may be present in critically ill patients as well, in which this may present a greater danger due to increased patient risk of hemodynamic instability. This apprehension was confirmed in our findings of varying response to passive cycling at differing cycling intensities, and was further emphasized by findings of reduced cerebral blood flow velocity at higher passive cycling intensities in septic patients. Both of these findings in septic patients raise concern regarding the safety of this intervention at higher cycling intensities in this patient population.

## 4.3   Limitations

Given the exploratory nature of both studies, our sample sizes were limited. As a result, our findings should be interpreted with caution, and future studies in healthy subjects and septic patients with a larger sample size can explore whether our findings are affected by variation in age, gender, baseline fitness level or comorbidities. The small sample size in our study limits the analysis of the results with respect to important covariates including patient age, sex, baseline health and fitness, comorbidities, and severity of illness. Future properly powered studies can explore these relationships further.

We did not collect detailed information about prior training, but our healthy cohort were drawn from the healthy population and excluded competitive athletes or sedentary or mobility-limited individuals, and our septic included enrollment of 10 consecutive septic patients. Future adequately powered studies should explore whether age or prior training have impact on observed responses.

We used transcranial Doppler to measure middle cerebral artery blood flow velocity as an indicator of global cerebral blood flow. This approach assumes that the diameter of the intonated vessel remains constant (12), which has not been confirmed in these experimental settings. Furthermore, transcranial Doppler does not allow assessment of the changes in regional cerebral blood flow (13), which would require advanced tomographic techniques such as computed

tomography or magnetic resonance imaging. However, given that we aimed to study critically ill patients early in the course of their illness when they are less likely to tolerate transport to medical imaging department, transcranial Doppler offered a safer alternative that allowed us to monitor changes in global cerebral blood flow with high temporal resolution at the patients' bedside.

Speckle-tracking echocardiography was used to determine cardiac function through assessment of subject ejection fraction and global longitudinal strain. However, the technique presents limitations given its operator-dependent use (14), and potential for suboptimal tracking of the endocardial border (15). To address these concerns, all echocardiograms were acquired by a trained echocardiographer, and suboptimal tracking through the provided software was minimized through manual delineation of the endocardial border.

Furthermore, our graded exercise protocol was structured as a stepwise ladder pattern, starting at 5 RPM and increasing to 55 RPMs, with 5 minutes at each stage. The 5-minute duration was chosen based on prior passive cycling or passive range of motion exercises studies (16–20), to allow equilibration of measured parameters after increase in cycling intensity. However, the stepwise ladder design may result in persistent effects, where intervention response builds from one stage to the next without an adequate recovery period. Whether the protocol design affects the observed results is unknown, but this was beyond the scope of our studies.

## 4.4  Future directions

While our study focused on adjusting exercise intensity, future work should explore the relationships between other aspects of passive exercise dosage (e.g. duration, and frequency) on hemodynamics, CBF, cardiac function, and functional outcomes in the critically ill patients, and determine whether patient or illness specific factors influence these relationships. These studies can also determine whether response patterns identified in healthy individuals in this study occur in the critically ill, report their incidence, and assess whether they are affected by variables such as age, fitness level, or pre-existing medical conditions.

Further investigation of patient specific responses to passive cycling is needed to ensure that this promising intervention is applied to the right patient at the right dose in order to maximize

benefit and prevent iatrogenic harm.  In septic patients, graded passive cycling was found to elicit variable magnitudes of change in cerebral blood flow, total peripheral resistance, and left ventricular function at variable cadence thresholds. Future studies should establish whether these changes are associated with clinical outcomes including cognitive impairment, vasopressor use, and functional outcomes.

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**Appendix A. Curriculum Vitae**

# Curriculum Vitae

Jennifer Chen

**Postsecondary Education**

Expected: 2021          **Advanced Diploma Candidate Cardiovascular Perfusion**
The Michener Institute of Education at UHN, Toronto, Ontario

Expected: 2020          **MSc Candidate Medical Biophysics**
The University of Western Ontario, London, ON
Supervisor: Dr. Christopher W. McIntyre

2013 – 2017          **BMSc Honors Specialization Pathology**
The University of Western Ontario, London, ON

**Scholarships and awards**

**Western Graduate Research Scholarship**
Western University, 2017

**Related Work Experience**
2016 - present          **Research Assistant**
Critical Care Trauma Centre
London Health Sciences Centre

**Presentations**

1. **Chen J**, Fiorini K, Zhou S, Martin C, McIntyre CW, Ball IM, Slessarev M. A scoping review of passive exercise in health subjects and ICU patients. ePoster presentation. *Critical Care Canada Forum 2019*. Toronto, Ontario, Canada.

2. **Chen J**, Martin C, McIntyre CW, Ball IM, Slessarev M. Effect of graded passive cycling on cerebral blood flow, cardiac function, and global hemodynamics in sepsis. ePoster presentation. *Critical Care Canada Forum 2018*. Toronto, Ontario, Canada.

3. **Chen J**, Tamasi T, McIntyre CW, Ball IM, Slessarev M. The effect of increasing passive cycling intensity on global hemodynamics, brain and heart perfusion in septic patients. Platform presentation. *London Health Research Day 2018*. London, Ontario, Canada.

4. **Chen J**, Tamasi T, McIntyre CW, Ball IM, Slessarev M. A model for assessing impact of graded passive exercise on global hemodynamics, brain and heart perfusion in septic patients: feasibility and safety study in healthy adults. ePoster presentation. *Critical Care Canada Forum 2017*. Toronto, Ontario, Canada.

**Peer-reviewed Publications**

1. **Chen J**, Martin C, McIntyre CW, Ball IM, Slessarev M. Impact of Graded Passive Cycling on Hemodynamics, Cerebral Blood Flow, and Cardiac function in Septic ICU Patients. *Accepted by Front Med.*
2. **Chen J**, Martin C, McIntyre CW, Ball IM, Duffin J, Slessarev M. Impact of Graded Passive Cycling on Hemodynamics, Brain, and Heart Perfusion in Healthy Adults. *Front Med* 2019;6:.
3. Honarmand K, Lalli RS, Priestap F, **Chen J**, McIntyre CW, Owen AM, Slessarev M. Natural History of Cognitive Impairment in Critical Illness Survivors: A Systematic Review. *Am J Respir Crit Care Med* 2020;doi:10.1164/rccm.201904-0816CI.