Neurocognitive impairment across the continuum of critical illness: exploration of acute insults, functional risk factors, and clinical monitoring tools.

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Abstract

Critically ill patients of all ages suffer from high burden of neurocognitive impairment during (i.e. delirium) and following (i.e. long term cognitive impairment) critical illness that is associated with worse patient and healthy system outcomes. Ischemia has emerged as a plausible mechanism given the high prevalence of hypotension and shock, ischemic injury on neuroimaging, and impairment of cerebral autoregulation in these patients. However, the burden of ischemic insults during critical illness and mechanisms responsible for these insults are poorly described. Furthermore, while baseline impairment in cerebrovascular function can render patients more vulnerable to ischemia, such baseline functional assessments in patients with high risk of critical illness have not been considered. Finally, the operational limitations of existing cognitive batteries preclude routine linkage of ischemic insults and baseline impairment in cerebrovascular function with neurocognitive outcomes. In this work we carried out three studies to address these knowledge gaps. In the first study, we showed that critically ill patients with respiratory failure or shock experience deviations in cerebral blood flow velocity consistent with ischemia or hyperemia for 17-24% of the observation time. These deviations occurred irrespective of the state of cerebral autoregulation and were not explained by concurrent changes in blood pressure or CO₂. These deviations represent a plausible ischemic insult that may explain high prevalence of ischemic injury in previous neuroimaging and histopathologic studies, and warrants further research to understand the underlying mechanism and link with neurocognitive outcomes. In the second study, we showed that hemodialysis patients have baseline impairment in cerebrovascular function prior to onset of critical illness, which may render them more vulnerable to ischemic injury during critical illness as a result of perturbation in cerebral blood flow shown in our first study. In our third study, we optimized an existing comprehensive web-based cognitive battery for monitoring cognitive outcomes in ICU patients, which should enable future linkage of ischemic insults and baseline impairment in cerebrovascular function from our first two studies with neurocognitive outcomes, as well enable routine clinical monitoring of cognitive recovery in ICU survivors.
Keywords

Cerebral blood flow, cerebral autoregulation, cerebrovascular reactivity, CO₂, intensive care unit, cognitive impairment
Summary for Lay Audience

Patients who are admitted to the intensive care units (ICU) often suffer from neurocognitive impairment both during and following their critical illness. During ICU stay, this neurocognitive impairment known as delirium is associated with increased risk of dying and prolongs the time that the patient stays on the ventilator and in hospital. Following discharge, many patients suffer from long-term cognitive impairment that can slow patient recovery and return to work and puts a huge burden on caregivers and society. Low brain blood flow during ICU stay is one potential mechanism that may be responsible for these neurocognitive impairments. However, the burden of low brain blood flow and responsible mechanisms are not well described. Furthermore, some patients may have impairment in the function of the brain blood vessels prior to ICU admission, which can make them more vulnerable to developing brain injury during critical illness. Finally, current cognitive tests that assess neurocognitive impairment are complex, expensive and take a long time, which makes it challenging to study the relationship between low brain blood flow and brain blood vessel function with neurocognitive impairment. In our first study, we showed that patients who are admitted to the ICU with low blood pressure or breathing failure spend up to one quarter of the time with low brain blood flow that is not counteracted by brain protective mechanisms. This may explain why many ICU patients develop brain injury and neurocognitive impairment. In the second study, we showed that dialysis patients have impaired baseline function of brain blood vessels prior to critical illness. This impairment can make them more vulnerable to brain injury during critical illness as a result of low brain blood flow that we showed in the first study. In the third study, we optimized an existing comprehensive web-based cognitive battery for monitoring neurocognitive outcomes in ICU patients. This tool will enable future studies of the relationship between low brain blood flow and brain blood vessel function with neurocognitive impairment, and routine clinical monitoring of cognitive recovery in ICU survivors.
Co-Authorship Statement

Chapter 4 has been adapted from the paper entitled “Feasibility of a web-based neurocognitive battery for assessing cognitive function in critical illness survivors” published in the PLoS One, 2019 by: Honarmand, Malik, Wild, Gonzalez-Lara, McIntyre, Owen, and Slessarev. Slessarev and McIntyre formulated the research idea and designed the study. Slessarev, Honarmand and Malik collected the data. Slessarev, Honarmand and Wild analyzed the data. Slessarev and Honarmand interpreted the data and prepared first manuscript draft. Each author contributed important intellectual content during manuscript drafting or revision and accepted accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.
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I want to thank my co-supervisor Dr Christopher McIntyre for teaching me the importance of always linking research questions back to the prevalent clinical problems, questioning established clinical dogmas and daring to create paradigm shifts in the clinical arena. His perseverance in the face of resistance, enthusiasm, will to innovate and conscious desire to push past boundaries in order to bridge research and innovation across disciplines embody the true essence of a clinician-scientist that I hope to emulate in my career.

I want to thank Dr Keith St Lawrence for his thoughtful critique and constructive suggestions as part of my advisory committee. I look forward to continued collaboration beyond my PhD, as we continue to investigate the nuances of cerebral perfusion and oxygenation in critically ill patients.

I want to thank my collaborators in the cognitive domain of this work including Professor Adrian Owen, Dr Kimia Honarmand, Ms Sabhyata Malik, Dr Conor Wild and Dr Laura E. Gonzalez-Lara for their expertise, insights, and interpretation of our cognitive results.

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<tr>
<td>Afib</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>APACHE II</td>
<td>Acute Physiologic Assessment and Chronic Health Evaluation II</td>
</tr>
<tr>
<td>ARDS</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>CAD</td>
<td>Coronary artery disease</td>
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<tr>
<td>CBF</td>
<td>Cerebral blood flow</td>
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<tr>
<td>CBFv</td>
<td>Cerebral blood flow velocity</td>
</tr>
<tr>
<td>CBS</td>
<td>Cambridge Brain Sciences cognitive battery</td>
</tr>
<tr>
<td>CHF</td>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
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<tr>
<td>CO</td>
<td>Cardiac Output</td>
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<tr>
<td>CO2</td>
<td>Carbon dioxide</td>
</tr>
<tr>
<td>CPP</td>
<td>cerebral perfusion pressure</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CVP</td>
<td>central venous pressure</td>
</tr>
<tr>
<td>CVR</td>
<td>Cerebrovascular reactivity to CO2</td>
</tr>
<tr>
<td>DBP</td>
<td>Diastolic Blood Pressure</td>
</tr>
<tr>
<td>DM</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
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<tr>
<td>HD</td>
<td>Hemodialysis</td>
</tr>
<tr>
<td>HR</td>
<td>Heart Rate</td>
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<tr>
<td>ICP</td>
<td>intracranial pressure</td>
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<tr>
<td>ICU</td>
<td>Intensive care unit</td>
</tr>
<tr>
<td>MAP</td>
<td>Mean arterial pressure</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-Mental State Examination</td>
</tr>
<tr>
<td>MODS</td>
<td>Multiple organ dysfunction syndrome score</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>Mxa</td>
<td>Index of dynamic autoregulation calculated from CBFv and MAP</td>
</tr>
<tr>
<td>NEMS</td>
<td>Nine equivalents of nursing manpower score</td>
</tr>
<tr>
<td>NIRS</td>
<td>Near infrared spectroscopy</td>
</tr>
<tr>
<td>PaCO2</td>
<td>Arterial partial pressure of CO2</td>
</tr>
<tr>
<td>PaO2</td>
<td>Partial pressure of arterial O2</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PetCO2</td>
<td>end-tidal partial pressure of CO2</td>
</tr>
<tr>
<td>PetO2</td>
<td>end-tidal partial pressure of O2</td>
</tr>
<tr>
<td>PRx</td>
<td>index of dynamic autoregulation estimated from ICP</td>
</tr>
<tr>
<td>RBANS</td>
<td>Repeatable Battery for the Assessment of Neuropsychological Status</td>
</tr>
<tr>
<td>R&lt;sub&gt;CV&lt;/sub&gt;</td>
<td>cerebrovascular resistance</td>
</tr>
<tr>
<td>SBP</td>
<td>Systolic Blood Pressure</td>
</tr>
<tr>
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<td>-------------------------</td>
</tr>
<tr>
<td>SOFA</td>
<td>Sequential Organ Failure Assessment score</td>
</tr>
<tr>
<td>TCD</td>
<td>Transcranial Doppler</td>
</tr>
<tr>
<td>WMH</td>
<td>White matter hyperintensities</td>
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</table>
Chapter 1

1 General Introduction

1.1 Neurocognitive impairment across a continuum of critical illness

Critical illness related neurocognitive impairment comprises a spectrum of acute and long-term disorders that occur during or following admission to the intensive care unit. Excluding direct injury to the brain as a result of trauma or large stroke, it can broadly present as coma, delirium or long-term cognitive impairment. Regardless of the presentation, neurocognitive impairment during critical illness has important consequences for patient, their families and caregivers, the healthcare system, and the broader society.

At the patient level, acute neurocognitive impairment (e.g. delirium) is associated with increased risk of dying and development of long-term cognitive impairment, which in turn impedes patients’ functional recovery and affects their quality of life. For families and caregivers, the newly acquired cognitive disabilities and functional dependency in their loved ones translate into significant psychological and emotional stress and financial burden, loss of employment, lifestyle interference and low health-related quality of life. At the healthcare system level, delirium is associated with increased length of mechanical ventilation and increased length of stay, which translate into higher healthcare costs, while at societal level long-term cognitive impairment prevents previously able economically active people from returning to the workforce, placing the burden of the care and sustenance on their families, caregivers and the state.

Given ageing of the global populations and increase in the number of intensive care unit (ICU) survivors due to projected increase in the incidence of critical illness and reduction in ICU mortality, the consequence of critical illness related neurocognitive impairment represent a public health problem that requires urgent and innovative solutions. In the current chapter, we will review the current body of knowledge related to acute (delirium) and long-term cognitive impairment, examine potential mechanisms that
may be responsible for this dysfunction, and identify current knowledge gaps that will be addressed in this body of work.

1.1.1 Terminology and definitions

ICU-related neurocognitive impairment can be broadly classified into coma, delirium and long-term cognitive impairment. In order to understand the differences between these states, it is important to consider two primary neurologic functions: 1) arousal or wakefulness, and 2) awareness of self and the environment. Arousal is anatomically localized to reticular activating system – a network of neurons that projects from brainstem to thalamus and cerebral cortex and is responsible for mediating arousal and sleep wake cycles. Awareness requires function and interplay of multiple cognitive domains including perception, attention, memory and executive function. Impairments in these two neurologic functions give rise to neurocognitive syndromes in critical illness.

In the acute critical care settings, a number of terms have been used to describe neurocognitive impairment including delirium, encephalopathy and sepsis-associated encephalopathy. Delirium was defined in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV as the disturbance in consciousness with inattention that develops over a short period of time due to a general medical condition and is not explained by pre-existing, established or evolving dementia. In the recent revision of this manual (DSM-V), the reference to consciousness was replaced with disturbance in attention and awareness. Furthermore, new criteria include an additional disturbance in cognition (Criterion C - e.g. memory, orientation, language, visuospatial ability, perception) and that disturbances in attention, awareness and cognition are not due to severely reduced level of arousal such as coma. In light of these changes, European and American Delirium Societies published a statement that patients with reduced arousal who are unable to complete cognitive testing should still be classified as having delirium unless they are clearly comatose. While critical care literature continues to use terms such as encephalopathy and sepsis-induced encephalopathy, it remains unclear whether these entities are clinically or pathophysiologically different from other causes of ICU delirium. As a result, to reduce
confusion, there is a call to use the term “delirium” uniformly to describe the syndrome of acute cognitive impairment in the ICU.10

1.1.2 Coma

1.1.2.1 Definition and clinical features of coma

Coma is a severe disruption of arousal and awareness functions and is differentiated from transient states such as syncope or concussion by its duration of greater than one hour. Comatose patients are unable to feel, speak or move in response to verbal, light or painful stimuli. They lack normal sleep wake cycles, may have altered brainstem reflexes, electric brain activity, and brain metabolism. Diagnosis of coma should exclude potential confounders that may mimic coma including intoxication, severe electrolyte abnormalities, sedatives, muscle relaxants, and seizures.

1.1.2.2 Causes of coma

Coma causes can be grouped into primary brain disorders and systemic causes. Primary brain causes include traumatic or cerebrovascular brain injury, neurologic infections, seizures or brain tumors. Systemic causes include cardiorespiratory arrest, pharmacologic and toxic exposures, sepsis, severe metabolic and physiologic derangements, and endocrine insufficiency.

1.1.2.3 Epidemiology of coma in the ICU

While epidemiology of coma is well described in neurological or neurosurgical population, it is less well understood in the ICU. The prevalence of non-traumatic coma varies between 28 and 75%.11 Coma is also common in patients receiving mechanical ventilation, where it occurs in 15-20% of patients, as well as elderly patients and those presenting with sepsis, with rates of over 30% and 16% respectively.12 Given that coma is potentially a by-product of sedation required to tolerate mechanical ventilation, the prevalence of non-sedation related coma may be lower than stated.
1.1.2.4 Outcomes in coma

Coma is considered a transitional state that eventually evolves towards resumption of consciousness, vegetative state, minimally conscious state or brain death. In vegetative state patients regain partial signs of arousal including spontaneous opening of the eyes, but they do not regain awareness of the self or the environment, failing to respond to external stimuli, fixate gaze or track objects. If this persists for more than 1 month, the patients are classified as being in the persistent vegetative state. Minimally conscious state differs from vegetative state in that the patient does has occasional, inconsistent but clear signs of self or environmental awareness. They may sporadically follow commands, respond to familiar objects or voices, attempt to imitate meaningful speech or engage in purposeful movement. Brain death is complete and irreversible cessation of brain and brainstem function characterized by absence of arousal, awareness, cranial nerve function, motor responses and spontaneous breathing.

Coma is an important prognostic factor in patients with brain injury. It is an important predictor of death in functional outcomes in patients with traumatic brain injury, cardiac arrest, and stroke. It is also one of the strongest independent predictor of death and length of stay. The Glasgow Coma Scale on admission was identified as the leading predictor of mortality in a large cohort of over 15,000 critically ill patients, which explains why it is integral component in most intensive care unit prognostic models.

1.1.3 Delirium

1.1.3.1 Definition and clinical features

Delirium is defined as an acute or fluctuating change in mental status with inattention, accompanied by either by disorganized thinking or altered level of consciousness. Unlike coma, patients with delirium retain elements of arousal and awareness. Delirium is sub-classified based on psychomotor status into 1) hyperactive delirium, characterized by agitation and combativeness, 2) hypoactive delirium, characterized by lethargy and withdrawal, and 3) mixed delirium, that shares features of both hyperactive and hypoactive delirium and fluctuates between these two types over time. While all three
types of delirium have been shown to be common in the critical ill, hypoactive and mixed delirium may be more prevalent and are likely less commonly identified due to lack of agitation.\textsuperscript{29} Patients that meet some, but not all, diagnostic criteria for delirium are often thought of as having sub-syndromal delirium. The outcomes for patients with sub-syndromal delirium fall in between those with full delirium and patients who have no delirium, suggesting a continuum of neurocognitive impairment severity.

1.1.3.2 Epidemiology of ICU delirium

Delirium occurs in 20-40\% of non-critically ill hospitalized patients.\textsuperscript{30} In the intensive care units, the prevalence is higher with rates as high as 80\% reported in both medical and surgical critically ill patients.\textsuperscript{1} The reported prevalence varies depending on the severity of illness and the instruments used to diagnose delirium. In a recent randomized controlled study comparing protocolized sedation with protocolized sedation plus daily sedation interruption, delirium was diagnosed in 53.8 \% of patients. Median time to onset of delirium was 3.5 days from enrollment in the study and delirium lasted a median of 2 days. Antecedent factors that were independently associated with the onset of delirium included use of restraints, administration of antipsychotic medications, and the dose of midazolam.\textsuperscript{31}

1.1.3.3 Risk factors for ICU delirium

A number of risk factors have been identified that may predispose patients to developing delirium in the ICU. Data from a large multicenter study identified male sex, surgical/trauma diagnosis, history of tobacco or alcohol use as risk factors for delirium.\textsuperscript{31} A recent systematic review of the literature identified 11 risk factors for developing ICU delirium that were associated with strong or moderate level of evidence. These included age, dementia, hypertension, pre-ICU emergency surgery or trauma, severity of illness (Acute Physiology and Chronic Health Evaluation II) score, mechanical ventilation, metabolic acidosis, delirium on the prior day, coma and multiple organ failure. Use of dexmedetomidine for sedation was associated with a lower delirium prevalence. Interestingly, gender was not identified as a risk factor for ICU delirium in this study.\textsuperscript{32} Sleep deprivation may play a role in the pathogenesis of ICU delirium. A recent
A recent systematic review and meta-analysis comparing delirious and non-delirious patients in the ICU showed that delirium was associated with higher relative risk of death (risk ratio of 2.19) and this association persisted even when analysis was adjusted for the severity of illness. Delirium was also associated with longer durations of mechanical ventilation, hospital and ICU lengths of stay, which explains why it also results in higher costs of care. The effects of delirium are not limited to ICU admission. In a large prospective observational study, ICU delirium was independently associated with worse global cognitive function and executive function at 3 and 12 months after discharge, suggesting a potential mechanistic link between acute ICU delirium and long-term cognitive function.

1.1.4 Long-term cognitive impairment

Long-term cognitive impairment is a common complication of critical illness. The reported prevalence of long-term cognitive impairment varies depending on the etiology of critical illness, time of assessment and cognitive instruments used.

1.1.4.1 Definition and clinical features

Long-term cognitive impairment has been defined as a perceived (subjective) or measured (objective) impairment on one or more cognitive domains. While a few studies have used patient or caregiver subjective perception of cognitive impairment, the majority of studies have used some cognitive instrument to measure patient performance and compare it to age- and sex- matched healthy controls. In the latter studies, cognitive impairment was defined if patient scores were 1-2 standard deviations below those from healthy controls. In a recent systematic review, we showed that the reported prevalence of cognitive impairment varies depending on the type of cognitive instrument used. For example, the use of single cognitive tests such as Trails Making Tests A/B or a dementia
screening battery such as a Mini-Mental State Examination (MMSE) is associated with a lower prevalence of cognitive impairment compared to comprehensive multi-domain cognitive batteries.\textsuperscript{37} Given that ICU-related long-term cognitive impairment affects multiple domains, the use of single tests or simple screening batteries will likely underestimate the incidence of cognitive impairment in ICU survivors.

Unlike Alzheimer’s dementia, which tends to affect delayed memory more than any other domains, critical illness cognitive impairment affects multiple cognitive domains including attention, memory, and executive function.\textsuperscript{36,38,39} Also, unlike Alzheimer’s, cognitive impairment after critical illness is not limited to older individuals, and affects patients across the age spectrum.\textsuperscript{36}. For majority of patients, the severity of cognitive impairment is comparable to that of mild cognitive impairment, with median global cognitive scores at 3 and 12 months being 1.5 standard deviations below population norms. However, at 3 months, 40\% of patients had global cognitive scores that were worse than those seen in moderate traumatic brain injury, while 26\% had scores comparable to patients with mild Alzheimer’s disease. These severe deficits persisted at 12 months, with 34 and 24\% patients having global scores that were comparable to moderate traumatic brain injury and mild Alzheimer’s disease respectively.\textsuperscript{36}

1.1.4.2 Epidemiology of critical illness cognitive impairment

The prevalence of long-term cognitive impairment in ICU survivors varies depending on the type of cognitive assessment (subjective vs objective), the cognitive instrument used (higher prevalence with comprehensive batteries that assess multiple cognitive domains), timing of assessment (higher prevalence immediately following ICU discharge), and ICU patient population (higher prevalence in patients with the Acute Respiratory Distress Syndrome, or ARDS).\textsuperscript{37}

Studies utilizing objective measures of cognition report higher prevalence of cognitive impairment than studies using subjective reports from patients and caregivers. However, while the prevalence of cognitive impairment measured using objective measures decreases with time from the ICU discharge, the prevalence of subjectively reported cognitive impairment increases. This suggests that ICU survivors may be initially
unaware of their newly acquired cognitive deficits. If true, this implies that some patients may lack insight into their cognitive deficits despite objective cognitive impairment at the time of discharge, either due to attribution of their cognitive deficits to the overall illness or poor self-appraisal. Given that cognitive function is an important determinant of functional recovery, failure to detect cognitive impairment at the time of discharge may result in missed therapeutic opportunity for some patients who may benefit from targeted cognitive interventions.

Studies that utilize comprehensive cognitive batteries report higher prevalence of cognitive impairment compared to studies that use simple dementia screening batteries such as the MMSE. For example, at ICU discharge the mean prevalence of cognitive impairment using MMSE was 36% compared to 61% if comprehensive cognitive batteries are used. Similarly, at 12 months following ICU discharge were 18 and 43% respectively. Given that MMSE was developed as a screening tool for dementia, which mostly involves memory domain of cognition, it may not be sensitive for detecting multi-domain cognitive impairment commonly seen in the ICU. Furthermore, it may also be prone to floor/ceiling effects.

The prevalence of cognitive impairment in ICU survivors appears to decrease with time from the ICU discharge. However, due to high attrition rate in some studies, it is hard to determine whether this reduction in the prevalence of cognitive recovery or a result of loss of patients with worse cognitive scores from study cohorts. In most studies, cognitive assessments occur at several discrete time points, most commonly at discharge, and at three, six and twelve months. Given that no rationale for the choice of these time interval is provided, it is likely that these intervals reflect the operational and resourcing framework of previous studies. Specifically, since most studies utilize pen and paper cognitive tests, repeated testing requires patients to return to clinic, which may be challenging for some ICU survivors given functional limitations, unwillingness to return to hospital for post-traumatic associations, and geographic dispersion of patients relative to tertiary care centres where most of these clinics are located. Moreover, administration of pen and paper cognitive batteries requires trained personnel, which is both costly and time consuming. As a result, repeated testing of cognition in ICU survivors with pen and
paper tests is limited to discrete time points and is not practical for large scale natural history studies of cognitive recovery in these patients.

Survivors of ARDS appear to have higher prevalence of cognitive impairment in the first 3 months following ICU discharge compared to other ICU survivors (approximately 80 vs 50%). This difference disappears at the 6 month mark and by 12 months there were no differences in the prevalence of cognitive impairment between different patient populations. While higher illness severity, longer duration of mechanical ventilation and ICU stay, lower oxygen (O₂) and higher carbon dioxide (CO₂) levels in ARDS patients may all contribute to worse cognitive outcomes, this hypothesis requires further evaluation with properly designed natural history studies. Loss of patients to follow up and inability of sicker patients to return to clinic for in-person cognitive testing are major barriers to such natural history studies and need to be addressed in order to enable future research in this area.

1.1.4.3 Risk factors for long-term cognitive impairment

Pre-existing cognitive function is often unknown in critical illness survivors. However, in one study, the prevalence of pre-existing cognitive impairment was higher in hospitalized patients who required admission to the ICU compared to those who did not (35 vs 18%). In that study, patients who had pre-existing cognitive impairment and required ICU admission were older, male and had higher initial severity of illness scores compared to ICU patients without pre-existing cognitive impairment. This suggests that older patients who are admitted to the ICU may have higher prevalence of cognitive impairment.

Given that critical illness is a sudden, unpredictable event, it is often not feasible to obtain baseline assessment of cognitive function prior to onset of critical illness. This remains a major limitation of many studies. Some studies employ screening questionnaires such as Informant Questionnaire on COgnitive Decline in the Elderly to rule out patients with pre-existing cognitive impairment or dementia. In one study, however, baseline cognitive function was measured and compared to that following hospitalization of sepsis in elderly patients. Non-sepsis hospitalizations served as
controls. The prevalence of moderate to severe cognitive impairment increased 10.6% in sepsis survivors, while there was no change in patients with non-sepsis hospitalizations. This increase in cognitive impairment was associated with a higher rate of functional limitations. These results suggest that an episode of critical illness may result in de novo cognitive impairment.

**Genetic factors**, such as the presence of the Apolipoprotein E4, a well-known risk factor for Alzheimer’s disease, may increase the risk of acute and potentially long-term cognitive impairment in critical illness. For example, in one study, presence of the Apolipoprotein E4 allele was the strongest predictor for the duration of delirium (odds ratio of 7.3). This odds ratio was higher than that for age (1.02), severity of illness score (0.98), diagnosis of sepsis, acute respiratory distress syndrome or pneumonia (1.73), duration of coma (1.32) or total dose of benzodiazepines (1.00).

**Hypoxemia**, especially in ARDS patients, has been shown to correlate with the degree of cognitive impairment. In one study, the duration and degree of hypoxemia correlated with the severity of cognitive impairment in attention, memory, intelligence, speed of processing, visuospatial skills and executive function scores. Similarly, lower partial pressure of oxygen in arterial blood was associated with cognitive impairment in a subset of patients from a large randomized controlled study examining conservative versus liberal fluid therapy in acute respiratory distress syndrome. However, the effect of hypoxemia on the brain may not be uniform across different ICU populations. In trauma patients, there was no association between hypoxemia and incident delirium or cognitive impairment at 1 year after discharge. Similarly, in a cohort of 64 mixed medical and surgical critically ill patients, brain imaging revealed atrophy in 26 patients, but this was not associated with hypoxemia. This suggests that mechanisms linking hypoxemia and cognitive impairment in ARDS may be different from the mixed medical surgical ICU population.

**Sepsis** has been associated with development of new cognitive impairment. In a large prospective study, Iwashyna et al showed that elderly patient who are hospitalized for severe sepsis have a 10% increase in the prevalence of moderate to severe cognitive
impairment compared to pre-hospitalization. The incidence of severe sepsis was highly associated with progression to moderate to severe cognitive impairment (odds ratio 3.34). The cognitive changes were accompanied by development of ~1.5 new functional limitations. These cognitive and functional changes persisted for at least 8 years after episode of sepsis, suggesting persistent burden of new cognitive and functional disability. In contrast, a control group of elderly adults who experienced non-sepsis hospitalization had no change in the prevalence of moderate to severe cognitive impairment and developed fewer (~0.4) new functional limitations. In another study, sepsis survivors had greater loss of left hippocampal volume compared to healthy controls, and this was associated with impairment in verbal learning and memory. Sepsis survivors also showed more low-frequency activity on electroencephalography, suggesting generalized brain dysfunction.

Glucose dysregulation has been associated with development of cognitive impairment. Using data from a randomized control trial comparing high vs. low tidal volume ventilation for acute respiratory distress syndrome, Hopkins et al. showed in a multivariate analysis that patients with highest blood glucose exceeding 8.5 mmol/L and those with variation in glucose exceeding 0.9 mmol/L were at higher risk of developing cognitive impairment (odds ratios of 2.96 and 3.26 respectively). In surgical ICU population, patients who experienced hypoglycemic episodes and those that did not showed impairment in several cognitive domains compared to healthy controls. However, in the visuospatial skills domain, the impairment in hypoglycemic group was greater than in non-hypoglycemic group.

Delirium is an important independent risk factor for long-term cognitive impairment. In a cohort of mixed medical and surgical ICU patients, a multivariate analysis that included delirium and coma duration, as well as mean daily doses of sedative and analgesic medications as independent variables, longer duration of delirium was an independent predictor for worse global cognitive scores at 3 and 12 months after discharge. In another study, duration of delirium was associated with worse cognitive outcomes after adjusting for age, education, pre-existing cognitive impairment, severity of illness, severe sepsis and total exposure to sedatives in the ICU. In contrast, duration of mechanical
ventilation did not predict worse cognitive outcomes, suggesting that duration of delirium is not merely a surrogate for duration of mechanical ventilation.\textsuperscript{55}

**Sedative and analgesic medication** exposure has been considered as a risk factor for development of cognitive impairment. However, in the largest study to date, the mean daily dose of benzodiazepines, propofol, dexmedetomidine and opiates was not associated with worse cognitive outcomes at 3 and 12 months.\textsuperscript{36} Furthermore, daily interruption and reduction of sedation had no effect on the delirium duration \textsuperscript{56} or cognitive outcomes at 12 months,\textsuperscript{57} despite reducing duration of coma, mechanical ventilation, ICU and hospital length of stay, and 1-year mortality.\textsuperscript{56}

**Sleep deprivation** appears to contribute to ICU delirium, and strategies to promote sleep in the ICU appear to reduce incidence and duration of the ICU delirium.\textsuperscript{33} Whether poor sleep or strategies aimed at improving sleep in the ICU affect long term cognitive outcomes is unclear.\textsuperscript{58}

### 1.1.4.4 Consequences of long-term cognitive impairment

Cognitive function is one of the best predictors of life quality, including academic and work success, levels of happiness and even life expectancy.\textsuperscript{59–62} Given the expected increase in the number of ICU survivors due to projected increase in the incidence of critical illness \textsuperscript{63} and reduction in ICU mortality, ICU-related cognitive impairment is an important public health problem that requires urgent and innovative solutions.

Cognitive impairment in ICU survivors has been associated with anxiety, depression and post-traumatic stress disorders.\textsuperscript{3} These ICU survivors also suffer from high rates of unemployment \textsuperscript{64} and impaired quality of life,\textsuperscript{65,66} placing a huge burden on the caregivers and society. At 12 months following ICU discharge, 40\% of ICU survivors remain unemployed,\textsuperscript{64} which is comparable or worse than in patients with traumatic brain injury\textsuperscript{67} or stroke.\textsuperscript{68} After returning to work, a third of survivors experience job loss, while up to two thirds of survivors experience occupation change, often with worsening employment status.\textsuperscript{64} These findings were persistent across geographical regions and
states of economies, suggesting that factors other than societal or economics play a role. It is conceivable that impairments in cognition may prevent previously able and employed individuals from returning to work and being able to complete their work duties as effectively as prior to their ICU illness. Given that gradual return to work, modified work schedule and job retraining have been shown to help with return to work in ARDS survivors, future studies should explore whether combination of cognitive and vocational rehabilitation can mitigate these problems.

1.2 Mechanisms of ICU-related neurocognitive impairment

While the exact mechanisms behind ICU-related neurocognitive impairment are still unclear, a number of pathogenesis hypotheses have been put forward.

1.2.1 The neuroinflammation hypothesis

This hypothesis proposes that delirium is a clinical manifestation of acute brain injury that occurs as a result of systemic inflammatory response. High levels of inflammatory markers such as C-reactive protein, procalcitonin, and interleukin-8 have been detected in patients who develop ICU delirium. Systemic inflammation can have several effects including: 1) Activation of endothelium and coagulation systems leading to thrombosis of the microcirculation and impairment in brain perfusion; 2) In animal models, a pro-inflammatory cytokine tumor necrosis factor-a has been shown to result in disruption of the blood-brain barrier and translocation of leukocytes and cytokines into the central nervous system leading to ischemia and neuronal death; 3) Activation of microglia (resident brain macrophages) can result in further neuronal injury and apoptosis via expression of adhesion molecules, production of pro-inflammatory cytokines (interleukin-1, tumor necrosis factor α, insulin like growth factor 1), metalloproteinases, reactive oxygen species, and increase in inducible nitric oxide synthase. These inflammation driven changes can impair cognition by affecting synaptic plasticity and long-term potentiation, as well as reducing brain synaptic connectivity via upregulation of the inhibitory gamma-aminobutyric acid (GABA) receptors. Upregulation of GABA receptors may explain why administration of benzodiazepines (GABA receptor A
agonists) for sedation in the intensive care units is associated with higher rates of delirium than sedation with other agents such as propofol or dexmedetomidine.\textsuperscript{79}

Inflammation may also contribute to the long-term cognitive impairment. Systemic inflammation during acute critical illness may activate brain microglial cells.\textsuperscript{80,81} Activated microglia sustain a state of chronic neuroinflammation that contributes to ongoing brain injury. Clinically this may manifest as failure of cognitive recovery in ICU survivors.

1.2.2 The cholinergic hypothesis

This hypothesis focuses on the effect of acetylcholine deficiency in critical illness. Acetylcholine is an important neurotransmitter in both central and peripheral nervous systems. Among other things, it is responsible for modulation of the inflammatory response, microglia and other neurotransmitter pathways. Acetylcholine level are low in critical illness due to: 1) decreased production as a result of choline and acetyl-CoA deficiencies, 2) inhibition of acetylcholine release by opiates, and 3) inhibition of acetylcholine receptors by anesthetic and anticholinergic medications.\textsuperscript{82} In the central nervous system, this leads to decreased inhibition of microglia via acetylcholine receptor, leading to propagation of neuroinflammation and resultant neuronal death.\textsuperscript{78} Given that acetylcholine is critical for modulating of other neurotransmitter pathways, there is excess of dopamine, norepinephrine and serotonin signalling, which contributes to hyperactive delirium. In the peripheral nervous system, acetylcholine release via the vagus nerve inhibits release of pro-inflammatory cytokines including interleukins 1, 6 and tumor necrosis factor-a. As a result of acetylcholine deficiency, there is increased release of these pro-inflammatory cytokines in critical illness, which contributes to neuroinflammatory brain injury.\textsuperscript{70}

1.2.3 Monoamine axis hypothesis

This hypothesis postulates that excess of activating neurotransmitters dopamine, norepinephrine and serotonin results in overstimulation of the central nervous system, leading to clinical presentation of hyperactive delirium.\textsuperscript{83} In one retrospective cohort, administration of dopamine for hemodynamic support was associated with nearly triple
the odds of developing delirium.\textsuperscript{84} Similarly, norepinephrine excess is associated with impaired attention, anxiety, mood, and hyperactive delirium. Reuptake inhibition of serotonin with pharmacologic agents has been associated with delirium.\textsuperscript{70}

1.2.4 Perfusion hypothesis

Given that critical illness is associated with systemic hypotension and impaired cardiac output, the perfusion hypothesis proposes that resultant global and/or regional changes in brain perfusion may contribute to development of delirium and long-term cognitive impairment. Evidence for this hypothesis comes from a number of neuroimaging studies that documented high prevalence of cortical and sub-cortical ischemic brain injury in ICU survivors, as well as several studies documenting impairment of cerebral autoregulation and its association with delirium. In the following sections, we will present a brief overview of the control of cerebral blood flow (CBF) and summarize existing knowledge from cerebral autoregulation and neuroimaging studies.

1.3 Control of cerebral blood flow

1.3.1 Determinants of CBF

The human brain is a highly metabolically active organ that, despite only contributing to the 2% of the total body weight, receives approximately 15-20% of the cardiac output.\textsuperscript{85} At rest, the brain utilizes nearly 20% of the basal oxygen consumption,\textsuperscript{86} and any disruption in brain blood flow can lead to acute and eventually irreversible injury with corresponding functional impairments.

The prevailing model of CBF defines it as a ratio of cerebral perfusion pressure (CPP) and cerebrovascular resistance (R\textsubscript{CV}) (see Equation 1).\textsuperscript{87}

\[
CBF = \frac{CPP}{R_{CV}} \quad \text{(Equation 1)}
\]

CPP, in turn, is a function of mean arterial pressure (MAP) and intracranial pressure (ICP) or central venous pressure (CVP). Under normal physiologic conditions, CVP exceeds ICP and determines CPP (Equation 2). In certain pathophysiologic conditions,
such as traumatic brain injury, increase in ICP can overcome CVP, and become the primary determinant of CPP (Equation 3).

\[
CPP = MAP - CVP \quad (\text{Equation 2})
\]

\[
CPP = MAP - ICP \quad (\text{Equation 3})
\]

Under this model, increase in systemic MAP will augment cerebral blood flow by increasing CPP. On the other hand, increase in ICP (e.g. as a result of increase in cerebral blood volume due to hemorrhage), will work to reduce CPP and cerebral blood flow. Given that hypotension is a common presentation of critical illness, reduction in MAP, unless counteracted by resuscitative measures and vasopressors, will induce ischemia via reduction in CPP.

According to Equation 1, cerebrovascular resistance is another important determinant of CBF. \( R_{CV} \) is primarily a function of the cross-sectional diameter of cerebral arterioles, which is modulated via four primary mechanisms: 1) global vasoactive factors, such as the arterial partial pressure of carbon dioxide (\( \text{PaCO}_2 \)),\(^{88} \) 2) reduction in global arterial oxygen content as a result of hypoxia\(^{89} \) or changes in hemoglobin concentration,\(^{90,91} \) 3) local vasoactive metabolites that are released in response to increase in neural activity (a process known as neurovascular coupling),\(^{92} \) and 4) autonomic signaling,\(^{93} \) especially during exercise.\(^{94} \) Figure 1-1 summarizes the relationship between CBF, MAP, arterial partial pressure of \( O_2 \) (\( \text{PaO}_2 \)) and \( \text{PaCO}_2 \).
Other factors not mentioned in Equation 1 that may contribute to regulation of CBF are cardiac output and arterial oxygen content. Cardiac output has recently emerged as an independent regulator of CBF, with several studies demonstrating cardiac output mediated changes in CBF on the background of constant MAP. Given that at rest the brain receives 15-20% of total cardiac output, these observations are relevant, and future work needs to discern how MAP, PaCO₂ and cardiac output integrate in the control of CBF in critically ill patients. CBF is also sensitive to changes in arterial oxygen content as a result of changes in hemoglobin, hematocrit and PaO₂. In patients with anemia, CBF increases as a result of vasodilation to maintain cerebral oxygen delivery. Correction of anemia in hemodialysis patients with recombinant human erythropoietin decreases CBF due to increase in cerebral oxygen delivery. However, in patients with arterial disease higher hemoglobin and hematocrit levels are associated with faster

Figure 1-1: Relationship between cerebral blood flow, mean arterial pressure (black line), arterial PCO₂ (red line) and PO₂ (green line). Adapted from reference.⁹⁵
decline in cerebral blood flow over 4 years.\textsuperscript{90} CBF also increases in response to hypoxia, but only at PaO\textsubscript{2} levels less than 50mmHg (Figure 1-1).\textsuperscript{97}

1.3.2 Cerebrovascular function and control of cerebral blood flow

Cerebrovascular function plays an important role in controlling CBF by inducing changes in the diameter of resistant arterioles in response to various stimuli. The main cerebrovascular mechanisms responsible for control of cerebral blood flow include neurovascular coupling, autonomic activity, cerebral autoregulation and cerebrovascular CO\textsubscript{2} reactivity. For the purpose of this work, we will focus on two mechanisms, namely cerebral autoregulation and cerebrovascular CO\textsubscript{2} reactivity.

1.3.2.1 Cerebral autoregulation

Cerebral autoregulation is a mechanism that works by altering the diameter of resistant arterioles to ensure stable CBF across a range of perfusion pressures.\textsuperscript{100} For example, a decrease in MAP would lead to a reduction in CPP and decrease in CBF if cerebrovascular resistance stays the same (see Equation 1 above). Autoregulation works to maintain CBF by lowering cerebrovascular resistance via dilation of resistant arterioles. Two types of cerebral autoregulation have been described: static and dynamic.\textsuperscript{101}

\textbf{Static autoregulation} refers to studies where MAP is manipulated to achieve several steady states and corresponding CBF values are recorded. In this model, autoregulation is said to be intact if CBF stays relatively constant over a range of MAP. Autoregulation is said to be impaired, if CBF varies with changes in MAP. This description of cerebral autoregulation was first described by Niels Lassen in 1959.\textsuperscript{102} Since its publication this classic description of cerebral autoregulation has been replicated in multiple medical texts (Figure 1-2). In this model, impairment of autoregulation can occur either at the extremes of MAP, or due to the loss of the “plateau” relationship between CBF and MAP as a result of loss of vasomotor control (e.g. with ischemia, stroke or sepsis).\textsuperscript{95} However, Lassen used data from multiple patients and studies to construct his classic curve,\textsuperscript{102} and recent studies have questioned whether the same phenomenon can be reproduced in individual subjects.\textsuperscript{97} One recent study showed that the relationship between CBF and
MAP in healthy volunteers is in fact linear. Furthermore, assessment of static autoregulation in clinical practice is not often practical, given that it usually requires pharmacologic manipulation of MAP.

Figure 1-2: Classic representation of the cerebral autoregulation. Adapted from references. In this model, increase in the mean arterial pressure in the autoregulation zone is counteracted by progressive vasoconstriction and reduction in the diameter of resistant arterioles. According to this model, impairment in autoregulation can occur either at the extremes of MAP (black dashed lines), or due to the loss of vasomotor control in the “plateau” region of this relationship as a result of pathophysiological state such as ischemia, sepsis or stroke (red dashed line).

**Dynamic autoregulation** has evolved as an alternative method of assessing cerebrovascular autoregulation. Unlike static autoregulation, it assumes that cerebral autoregulation works as a high-pass filter and assesses the relationship between continuously measured CBF and MAP in the time or frequency domains (Figure 1-3). In the first case, a moving window is used to compute the correlation coefficient between
continuously measured CBF and MAP in windows where MAP varies by at least 5 mmHg\textsuperscript{108}. Dynamic autoregulation is said to be impaired if correlation coefficients exceed a specific threshold (e.g. >0.3 in traumatic brain injury patients, where it is linked to poor cognitive outcomes)\textsuperscript{109} or if correlation between CBF and MAP is statistically significant (e.g. in patient with respiratory failure or shock).\textsuperscript{110} Utilizing the model shown in Figure 1-2, loss of autoregulation can occur as a result of extremes of MAP, or due to loss of the vasomotor control of CBF and autoregulatory “plateau” as a result of pathophysiology state (e.g. sepsis).

In the frequency domain methods, a transfer function is used to compute gain, phase and coherence between continuously monitored CBF and MAP signals.\textsuperscript{111,112} Increase in gain and coherence, and decrease in phase between the two signals are often interpreted as an impairment in dynamic cerebral autoregulation (Figure 1-3).\textsuperscript{113,114}
Figure 1-3: Two approaches for assessing dynamic autoregulation. Adapted from references. Both approaches look at continuous cerebral blood flow (CBF) and mean arterial pressure (MAP) signals using a time-defined window. Panel A - In the temporal domain, the signals from the moving window are correlated using Pearson or Spearman correlation if MAP varies by at least 5mmHg. If the correlation coefficient is $\leq 0.3$ and/or the correlation is not significant, then autoregulation is assumed to be intact. On the other hand, if correlation coefficients $>0.3$ and/or is statistically significant, then autoregulation is impaired. Panel B – In the frequency domain, transfer function analysis is used to calculate gain, phase and coherence between two signals. Gain represents the damping effect of autoregulation on the magnitude of the blood pressure oscillations. Low gain represents active autoregulation, whereas an increase in gain represents impaired autoregulation. Phase is considered a surrogate measure for the time delay of the autoregulation response. Translating phase shift into time domain, phase shift of zero indicates no time delays between changes in CBF and MAP, and therefore loss of autoregulation, while positive phase would translate to a delay between CBF and MAP fluctuations and active autoregulation. Coherence describes whether the relationship between input and output signals is linear such that coherence approaching unity in a specific frequency suggests linear relationship, while coherence approaching zero suggests no relationships between signals. As a result, increase in coherence is interpreted as loss of autoregulation.
While both static and dynamic autoregulation have been assessed in critically ill patients,\textsuperscript{100,116–119} dynamic methods have gained popularity because they can be estimated using spontaneous variations of CBF and MAP (i.e. they do not require interventions that change MAP).\textsuperscript{120} Furthermore, while many different methods for measuring CBF exist, computations of dynamic autoregulation at the bedside imposes several practical constraints in that the methods for monitoring CBF need to be a) non-invasive, b) portable and applicable at the bedside, and c) have high temporal resolution. As a result, while tomographic imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) provide excellent spatial resolution, they are not appropriate for monitoring dynamic autoregulation at the bedside. Instead, transcranial Doppler (TCD) and near infrared spectroscopy have emerged as the methods of choice in this application.\textsuperscript{116,120} Another option is to utilize ICP monitor, but given that this an invasive procedure, it is restricted to patients who already require ICP monitor for clinical indications, such as patients with traumatic brain injury.\textsuperscript{120}

Several studies have assessed dynamic autoregulation and linked it to clinical outcomes in critically ill patients. In patients with traumatic brain injury, numerous studies have demonstrated impaired dynamic cerebral autoregulation and its association with worse neurologic outcomes as measured by the Glasgow outcome scores.\textsuperscript{121} This relationship was observed whether time or frequency domain methods of dynamic autoregulation were used.\textsuperscript{107} However, in contrast to studies of animal models or healthy subjects where the timing of critical illness insult is known and controlled, clinical studies enroll patients within a specific time frame of ICU admission. This confounds interpretation of clinical findings since the onset of insult is difficult to estimate precisely. As a result, there is disagreement between study findings that is most evident from studies in sepsis patients.

In sepsis, effectiveness of cerebral autoregulation appears to depend on the time from sepsis onset and the methods used to assess cerebral autoregulation.\textsuperscript{122} In one study, static autoregulation in early sepsis was intact.\textsuperscript{123} In other studies of experimental sepsis in healthy volunteers, dynamic autoregulation is actually enhanced in the early stages of sepsis.\textsuperscript{124,125} However, other studies showed that patients with sepsis have impaired dynamic cerebral autoregulation, and this impairment was associated with development
of delirium.\textsuperscript{118,126} In patients with respiratory failure or shock, cumulative duration of impaired autoregulation during the first 72 hours of the ICU admission is associated with development of delirium.\textsuperscript{110} While these studies suggest that cerebral autoregulation is an important measure of vasomotor control of CBF that is linked to important patient-centred outcomes, the variability in results across patient populations suggests that additional factors that influence vasomotor control of CBF, including CO\textsubscript{2}, may be important.

1.3.2.2 Cerebrovascular CO\textsubscript{2} reactivity

Another way to interrogate cerebrovascular function is to quantify CBF responsiveness to a vasodilatory stimulus. CO\textsubscript{2} is a potent vasodilator that induces 3-5\% change in CBF per unit change in PaCO\textsubscript{2}.\textsuperscript{127} Given that manipulation of CO\textsubscript{2} is relatively easy and non-invasive (i.e. does not require intravenous administration of vasodilating substances), cerebrovascular reactivity to CO\textsubscript{2} (CVR) is commonly used clinically to assess the state of vasomotor control of CBF.\textsuperscript{97,128}

There are several ways to induce changes in CO\textsubscript{2} including 1) breath holding, 2) hyperventilation, 3) inhalation of exogenous CO\textsubscript{2}, 4) rebreathing, 5) administration of acetazolamide, and 6) independent control of CO\textsubscript{2} and O\textsubscript{2} using dynamic end-tidal forcing or prospective control methods.\textsuperscript{129} The advantages and disadvantages of different CO\textsubscript{2} stimuli are summarized in Table 1-1. While breath holding, hyperventilation, rebreathing, acetazolamide administration and inhalation of exogenous CO\textsubscript{2} are all simple ways to induce changes in PaCO\textsubscript{2}, they have several disadvantages including 1) lack of precision in the magnitude of CO\textsubscript{2} change, which confounds comparison of CBF response to CO\textsubscript{2} between subjects, 2) slow rate of change in PaCO\textsubscript{2}, which precludes accurate assessment of the dynamics of CBF response to CO\textsubscript{2}, and 3) associated change in arterial partial pressure of O\textsubscript{2} (PaO\textsubscript{2}), which preclude assessment of true CBF response to CO\textsubscript{2} given that increase in PaO\textsubscript{2} can induce vasoconstriction independent of the changes in CO\textsubscript{2}.\textsuperscript{130–132} Dynamic end-tidal forcing methods overcomes these limitations and have been used extensively in the physiology labs to study the independent effects of O\textsubscript{2} and CO\textsubscript{2} on CBF.\textsuperscript{127,133–135} However, high gas flow requirements of these methods have limited their use outside of physiology labs.
Table 1-1: Comparison of different CO₂ stimuli for measurement of cerebrovascular reactivity to CO₂ (see 129 for more details)

<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
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| Breath holding                | Simple to administer (no additional equipment required)                     | - Small magnitude of change in PaCO₂ as the rate of rise in PaCO₂ is dependent on metabolic CO₂ production and participant’s ability to hold their breath.  
- Hard to measure actual change in PaCO₂ (need to estimate from the end-tidal partial pressure of CO₂, PetCO₂)  
- Slow rate of rise in CO₂ prevents assessment of the dynamics of CBF response to CO₂. |
| Hyperventilation              | Simple to administer (no additional equipment required)                     | - Associated change in arterial partial pressure of O₂ (PaO₂), which can independently change CBF 130,131,136                                                                                   |
| Inhalation of exogenous CO₂  | Relatively simple to assemble and administer via face mask                 | - Unpredictable change in PaCO₂ - The actual change in PaCO₂ depends on the participant’s ventilatory sensitivity to CO₂ – i.e. CO₂-induced increase in alveolar ventilation and CO₂ elimination can sometimes negate (or even exceed) the increase in inspired CO₂, resulting in no change (or lowering) of PaCO₂ 132  
- Slow rate of rise in CO₂ prevents assessment of the dynamics of CBF response to CO₂.  
- Associated increase PaO₂ - unable to discern effect of O₂ vs CO₂ on CBF |
<table>
<thead>
<tr>
<th>Method</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
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| Rebreathing                 | Relatively simple to administer, can be used to quantify limits of CBF response to CO₂<sup>137</sup> | • Slow rate of rise in CO₂ (depends on subjects metabolic CO₂ production).  
• Variable tolerance by subjects  
• Variable O₂ (unless servo-controlled) |
| Acetazolamide               | Relatively simple to administer                                            | • Unpredictable rise in PaCO₂  
• Slow rate of rise in CO₂ prevents assessment of the dynamics of CBF response to CO₂. |
| Dynamic end-tidal forcing   | • Precise and independent changes in PaCO₂ / PaO₂  
• Fast changes in PaCO₂ allow assessment of dynamics of CBF response | • Complex and bulky set up  
• High rate of use of source gases  
• Limited to physiology research laboratories |
| Prospective targeting<sup>138</sup> | • Precise and independent changes in PaCO₂ / PaO₂  
• Fast changes in PaCO₂ allow assessment of dynamics of CBF response  
• Mobile – can be used in MRI / at the bedside | • Expensive - requires special gas blender (RespirAct<sup>TM</sup>) |

As part of my Master of Science thesis,<sup>139</sup> I developed a novel method to prospectively target and independently control both CO₂ and O₂ for the purpose of vascular reactivity studies. Unlike dynamic end-tidal forcing methods that control end-tidal gases, prospective targeting actually controls PaCO₂ and PaO₂.<sup>140</sup> In addition to enabling precise and independent control of PaCO₂ and PaO₂, this approach allows rapid changes in arterial gases that enabled studies of the dynamics of CBF response to CO₂ using step<sup>141,142</sup> or sinusoidal<sup>143</sup> changes in PaCO₂. Its relative portability has enabled a range of vascular reactivity studies using MRI and PET/CT in both the brain,<sup>128</sup> spinal cord,<sup>144</sup> heart,<sup>145</sup> liver<sup>146</sup> and kidney.<sup>147</sup> The precision in the magnitude of the CO₂ change with prospective targeting also enabled assessment of cerebrovascular reserve, identifying
thresholds for vasoconstriction and vasodilation of cerebral vasculature in response to CO₂.\textsuperscript{148}

Impairments in CVR have been associated with the increased risk of stroke,\textsuperscript{149} cognitive impairment\textsuperscript{150,151}, cortical thinning,\textsuperscript{152} and leukoaraisoasis.\textsuperscript{153} In concussion, CVR helps differentiate between concussed and normal patients despite similar anatomic and global resting CBF measurements in both groups.\textsuperscript{154,155} In critically ill patients, impaired CVR has been reported in patients with TBI,\textsuperscript{156–158} sepsis,\textsuperscript{159} and subarachnoid hemorrhage.\textsuperscript{160}

The relationship between cerebral autoregulation and CVR is not fully understood. While both methods likely examine different physiologic control mechanisms (blood pressure regulation vs. CO₂ regulation), there is likely an interplay between the two, especially given that changes in CO₂ also induce changes in MAP\textsuperscript{161} that can have an independent effect on CBF and modulate cerebral autoregulation.\textsuperscript{117} As a result, there is a call for an integrative approach to assessment of cerebrovascular function at the bedside.\textsuperscript{97}
1.4 Neuroimaging and neuromonitoring methods

A number of different neuroimaging and neuromonitoring methods have been used to assess brain structure and function in critically ill patients. These can be broadly classified into:

1) **Invasive bedside techniques** – these include measurements with sensors inserted into brain parenchyma, brain ventricles, or those that require exposure of brain tissue; these methods include intracranial pressure monitoring (ICP), brain tissue oxygen monitoring, laser Doppler flowmetry, and thermal diffusion, and are more commonly used in the patients with traumatic brain injury that otherwise require invasive procedures;

2) **Non-invasive bedside monitors** – these include transcranial Doppler (TCD) and near infrared spectroscopy (NIRS). TCD monitors cerebral blood flow velocity in large intracranial vessels, while NIRS monitors regional brain tissue oxygenation. Both monitors have high temporal resolution, which enables calculation of dynamic cerebral autoregulation indices when their outputs are analyzed against changes in MAP.\(^{120}\)

3) **Tomographic imaging methods** – these include CT, MRI and positron emission tomography (PET). All three methods have the advantage of high spatial resolution for assessment of brain structure, CBF and function, but are at present not suitable for bedside monitoring due to their size, limited temporal resolution and radiation exposure.\(^{162}\)

The benefits and disadvantages of each methods for assessment and monitoring of critically ill patients are summarized in Table 1.2.
Table 1-2: Summary of neuroimaging and neuromonitoring methods

<table>
<thead>
<tr>
<th>Modality</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Use in critical care</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICP monitor</td>
<td>Portable, high temporal resolution, enables computation of dynamic autoregulation index PRx</td>
<td>Invasive, parenchymal monitors may not reflect global ICP</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>Brain tissue oxygen monitoring</td>
<td>Direct measure of cerebral metabolism and oxygenation, although based on numerous assumptions</td>
<td>Poor spatial resolution, unclear relation to outcomes</td>
<td>Traumatic brain injury</td>
</tr>
<tr>
<td>Laser Doppler flowmetry</td>
<td>Direct non-invasive measure of perfusion</td>
<td>Requires tissue exposure, so is invasive</td>
<td>Experimental use only</td>
</tr>
<tr>
<td>TCD</td>
<td>Portable, high temporal resolution, non-invasive, enables computation of dynamic autoregulation indices Mx or Mxa</td>
<td>Operator dependent, only measures CBFv in large intracranial vessels, indirect measure of CBF</td>
<td>Traumatic brain injury, subarachnoid hemorrhage, hypoxic ischemic brain injury, sepsis, brain death assessment</td>
</tr>
<tr>
<td>NIRS</td>
<td>Portable, high temporal resolution, non-invasive, enables computation of dynamic autoregulation index COx</td>
<td>Limited skull penetration, artifacts due to contamination from scalp perfusion, regional monitoring of small portion of cerebral cortex, limited spatial resolution, indirect measure of perfusion</td>
<td>Traumatic brain injury, subarachnoid hemorrhage, hypoxic ischemic brain injury, sepsis, brain death assessment and shock</td>
</tr>
<tr>
<td>CT</td>
<td>High spatial resolution, assessment of regional CBF and perfusion (with contrast)</td>
<td>Not portable, radiation, limited temporal resolution (not suitable for continuous monitoring)</td>
<td>Most critically ill patients that are stable, based on availability of imaging modality</td>
</tr>
<tr>
<td>Modality</td>
<td>Advantages</td>
<td>Disadvantages</td>
<td>Use in critical care</td>
</tr>
<tr>
<td>----------</td>
<td>------------</td>
<td>---------------</td>
<td>---------------------</td>
</tr>
<tr>
<td>MRI</td>
<td>High spatial resolution, detailed examination of brain structure including white matter tracts, assessment of regional CBF, functional studies</td>
<td>Not portable, limited access in some hospitals, expensive, limited temporal resolution</td>
<td>Most critically ill patients that are stable, based on availability of imaging modality</td>
</tr>
<tr>
<td>PET</td>
<td>Good spatial resolution, detailed examination of CBF, brain metabolism and function including inflammation</td>
<td>Expensive, limited access, radiation</td>
<td>Most critically ill patients that are stable, based on availability of imaging modality</td>
</tr>
</tbody>
</table>

ICP = Intracranial pressure, PRx = index of dynamic autoregulation computed from correlation between ICP and cerebral perfusion pressure, TCD = transcranial Doppler, CBFv = cerebral blood flow velocity, Mx and Mxa = indices of dynamic autoregulation computed from correlation between CBFv and cerebral perfusion pressure (Mx) or mean arterial pressure (Mxa), CT = computed tomography, MRI = magnetic resonance imaging, PET = positron emission tomography.
1.5 Neuroimaging studies in ICU patients

Delirium and cognitive impairment in ICU patients represent impairments in brain function. Several prior studies have examined whether these functional changes are associated with changes in brain structure. In this section we will review the prevalence and patterns of structural brain lesions across different ICU patient populations from previous studies. We will then review the links between these structural lesions, clinical factors and clinical outcomes.

1.5.1 Prevalence of structural lesions in ICU patients

Neuroimaging studies in ICU patients have identified a various types of brain lesions that have been associated with clinical factors and clinical outcomes. Among critically ill patients, common abnormalities on CT and MRI include atrophy, white matter hyperintensities (WMHs), hemorrhage, infarcts and encephalomalacia. The prevalence of these lesions from different ICU populations is summarized in Table 1-3.

Table 1-3: Prevalence of structural changes on CT/MRI Imaging in ICU patients

<table>
<thead>
<tr>
<th>Population</th>
<th>Number of patients</th>
<th>Normal</th>
<th>Atrophy</th>
<th>WMH</th>
<th>Infarcts or Encephalomalacia</th>
<th>Hemorrhage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed</td>
<td>210</td>
<td>11-36%</td>
<td>41%</td>
<td>30-71%</td>
<td>6-40%</td>
<td>7-11%</td>
</tr>
<tr>
<td>Sepsis</td>
<td>88</td>
<td>22-88%</td>
<td>-</td>
<td>21-56%</td>
<td>13-30%</td>
<td>-</td>
</tr>
<tr>
<td>ARDS</td>
<td>15</td>
<td>47%</td>
<td>47%</td>
<td>7%</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Delirium</td>
<td>8</td>
<td>13%</td>
<td>13%</td>
<td>75%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

ARDS = Acute Respiratory Distress Syndrome, WMH = White Matter Hyperintensity

Data was extracted from the following studies 51,163–169
While many patients have normal structural scans, there is a high prevalence of generalized atrophy and white matter hyperintensities (WMH) across all populations. The difference in the prevalence of white matter lesions between populations may suggest alternative pathophysiologic processes, but it also may be due to difference in imaging modalities. For example, WMH were detected in 7% of patients with CT in ARDS patients\textsuperscript{163} versus in 75% of delirious patients using MRI.\textsuperscript{164} More precise quantitative MRI techniques, such as Diffusion Tensor Imaging, have been used to demonstrate worse white matter integrity as measured by the fractional anisotropy in patients with delirium.\textsuperscript{164} Such techniques may identify pre-clinical injury patterns that may not be apparent on regular CT or MRI scans.

1.5.2 Patterns of brain lesions in ICU patients

Brain atrophy affects both grey and white matter, as well as distinct brain structures responsible for specific cognitive functions. Diffuse atrophy, as indicated by higher CT ventricular volumes and ventricular to brain ratios compared to age and sex matched healthy controls, was observed in ARDS patients.\textsuperscript{163} Similar changes were seen in patients with shock and respiratory failure.\textsuperscript{170} Compared to healthy controls, ICU survivors have smaller white matter and hippocampal volumes at 6-24 months following ICU discharge,\textsuperscript{171} and left hippocampal atrophy was also shown in sepsis survivors.\textsuperscript{52} These abnormalities are supported by autopsy findings from patients with ARDS and sepsis that show ischemic hypoxic injury in hippocampus, pons and striatum.\textsuperscript{172}

WMH lesions have been demonstrated in multiple locations including periventricular white matter and centrum semiovale.\textsuperscript{51} The prevalence of these lesions varies, with the highest seen in frontal (80%) and parietal (48%) lobes, followed by occipital (19%) and temporal lobes (14%) as well as brainstem (15%) and cerebellum (5.8%).\textsuperscript{169} In patients with septic encephalopathy, hyperintense lesions also localize to frontal and periventricular brain regions.\textsuperscript{166} Imaging with quantitative MRI in patients with respiratory failure or shock revealed abnormalities in white matter integrity in the genu of corpus callosum and anterior limb of internal capsule at hospital discharge and at 3 months.\textsuperscript{173}
1.5.3 Associations between structural lesions and clinical factors

In the general ICU population, brain atrophy does not appear to be associated with any of the clinical factors including age, admission diagnosis, presence of co-morbid medical conditions, including psychiatric conditions or a history of substance abuse, hospital or ICU length of stay, duration of mechanical ventilation, severity of illness scores (e.g. APACHE II), or hypoxemia.\textsuperscript{51} Similarly, in ICU survivors at 6-24 months post discharge, clinical factors including severity of illness, duration of stay and duration of mechanical ventilation were not associated with general atrophy or smaller hippocampal volumes.\textsuperscript{171} This was also true in the ARDS cohort, where there was no correlations between ventricle-to-brain ratio or ventricular volumes and clinical variables including ICU and hospital lengths of stay, duration of mechanical ventilation, APACHE II scores, and duration and severity of hypoxemia.\textsuperscript{163}

In contrast, hospitalizations for critical illness or major surgical procedures were associated with increased atrophy as measured by increased ventricular size in a large population study that included MR imaging from 885 patients.\textsuperscript{174} In another study, duration of delirium was associated with higher ventricle-to-brain ratios at hospital discharge and 3 months, as well as smaller volumes of frontal lobe and hippocampus, after adjusting for age, severity of illness, and sepsis.\textsuperscript{170} Autopsy findings suggest that duration of hypotension may be a risk factor for development of hippocampal lesions in patients with sepsis and ARDS who develop delirium during their ICU stay.\textsuperscript{172}

White matter hyperintensities are associated with older age, higher severity of illness (as measured by the Simplified Acute Physiology Score II), prior stroke and smoking in ICU patients who had MRI imaging done for acute change in neurologic status.\textsuperscript{169} In patients with delirium, the severity of these lesions correlates with older age.\textsuperscript{164} In septic shock patients, the severity of WMH correlates with the duration of septic shock,\textsuperscript{167} but not shock severity or other biologic markers of inflammation or endothelial activation.\textsuperscript{165} Finally, quantitative MRI methods demonstrate that longer duration of delirium is associated with worse white matter integrity as measured by fractional anisotropy with diffusion tensor imaging MRI in patients with respiratory failure and shock.\textsuperscript{173} However, delirium duration was not associated with any patterns of activation in a functional MRI
study that assessed 47 patients with respiratory failure or shock at discharge and at 3 months.\textsuperscript{175}

In ICU patients who develop acute neurocognitive impairment requiring MRI, new cerebral infarcts are associated with cardiovascular surgery,\textsuperscript{169} or cardioembolic and thromboembolic factors.\textsuperscript{169} In another study, ischemic stroke was independently associated with disseminated intravascular coagulation and focal neurologic signs, but not with the severity of hypotension.\textsuperscript{165}

In summary, duration of delirium and hypotension are the only consistent factors that appears to be associated with brain atrophy. Similarly, longer duration of delirium and septic shock are associated with worse white matter integrity. These observations suggest that delirium likely represents a clinical manifestation of subcortical white matter injury and, given lack of association between inflammation and white matter injury, support the perfusion hypothesis. Some support for this is gained from neuroimaging studies employing xenon-enhanced CT that showed > 40\% reduction in overall cerebral blood flow in delirious patients, with greater reduction occurring in subcortical and occipital regions.\textsuperscript{176} In another study employing single-photon emission computed tomography, reduction in regional cerebral blood flow was seen in the frontal and parietal regions of delirious geriatric patients.\textsuperscript{177} Impairment in cerebral blood flow can result in reduction of oxygen delivery to metabolically active brain tissue resulting in ischemia. Indeed, recent prospective studies showed that low brain tissue oxygenation as measured by cerebral oximetry was an independent predictor of delirium in the critically ill\textsuperscript{178} and septic shock\textsuperscript{179} patients. Furthermore, impairment of cerebral autoregulation within 72 hours of ICU admission is also associated with development of delirium,\textsuperscript{110} suggesting that dysregulation of adaptive mechanisms such as autoregulation may play a role in delirium pathogenesis.
1.5.4 Associations between structural brain lesions and clinical outcomes

In a large population study, brain atrophy was associated with hospitalization and worse executive function. Atrophy was worse with increasing number of hospitalizations, hospitalisation for major surgery, and hospitalization for critical illness. The decline in executive function was worse with increasing number of hospitalizations and hospitalization for critical illness, although large proportion of observed changes in executive function occurred independent of observed structural changes. In sepsis survivors, greater loss of left hippocampal volume was associated with impairment in verbal learning and memory. In patients with delirium, generalized brain atrophy and smaller volumes of superior frontal lobe and hippocampus were associated with worse global cognitive scores and worse executive function at 12 months. In contrast, in ARDS patients, brain atrophy or ventricular enlargement did not correlate with neurocognitive scores.

The degree of white matter hyperintensity appear to correlate with septic shock duration and functional outcomes as measured by the Glasgow Outcome Scale. In patients with delirium, WMH on MRI were associated with impairments in memory, executive function, and attention at three months, despite the absence of baseline cognitive impairment. Similarly, pre-clinical impairment of white matter integrity in the corpus callosum and anterior limb of internal capsule at hospital discharge and 3 months is associated with worse cognitive scores at 3 and 12 months.

Among ICU patients with new ischemic lesions on MRI, only 32% (19/59) had clinical evidence of focal neurologic deficits, suggesting that non-focal ischemia is a common etiology for acute neurologic status change in the ICU. In another study, ischemic stroke was independently associated with increased mortality and worse functional outcomes at 6 months as measured by the Glasgow Outcome Scale.

Functional MRI activation patterns at 3 months following discharge in patients with respiratory failure and shock were not associated with cognitive outcomes at 12 months as measured by the Repeatable Battery for the Assessment of Neuropsychological Status.
(RBANS) cognitive battery and Trails B test\textsuperscript{175} Interestingly, most patients had difficulty completing the N-back task as part of their functional MRI paradigm, which reflect poor working memory ability in this patient cohort. In fact, these patients had worse performance on the N-back task than other medical populations who suffer from frontal lobe deficits including patents with multiple sclerosis, Parkinson’s disease, traumatic brain injury and mild cognitive impairment. Given that RBANS does not include any direct or indirect measures of working memory, failure to detect association between brain activation patterns and cognitive outcomes may be due to the limitations of the cognitive outcomes measure used in this study.
1.6 Study Aims, Objectives and Hypotheses

Survival with preserved cognitive function is an important outcome of critical illness for both patients and clinicians. Prior studies have documented high prevalence of delirium and cognitive impairment in ICU patients that are associated with impairment in dynamic autoregulation and high prevalence of ischemic lesions on neuroimaging. However, the proportion of time that critically ill patients experience ischemia or hyperemia earlier in the course of critical illness is not well established. Furthermore, whether these periods of perturbation in CBF are associated with impairment in dynamic autoregulation or spontaneous fluctuations in MAP or CO$_2$ is unknown.

Prior studies have also documented impaired cerebrovascular function during critical illness. However, it is not clear whether this impairment develops prior to or during critical illness. Given that certain patient groups are at higher risk of critical illness, it is important to establish whether they have pre-ICU impairment in cerebrovascular function. This would be important for interpreting the effects of ICU exposures (such as ischemia and hyperemia) and therapeutic interventions on post-ICU cognitive outcomes in these patients, and for patient stratification in future observational and interventional trials.

Finally, prior studies have used a number of methods to detect cognitive impairment in ICU patients. However, some of these methods are too simple and unable to detect multi-domain cognitive impairment that is common in ICU patients, while other more comprehensive methods are too cumbersome and impractical for routine use in clinical practice and are therefore limited to research studies. There is a pressing need to establish a practical and comprehensive method for assessing neurocognitive outcomes in ICU patients. Such method would be critical in linking ICU exposures (such as ischemia and hyperemia) and pre-ICU functional risk factors (such as impairment in cerebrovascular function) with neurocognitive outcomes.

The overall aim of this work is to: 1) document the cumulative burden of ischemia and hyperemia during early phases of critical illness, and assess its association with impaired dynamic autoregulation and perturbations in MAP and CO$_2$, 2) to identify whether
patients at higher risk of critical illness have pre-ICU impairment in cerebrovascular function, and 3) to develop a clinically feasible yet comprehensive method for assessing neurocognitive outcomes in ICU patients. To achieve this, we have identified three specific aims and corresponding objectives and hypotheses.

**Specific Aim 1 (SA1):** To determine the proportion of time that cerebral blood flow velocity (CBFv) deviates spontaneously beyond previously reported ischemic or hyperemic thresholds in critically ill patients with respiratory failure and/or shock within 48 hours of ICU admission, and to establish whether these deviations are associated with impairment in dynamic autoregulation and changes in MAP or CO₂. **Rationale:** Ischemia has evolved as a plausible mechanism for delirium and long-term cognitive impairment in critically ill patients owning to high prevalence of ischemic injury on neuroimaging and histopathology. In prior studies of cardiac surgery patients, the cumulative duration of CBF deviations beyond ischemic thresholds was associated with major clinical complications including stroke and delirium and development of new ischemic lesions on neuroimaging. If similar CBFv deviations occur in critically ill patients with respiratory failure or shock, it may constitute an important ischemic insult, especially if accumulated over time in the ICU. Since hemodynamic instability (and associated perturbations in CBFv) are more likely to occur in the earlier stages of critical illness, we restricted our observation period to the first 48 hours from ICU admission. Given that dynamic cerebral autoregulation is commonly impaired in critical illness and that this impairment is associated with poor clinical outcomes, we assessed whether spontaneous CBFv deviations were more likely during periods of impaired dynamic cerebral autoregulation. Finally, since CBF is sensitive to changes in CO₂ and MAP and, given that both of these variables can be controlled and optimized in the ICU as potential therapeutic targets, we assessed the relative contribution of concurrently measured spontaneous changes in MAP and CO₂ to observed CBFv deviations. **Objectives:** 1) to determine the proportion of time that CBFv deviates spontaneously beyond previously reported ischemic and hyperemic thresholds in critically ill patients with respiratory failure and/or shock within 48 hours of ICU admission, 2) to assess whether these CBFv deviations are more common during periods of impaired clinical index of dynamic
cerebral autoregulation, and 3) to assess the relative contribution of changes in MAP and CO$_2$ to observed CBFv deviations. **Hypotheses:** 1) CBFv deviates beyond ischemic/hyperemic thresholds for a substantial proportion of the observation period, 2) CBFv deviations will be more common during periods of impaired dynamic cerebral autoregulation, and 3) spontaneous changes in MAP and CO$_2$ explain over 50% of the observed CBFv deviations.

**Specific Aim 2 (SA2):** To assess whether patients with a high risk of critical illness have impaired baseline cerebrovascular function prior to ICU admission. **Rationale:** While previously healthy individuals can develop sudden critical illness (e.g. due to trauma or infection), the majority of critically ill patients have pre-existing chronic comorbidities that are rarely accounted for in critical care research. Incorporating the pre-ICU assessment of baseline cerebrovascular function is essential for interpreting the effects of ICU exposures and interventions, such as those assessed by SA1, on patients outcomes. Given that hemodialysis (HD) patients are at higher risk of developing critical illness compared to the general population, they represent a well-defined clinical population that is at risk for experiencing ischemic insults (such as those studied in SA1) and associated cognitive impairment during critical illness. Whether HD patients have a pre-ICU impairment in cerebrovascular function that can make them vulnerable to ischemic insults during critical illness is unknown. We assessed CVR as a marker of cerebrovascular function in HD patients, and compared it to that in healthy individuals and patients with chronic kidney disease (CKD) who are not yet receiving dialysis. Given that CVR has emerged as an early functional marker of brain tissue at risk for subsequent injury, and since impaired CVR is associated with increased risk of stroke and cognitive impairment, establishing whether HD patients have pre-ICU impairment in CVR would be important for interpreting the effects of ICU exposures and interventions on neurocognitive outcomes in this patient population. **Objectives:** 1) To assess cerebrovascular function using CVR in HD patients, and compare it to CVR in patients with Stage 4 or 5 CKD (i.e. not requiring dialysis) and healthy participants. **Hypothesis:** HD patients will have impaired CVR compared to CKD patients and healthy participants.
Specific Aim 3 (SA3): To establish a clinically feasible and accurate method for assessing neurocognitive outcomes in ICU patients. **Rationale:** Survival with preserved cognitive function is consistently ranked at the top of clinical outcomes hierarchy by both patients and clinicians. In order to assess the impact of CBFv deviations (Specific Aim 1) and impaired CVR (Specific Aim 2) on cognitive outcomes in ICU patients, we require a clinically feasible method for assessing cognition across multiple cognitive domains. However, current cognitive instruments that have been used in prior ICU studies are not optimized for the use in critically ill patients. They include single cognitive tests or simple screening dementia tools that are inadequate for detection of multi-domain cognitive impairment seen in ICU patients. Comprehensive cognitive batteries are not practical for routine clinical use as the need specially trained individuals to administer, require patients to come into clinic, and take long time to complete. Modern web-based cognitive batteries represent an attractive alternative that combine ease of administration and scoring with comprehensiveness. However, whether these web-based cognitive batteries are feasible for use in ICU patients and can detect cognitive impairment across multiple cognitive domains is unknown. Given that web-based batteries require patient participation and ability to use computers or tablets, and since many ICU patients may have cognitive or physical limitation at the time of ICU discharge, we anticipate that some patients will have difficulty completing web-based cognitive testing. It is therefore important to establish the feasibility of using web-based cognitive battery in ICU patients prior to applying it as an outcome measure in future studies. By establishing the clinical feasibility and accuracy of web-based cognitive batteries, we will provide a robust method for assessing this important patient-centered outcome. This method can be utilized in future research studies that assess preventative, therapeutic and rehabilitative interventions, as well as for delivering prognosis to patients and families, and assisting with the healthcare utilization planning. **Objective:** 1) To assess the clinical feasibility and ability of web-based cognitive battery Cambridge Brain Sciences to detect cognitive impairment in ICU patients at or following ICU discharge. **Hypotheses:** 1) We will identify feasibility issues with using Cambridge Brain Sciences for cognitive testing in ICU patients, and 2) Cambridge Brain Sciences battery will detect multi-domain cognitive impairment in ICU patients at or following ICU discharge.
1.7 Research Approach

1.7.1 Challenges of clinical research

Clinical research is challenging and designing a perfect experiment is difficult due to a number of conceptual and practical limitations. These challenges are even more acute in the ICU, where research protocols must be balanced against the severity and dynamics of evolving critical illness, ongoing active clinical interventions, and the constraints of available measurement tools and associated analytical methods. In contrast to basic science experiments and healthy volunteer laboratory studies, where multiple variables can be controlled and accounted for, clinical research in ICU settings requires acknowledgement and embracement of potential clinical biases, confounders and limitations of measurement tools and methods. While basic science and healthy volunteer experiments can be designed to study and dissect specific physiologic and pathophysiologic mechanisms, this is rarely possible in ICU patients, especially in the acute phases of evolving critical illness. Some of the reasons for this include:

1. **Heterogeneity of patients** – excluding few specific cases, the majority of critically ill patients are a heterogenous group that varies in age, pre-morbid health and physiologic reserve. As a result, their responses to the stress of critical illness differ and are difficult to control for even in large scale randomized controlled studies.

2. **Critical illness syndromes** – unlike other clinical specialties that manage defined diseases with well-established pathophysiologic mechanisms, ICU care, especially in the early stages of patient presentation, primary deals with clinical syndromes (i.e. a collection of symptoms and signs rather than a clearly defined pathophysiologic state). The same syndrome (e.g. acute respiratory distress syndrome) can result from different underlying pathophysiologic processes (e.g. pancreatitis versus viral pneumonia), but these differences are often not apparent in the early stages of critical illness. As a result, while both groups of patients present with acute respiratory failure and are often lumped together in clinical ICU studies, their underlying mechanisms of lung injury can be different and may
not be amenable to the same therapeutic interventions. However, the challenge here is in balancing the careful scientific dissection of individual pathophysiologic mechanisms previously identified in basic science or healthy volunteers against the pragmatic need to identify viable clinical therapeutic targets.

3. **Variable time from illness onset to ICU admission** – unlike experimental models of critical illness, where onset of illness and subsequent measurements and interventions can be carefully timed, critically ill patients tend to present at various time points in the trajectory of their evolving illness. While most clinical studies use ICU admission as time zero, few of these acknowledge that the true time zero varies between patients and is often imprecise (estimated from clinical history). Given that temporal evolution of illness can affect physiologic measurements and response to interventions, this is a major limitation of most clinical studies in this arena.

4. **Practical limitations of available instruments** – Basic science laboratory studies benefit from the ability to use precise and often quite invasive instruments to obtain very accurate measurements under carefully controlled experimental conditions. Similarly, research in healthy volunteers or ambulatory patients allows the use of comprehensive research tools (e.g. MRI or PET) that are not practically available at the bedside in the ICU during acute phases of critical illness. Critically ill patients are often too unstable for transport to research scanners in the early phases of critical illness, while use of more precise invasive tools is limited due to increased risk to the patient and need for consent from already distressed substitute decision makers. As a result, acute phase studies need to compromise practicality of available tools against their many limitations and imprecisions.

5. **Practical limitations of available analysis methods** – control of cerebral blood flow is a complex process that involves multiple mechanisms. Studies in basic science laboratories or in healthy volunteers enable simultaneous collection of multiple data points that track these various mechanisms, followed by integration
of these data to obtain comprehensive understanding of the relative contribution of these mechanisms to observed measurements. While a similar approach is much needed in the ICU, it remains practically challenging due to limitations of available equipment, space, and the urgent need for ongoing patient resuscitation and treatment. As a result, most clinical studies of the physiology in critically ill patients are limited by the lack of such comprehensive data and have to acknowledge that their inferences about the truth are limited and incomplete. This, however, does not preclude interpretation of available data and its use in clinical practice, especially if observed physiologic findings are linked to important clinical outcomes (e.g. impairment in dynamic autoregulation indices with delirium or neurocognitive outcomes).\textsuperscript{110,116,118,122,186}

1.7.2 Choice of instruments and analysis methods

To address some of the clinical research challenges outlined in the previous section, we had to compromise between comprehensiveness, accuracy and practicality when selecting instruments and analysis methods for this work. The following section summarizes some of these compromises and provides the rationale for our choices. Ultimately, the instruments and analysis methods were selected based on their utility for use in clinical settings and prior validation against patient-centered outcomes.

**Transcranial Doppler for monitoring CBF** – to address our Specific Aims 1 and 2, we chose to use transcranial Doppler to measure CBF\textsubscript{v} as an index of global CBF. Transcranial Doppler is frequently used in both clinical and research studies in critically ill patients for this purpose. In terms of advantages, it offers high temporal resolution that allows beat by beat measurement of CBF\textsubscript{v} in large intracranial vessels. The high temporal resolution enables correlation with the concurrently measured MAP for calculation of dynamic index of cerebral autoregulation M\textsubscript{xa}. The main disadvantages of transcranial Doppler include poor spatial resolution (i.e. measurement of blood flow velocity in one of the major intracranial vessels at any given time), its operator dependence, and the dependence of the measured absolute velocity on the angle of insonation. However, while tomographic modalities such as CT and MRI provide better spatial resolution, they are not feasible for continuous monitoring of cerebral blood flow
over hours since they are too bulky to employ at the bedside in the ICU and patients are too sick to be transported safely from the ICU to the imaging department. Challenges with operator dependence and angle of insonation can be mitigated by using experienced operators and expressing CBFv as the percent change from patient’s own baseline to facilitate between patient comparisons. Unlike CT or MRI, transcranial Doppler only measures CBFv and not bulk flow. Assessment of cerebral blood flow requires simultaneous measurement of the vessel diameter. As a result, changes in cerebral blood flow velocity are only proportional to changes in cerebral blood flow as long as the vessel diameter stays constant, which is not the case under some circumstances such as hypercapnia, where CBFv underestimates changes in CBF by about 8%. Using CBFv to measure CVR may therefore result in underestimated CVR values. However, this does not preclude comparison of relative differences in CVR between participant groups as long as the same CBFv method and magnitude of change in CO₂ is used in all groups.

**Mxa as an index of dynamic cerebral autoregulation** – To address part of Specific Aim 1, we chose to use Mxa as an index of dynamic cerebral autoregulation. This index is calculated from continuous measurements of CBFv and MAP. In this method, a moving window advanced in 1-minute steps is used to compute correlation coefficient between continuously measured CBFv and MAP. In previous studies, the width of the moving window varied from 5 to 60 minutes. Dynamic autoregulation is said to be impaired if correlation coefficients exceed a specific threshold (e.g. >0.3 in traumatic brain injury patients) or if correlation between CBF and MAP is statistically significant (e.g. in patient with respiratory failure or shock). One of the theoretical concerns with this method is that it assumes that within any given window there is enough variation in MAP to enable correlation of MAP versus CBFv. As a result, if there is no variation in MAP, then correlation between MAP and CBFv (and hence Mx) cannot be done. While this is a valid concern, setting MAP window length to at least 5 minutes or more, advancing the moving window in 1-minute steps and recording the data over several hours would minimize the potential for windows with no variation in MAP. Additionally, only calculating Mx in windows where MAP varies by at least 5 mmHg is an accepted way to mitigate this issue and this method was employed in our analysis. Despite these theoretical limitations, Mxa (and a similar index, COx, derived using near infrared
spectroscopy) has been validated in many clinical studies of critically ill patients with various pathologies and has become an established clinical marker of impaired autoregulation in critical care. Impaired Mxa (or its equivalent, COx), have been associated with delirium and poor neurologic outcomes in patients with respiratory failure, shock, sepsis and traumatic brain injury.\textsuperscript{110,116,186} As a result, existing validation of Mxa against poor clinical outcomes warrants its use as a marker of dynamic autoregulation despite its potential technical limitations.

**CVR as an index of vasomotor control of cerebral blood flow**- To address Specific Aim 2, we chose to use CVR as an index of cerebrovascular function. The role of cerebrovascular function in the control of CBF is complex and involves multiple mechanisms including cerebral autoregulation, neurovascular coupling, CVR and autonomic activity.\textsuperscript{87,88} While there are differences between these individual mechanisms, they all exert their effect on CBF through changes in cerebrovascular resistance by changing the diameter of resistant arterioles. While the relative contribution of each of these mechanisms to maintaining brain health is unclear, impairment in cerebral autoregulation and CVR are both associated with worse neurological outcomes and disease states. In clinical settings, assessment of cerebral autoregulation is often done using either controlled manipulation of MAP using pharmacologic agents (i.e. static autoregulation), or by monitoring CBF response during spontaneous fluctuations in MAP (i.e. dynamic autoregulation). Pharmacologic manipulation of MAP provides a controlled assessment of CBF response across a range of MAP but is invasive and cumbersome. Dynamic autoregulation is non-invasive but has a limited range of MAP across which CBF response is assessed. In contrast, CVR can assess CBF response across a range of CO\textsubscript{2} values and is relatively non-invasive. The use of prospective targeting and dynamic end-tidal forcing methods allows precise and reproducible manipulation of CO\textsubscript{2}, which enables between participant comparison of global and regional CVR. In the last decade, prospective targeting method has enabled a series of studies in healthy participants and patient cohorts using a wide range of instruments for CBF measurements. These studies have clearly linked impairment in CVR with increased risk of stroke,\textsuperscript{149} cognitive impairment\textsuperscript{150,151}, cortical thinning,\textsuperscript{152} and leukoaraiosis.\textsuperscript{153} In concussion, CVR helps differentiate between concussed and normal patients despite similar anatomic and global
resting CBF measurements in both groups.\textsuperscript{154,155} In critically ill patients, impaired CVR has been reported in patients with TBI,\textsuperscript{156–158} sepsis,\textsuperscript{159} and SAH.\textsuperscript{160} As a result, CVR has emerged as a reliable and reproducible non-invasive clinical marker of brain health and vasomotor control of CBF, and was therefore chosen in this study as a method to assess vasomotor control of CBF in HD patients.

**Finapres for monitoring arterial blood pressure for SA2** – We used Finapres NOVA (Finapres, Finapres Medical Systems, Netherlands) to measure hemodynamic parameters including arterial blood pressure non-invasively. While intra-arterial blood pressure monitoring is the gold standard for continuous blood pressure measurements, it is invasive and is associated with complications including hematomas, ischemic necrosis and infections.\textsuperscript{189–191} Furthermore, placement of arterial cannulas in HD patients is technically challenging due to widespread vascular diseases and should be restricted to ICU settings to preserve vascular access. Given that our study was carried out in the laboratory settings on ambulatory HD and CKD patients, as well as healthy volunteers, we elected to use Finapres as the available non-invasive modality. Non-invasive methods such as Finapres are validated in critical care\textsuperscript{192,193} and hemodialysis\textsuperscript{194,195} settings, and used it prior CVR studies.\textsuperscript{196–198} While its accuracy and precision are not interchangeable with direct intra-arterial measurements,\textsuperscript{199,200} it has become an accepted non-invasive alternative in physiological and clinical studies.\textsuperscript{200–204}
REFERENCES


173. Morandi, A. *et al.* The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by


Chapter 2

2 Spontaneous Cerebral Blood Flow Deviations in Critically Ill Patients: Potential Insult Contributing to Ischemic and Hyperemic Injury.

Delirium and long-term cognitive impairment are a common complication of critical illness. Cerebral blood flow (CBF) mediated brain injury (i.e. ischemia and hyperemia) have evolved as plausible biologic mechanisms responsible for these neurocognitive impairments given high prevalence of ischemic injury on neuroimaging and histopathology. While dysfunction in cerebral autoregulation, commonly reported in the critically ill, would make these patients vulnerable to ischemia and hyperemia, the proportion of time that CBF deviates beyond ischemic and hyperemic thresholds during early stages of critical illness is not been well established. Furthermore, whether these deviations are more likely during periods of impaired dynamic cerebral autoregulation is unknown. Finally, since CBF is sensitive to changes in CO$_2$ and MAP and, given that both of these variables can be controlled and optimized in the ICU as potential therapeutic targets, we assessed the relative contribution of changes in MAP and CO$_2$ to observed CBFv deviations. In this study, we document the proportion of time that CBF velocity (CBFv) deviates above and below predetermined thresholds in 12 critically ill patients with respiratory failure or shock within 48 hours of ICU admission. We also examined whether these CBFv deviations were more likely during periods of disturbed dynamic autoregulation as measured by clinically validated index Mxa, and assessed the relative contribution of concurrently measured spontaneous changes in MAP and CO$_2$ on the observed CBFv deviations. We demonstrated that CBFv deviates from its baseline by more than 20-30% for 17-24% of the observation time. These CBFv deviations occurred during periods of both preserved and impaired autoregulation, which was impaired 20-35% of the observation time in our cohort, and were not fully explained by associated spontaneous variations in MAP and CO$_2$. Future work should utilize multimodal monitoring to better delineate mechanisms responsible for observed deviations in CBFv, and to assess whether the cumulative burden of these deviations is associate with clinically relevant outcomes, such as cognitive impairment.
2.1 Introduction

Critically ill patients have a high prevalence of acute (delirium) and long-term cognitive impairment. Ischemic and hyperemic injury have both emerged as plausible biologic mechanisms due to common finding of ischemic lesions on neuroimaging and histopathology, disturbed autoregulation and circulatory stress in this patient population. While spontaneous variation in CBF are common in both healthy adults and patients with primary brain pathology, the proportion of time that CBF deviated beyond ischemic and hyperemic thresholds in critically ill patients without brain injury has not been well described.

In a setting of critical illness, failure of protective mechanisms such as cerebral autoregulation and brain blood brain barrier can make the brain vulnerable to injury during perturbations in CBF that exceed ischemic or hyperemic thresholds. While such thresholds have not been explicitly defined in non-brain injured critically ill patients, prior studies in cardiac surgery patients have shown that the duration of cerebral oxygenation deviation below 10% from baseline was associated with development of new ischemic lesions. Baseline CBF in healthy humans is higher in grey (~50-55 ml/100g/min) than in white (~20-25 ml/100g/min) matter, as are thresholds for cerebral infarction in patients with stroke. As a result, while 10-20% deviation in CBF from baseline may not induce overt ischemia in the grey matter, it may exceed ischemic thresholds (17-18 ml/100g/min) in the white matter and result in functional impairment or injury, especially if accumulated over time. "Such mechanism would explain the high prevalence of white matter abnormalities in the critically ill."

In this study, we aimed to determine the proportion of time that CBF deviated beyond previously reported ischemic and hyperemic thresholds in a cohort of critically ill patients without brain injury early in the course of their critical illness. In secondary analysis, we assessed whether these deviations in CBF were more common during periods of impaired dynamic autoregulation. Finally, we used regression analysis to determine the relative contribution of variations in MAP and end-tidal partial pressure of CO₂ (PetCO₂) to these deviations in CBF.
2.2 Materials and Methods

Study design and Participants

This was a single-centre prospective observational cohort study that was approved by Western University Health Sciences Research Ethics Board (protocol number 106955) and carried out at the Critical Care Trauma Centre, London Health Sciences Centre. We enrolled consecutive adult (age ≥ 18 years) patients within 48 hours of admission to the ICU who presented with a diagnosis of respiratory failure requiring mechanical ventilation > 24 hours and/or shock (defined as the requirement for vasopressors). All participants had an indwelling arterial catheter for continuous monitoring of arterial blood pressure. We excluded patients presenting with primary neurologic diagnosis or known cerebrovascular diseases. Signed informed consent was obtained from patient’s substitute decision maker prior to enrollment in the study. The measurements were made on the day of enrollment into the study.

Cerebral blood flow velocity monitoring

We used transcranial Doppler to measures middle cerebral artery blood flow velocity (CBFv) as an indicator of global CBF. We used 2-MHz transcranial Doppler probes (ST3, Spencer Technologies, USA) to insonate one/both middle cerebral arteries through the transtemporal window. The middle cerebral arteries were identified using standard technique described in the literature, and the probes were fixed in place using provided head frame (Spencer Technologies, Redmond, WA, USA). Adequacy of CBFv signals was continuously monitored throughout the 8 hours of observation by study investigators, and probes were readjusted as needed to ensure same angle of insonation within the same patient and good signal power. Blood flow velocity was sampled and recorded continuously at 125 Hz on ST3 device.

Hemodynamic and CO₂ monitoring

Arterial blood pressure was monitored using an indwelling arterial catheter placed into radial, brachial or femoral arteries. CO₂ was monitored using continuous in-line capnography module integrated into the ventilator circuit (S/5, Datex-Ohmeda, GE
Healthcare, USA). The transduced arterial pressure and expired CO$_2$ were displayed on clinical monitors (S/5, Datex-Ohmeda, GE Healthcare, USA) and continuous waveforms were recorded at 300 Hz on a laptop computer using S5-collect software (Datex-Ohmeda, GE Healthcare, USA).

**Study protocol and data collection**

Following enrollment in the study, baseline demographic, comorbidity and clinical data were obtained from patients’ medical charts and recorded in dedicated case report forms. Waveform cerebral blood flow velocity, arterial pressure and CO$_2$ data were recorded continuously for up to 8 hours and exported as coma-separated values for offline analysis. The data was then uploaded into a custom waveform viewer (LabView, National Instruments, Austin, Texas, USA), where it was aligned using time stamps and processed to ensure adequacy of all signals. Artifacts and sections with poor signals (e.g. CO$_2$ and blood pressure calibration artifacts, coughing, movement resulting in poor signals) were excluded from the analysis. The software then used LabView peak detector function to identify end-tidal CO$_2$ and systolic, diastolic and mean arterial pressures and cerebral blood flow velocity, which were then checked by investigators to ensure appropriate identification of these values from continuous traces. Inappropriately picked values were manually readjusted or excluded from the analysis (e.g. double end-tidal picking due to ventilator asynchrony). Resulting data were averaged over 5 second intervals and exported as comma-separated values for further analysis in Python and Excel. To allow comparison between participants, CBFv was expressed as percent change from participant’s baseline. To calculate primary outcome, we computed the proportion of total recording time that CBFv deviated from baseline above or below thresholds of 5, 10, 15, 20, 25 and 30%. Given that CBF ischemia thresholds have not yet been defined in this patient population, we used a range of thresholds that encompasses previously reported thresholds for ischemia in other patient populations, as well as thresholds that would equate to white matter ischemia.
Figure 2-1: Method for computing the proportion of time that patient’s CBFv (black line) deviated from baseline above and below pre-determined thresholds (blue shaded areas). The three panels above are taken from a single 20-min window from one patient and show CBFv data plotted versus time. The total time that CBFv deviates from baseline into shaded areas in each 20-min window is shown in blue (both absolute and percent of total).

**Dynamic autoregulation analysis**

For our secondary analysis, we computed a clinically validated index of dynamic autoregulation (Mxa)\(^28\) by calculating Spearman’s correlation coefficient between CBF and MAP values within a moving time window advanced in 1-minute steps. In keeping with previous definitions, we defined disturbed autoregulation as Mxa values >0.3 that were statistically significant (p<0.05).\(^29\) Spearman’s method was used instead of Pearson’s as we could not assume the linearity in the relationship between MAP and CBF. To determine the impact of window length on calculation of Mxa, we varied the window length across a range of values (5, 10, 15, 20, 30 and 60 minutes). Mxa was only computed in windows that had at least 5 mmHg variation in MAP.\(^30\) We expressed the duration of disturbed autoregulation for each patient as a fraction of the total analysis time minus the time that Mxa could not be assessed. Figure 2-2 demonstrates how Mxa was computed using data from a representative patient.
Figure 2-2: Sample data from a representative patient showing computation of Mxa. 
Panel A shows 20 minute tracing of CBFv and MAP from a representative patient. Two 5 minute windows are shown to demonstrate periods where autoregulation was impaired (red) versus preserved (green). Panel B zooms in on CBFv and MAP data from the red window in Panel A. Panel C shows Spearman correlation of data from Panel B, with Mxa (r=0.738) exceeding threshold (>0.3) and correlation being statistically significant (p < 0.001). This suggests impaired dynamic cerebral autoregulation for the selected window. Panel D zooms in on CBFv and MAP data from the green window in Panel A. Panel E shows Spearman correlation of data from Panel D, with Mxa (r=0.038) below threshold (>0.3) and non-significant correlation (p < 0.772), suggesting preserved dynamic cerebral autoregulation for the selected window.
**Relationship between CBFv deviations and state of dynamic autoregulation**

To establish whether CBFv deviations beyond thresholds were longer in duration if dynamic autoregulation was impaired, we compared the fraction of time that CBFv deviated above and below thresholds when autoregulation was impaired versus when it was preserved. In each patient, we used 5-min moving windows to compute Mxa as described above in order to assess whether autoregulation was preserved or impaired. We then computed the time (as a fraction of the 5-min window) that CBFv deviated above/below CBF thresholds within the same window. We summarized the data within patients by comparing the cumulative time that CBFv deviated above/below CBF thresholds depending on the state of dynamic autoregulation (preserved vs. impaired). We then compared results across patients. We used 2-way ANOVA and Sidak’s multiple comparison test to assess statistical difference between groups.

**Regression analysis to determine the relative impact of MAP and CO2 on CBFv**

To establish the contribution of variations in MAP and CO2 to observed deviations in CBF, we performed a multiple linear regression analysis with MAP and CO2 as independent variables and CBF as a dependent variable. Regression analysis was done within the same moving time window as Mxa that was advanced at 1-minute interval. To determine the impact of window length on the outcome of regression analysis, we varied it across a range of values (5, 10, 15, 20, 30 and 60 minutes). Regression analysis was completed only in windows that had at least 5mmHg variation in MAP and at least 1mmHg variation in CO2 (the lower magnitude of variation in CO2 was accepted since CBFv is exquisitely sensitive to changes in CO2, ~3-5% change per mmHg change in CO2).\(^{31}\) Regression coefficients of determination (R\(^2\)) for each window length were summarized in each patient and across patients.

**Statistical analysis**

Statistical analysis was performed using the GraphPad Prism software version 8.3 for macOS (GraphPad Software, San Diego, CA, U.S.A.). Categorical variables are reported as counts and percentages of total. Continuous data were analyzed for normal distribution
using the Shapiro-Wilk normality test and were reported as mean and standard deviation for normally distributed data; otherwise, data were summarized using median and interquartile range. We used 2-way ANOVA and Sidak’s multiple comparison test to assess for difference in the duration of CBFv deviations above/below thresholds between windows with preserved vs impaired autoregulation. For all statistical comparisons, a p-value of <0.05 was considered significant.

2.3 Results

Seventeen patients were enrolled in the study. Five patients were excluded (2 due to loss of signals, 2 due to recording equipment malfunction, 1 due to inability to obtain transcranial Doppler signal), leaving 12 patients in the final analysis (Figure 2-3).

![Patient enrollment flow diagram](image)

**Figure 2-3: Patient enrollment flow diagram.**

Patients baseline characteristics are summarized in Table 2-1. Median (interquartile range, IQR) age was 62 (43, 80) years, there were fewer females in our cohort (3/12 patients), and all patients had respiratory failure and required vasopressors for shock. The most common comorbidities included dyslipidemia, obstructive lung disease, and cardiovascular disease. Median (IQR) SOFA score on the day of testing was 10 (7, 12) and arterial to end-tidal PCO₂ difference was 8 (4, 17) mmHg.
### Table 2-1: Patient baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>12</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62 (43, 80)</td>
</tr>
<tr>
<td>Females, n (%)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>MODS score, median (IQR)</td>
<td>6 (5, 8)</td>
</tr>
<tr>
<td>NEMS score, median (IQR)</td>
<td>39 (28, 39)</td>
</tr>
<tr>
<td>SOFA score, median (IQR)</td>
<td>10 (7, 12)</td>
</tr>
<tr>
<td>Arterial-end-tidal PCO$_2$ difference (mmHg)</td>
<td>8 (4, 17)</td>
</tr>
<tr>
<td>Admission diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>Respiratory failure requiring mechanical ventilation</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Shock requiring vasopressors</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Ventilation mode, n (%)</td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Controlled</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (25)</td>
</tr>
<tr>
<td>CAD</td>
<td>3 (25)</td>
</tr>
<tr>
<td>CHF</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Afib</td>
<td>2 (17)</td>
</tr>
<tr>
<td>DM</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Obstructive lung disease</td>
<td>4 (33)</td>
</tr>
<tr>
<td>Restrictive lung disease</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

Values are expressed as counts (%) or as medians (IQR). MODS = multiple organ dysfunction syndrome, NEMS = nine equivalents of nursing manpower, SOFA = sequential organ failure assessment, CAD = coronary artery disease, CHF = congestive heart failure, Afib = atrial fibrillation, DM = diabetes mellitus.

Figure 2-4 shows mean CBFv (expressed as percent change from baseline), MAP and PetCO$_2$ data for all patients. Mean ± standard deviation CBFv was 0.4 ± 17.1%, MAP 78.1 ± 11.5 mmHg, and PetCO$_2$ was 36.0 ± 8.7 mmHg.
Figure 2-4: Mean cerebral blood flow velocity (CBFv), mean arterial pressure (MAP), and end-tidal PCO2 (PetCO2) across all patients. Error bars represent standard deviation. CBF was expressed as percent change from baseline to enable comparison across patients.
**CBFv deviation above and below thresholds**

Mean ± standard deviation of the observation periods was 462.6 ± 39.8 min across all patients. After removal of artifacts, the mean ± standard deviation of observation period available for analysis was 379.2 ± 72.6 min. Table 2-2 summarizes the proportion of time that CBFv was above or below specific thresholds across patients (individual results are provided in Appendix A in Table 6-1)

**Table 2-2: Proportion of time CBFv was above or below specific thresholds**

<table>
<thead>
<tr>
<th>CBFv Threshold (% from baseline)</th>
<th>Proportion of analysis time that CBFv was</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Above threshold</td>
</tr>
<tr>
<td>5</td>
<td>0.43 ± 0.31</td>
</tr>
<tr>
<td>10</td>
<td>0.31 ± 0.31</td>
</tr>
<tr>
<td>15</td>
<td>0.2 ± 0.31</td>
</tr>
<tr>
<td>20</td>
<td>0.15 ± 0.31</td>
</tr>
<tr>
<td>25</td>
<td>0.13 ± 0.31</td>
</tr>
<tr>
<td>30</td>
<td>0.12 ± 0.3</td>
</tr>
</tbody>
</table>

CBFv deviated by more than 10, 20 or 30% from baseline for approximately 52, 24 and 17% of the observation time (Table 2-2). There were more deviations above than below the baseline (Figure 2-5). CBFv deviated by 10-20% below baseline for an average of 9-21% of the observation time.
Figure 2-5: Proportion of time that cerebral blood flow velocity (CBFv) deviated from baseline (y axis) above (Panel A) or below (Panel B) CBFv thresholds (x-axis). Error bars represent standard deviations.

Dynamic Autoregulation

Across patients, dynamic autoregulation was disturbed 20-35% of the observation time depending on the length of the window used to calculate Mxa (Table 2-3). In keeping with the previous studies, longer window length was associated with the larger fraction of observation time with disturbed autoregulation (Figure 2-6).
Table 2-3: Duration of disturbed autoregulation as a function of window length for calculating Mxa.

<table>
<thead>
<tr>
<th>Window Length (min)</th>
<th>Fraction of observation time with disturbed autoregulation (median, IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>0.20 ± 0.16</td>
</tr>
<tr>
<td>10</td>
<td>0.23 ± 0.20</td>
</tr>
<tr>
<td>15</td>
<td>0.25 ± 0.22</td>
</tr>
<tr>
<td>20</td>
<td>0.27 ± 0.24</td>
</tr>
<tr>
<td>25</td>
<td>0.30 ± 0.25</td>
</tr>
<tr>
<td>30</td>
<td>0.35 ± 0.28</td>
</tr>
</tbody>
</table>

Figure 2-6: Fraction of the observation time with disturbed autoregulation as a function of window length used to calculate Mxa. Circles are mean values, Error bars are SD.
Relationship between CBFv deviations and state of dynamic autoregulation

Individual patient data are shown in Figure 6-1, Figure 6-2 and Table 6-2 in Appendix B. While the proportion of time that CBFv deviated above/below CBF thresholds varied across patients, the state of autoregulation within patients had little effect on the duration of these CBFv deviations. In fact, in some patients (e.g. patient 7) CBFv deviations were more common during periods of preserved autoregulation. In another patient (patient 1), CBFv deviations above thresholds were longer during periods of impaired autoregulation while those below thresholds were longer during periods of preserved autoregulation. Across patients, the state of dynamic autoregulation had no impact on the duration of CBFv deviations above or below thresholds (Figure 2-7 and Table 2-4).

Figure 2-7: Relationship between CBFv deviations above/below thresholds and state of dynamic autoregulation across patients. Circles denote preserved autoregulation, while squares denote impaired autoregulation.
Table 2-4: Relationship between CBFv deviations above/below thresholds and state of dynamic autoregulation across patients.

<table>
<thead>
<tr>
<th>CBF threshold</th>
<th>Time CBFv ABOVE threshold (fraction of 5-min window time)</th>
<th>Time CBFv BELOW threshold (fraction of 5-min window time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AR Preserved</td>
<td>AR Impaired</td>
</tr>
<tr>
<td>5</td>
<td>0.449 ± 0.306</td>
<td>0.398 ± 0.217</td>
</tr>
<tr>
<td>10</td>
<td>0.335 ± 0.324</td>
<td>0.268 ± 0.194</td>
</tr>
<tr>
<td>15</td>
<td>0.212 ± 0.314</td>
<td>0.181 ± 0.204</td>
</tr>
<tr>
<td>20</td>
<td>0.152 ± 0.318</td>
<td>0.125 ± 0.214</td>
</tr>
<tr>
<td>25</td>
<td>0.138 ± 0.313</td>
<td>0.100 ± 0.210</td>
</tr>
<tr>
<td>30</td>
<td>0.128 ± 0.305</td>
<td>0.086 ± 0.202</td>
</tr>
</tbody>
</table>

While CBFv deviations during periods of impaired autoregulation are expected, the surprising finding in this analysis was that CBFv deviations occurred for substantial proportion of time during periods of preserved dynamic autoregulation. For example, during periods of preserved autoregulation, across patients CBFv deviated by 10-20% above baseline for 15-34% of observed time and by 10-20% below baseline for 10-22% of observed time.
Regression analysis

Multiple regression analysis with MAP and CO₂ as independent variables and CBFv as a dependent variable yielded very low $R^2$ values across patients. Figure 2-8 shows sample analysis from a representative patient.

Figure 2-8: Sample regression analysis from a representative patient. Panel A shows CBFv, MAP and PetCO₂ data for the entire duration of the recording. Panel B shows a 5-min moving window (same as used to calculate Mxa) from which multiple linear regression is calculated (Panel C) revealing low $R^2$ for this window. Panel D shows an adjacent 5-min window (2 minutes across), where again multiple linear regression is calculated (Panel E), revealing slightly higher, yet still small, $R^2$. This analysis was repeated for each patient using moving windows of various lengths.
Table 2-5 shows within patient results of the regression analysis.

Table 2-5: Within patient results of the multiple linear regression analysis with MAP and CO2 and independent variables and CBF as a dependent variable.

<table>
<thead>
<tr>
<th>Patient</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>30</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.166 ± 0.129</td>
<td>0.166 ± 0.129</td>
<td>0.164 ± 0.160</td>
<td>0.18 ± 0.177</td>
<td>0.205 ± 0.197</td>
<td>0.234 ± 0.216</td>
</tr>
<tr>
<td>2</td>
<td>0.176 ± 0.179</td>
<td>0.192 ± 0.185</td>
<td>0.210 ± 0.184</td>
<td>0.219 ± 0.184</td>
<td>0.217 ± 0.184</td>
<td>0.173 ± 0.170</td>
</tr>
<tr>
<td>3</td>
<td>0.323 ± 0.276</td>
<td>0.390 ± 0.279</td>
<td>0.419 ± 0.275</td>
<td>0.451 ± 0.274</td>
<td>0.506 ± 0.269</td>
<td>0.583 ± 0.237</td>
</tr>
<tr>
<td>4</td>
<td>0.125 ± 0.119</td>
<td>0.106 ± 0.118</td>
<td>0.100 ± 0.104</td>
<td>0.106 ± 0.109</td>
<td>0.115 ± 0.124</td>
<td>0.138 ± 0.157</td>
</tr>
<tr>
<td>5</td>
<td>0.081 ± 0.085</td>
<td>0.051 ± 0.054</td>
<td>0.043 ± 0.040</td>
<td>0.039 ± 0.032</td>
<td>0.035 ± 0.029</td>
<td>0.028 ± 0.032</td>
</tr>
<tr>
<td>6</td>
<td>0.148 ± 0.162</td>
<td>0.107 ± 0.125</td>
<td>0.102 ± 0.134</td>
<td>0.097 ± 0.140</td>
<td>0.092 ± 0.127</td>
<td>0.079 ± 0.091</td>
</tr>
<tr>
<td>7</td>
<td>0.108 ± 0.141</td>
<td>0.094 ± 0.104</td>
<td>0.110 ± 0.128</td>
<td>0.127 ± 0.142</td>
<td>0.160 ± 0.164</td>
<td>0.197 ± 0.162</td>
</tr>
<tr>
<td>8</td>
<td>0.060 ± 0.073</td>
<td>0.043 ± 0.062</td>
<td>0.038 ± 0.052</td>
<td>0.035 ± 0.048</td>
<td>0.032 ± 0.042</td>
<td>0.027 ± 0.022</td>
</tr>
<tr>
<td>9</td>
<td>0.181 ± 0.180</td>
<td>0.184 ± 0.207</td>
<td>0.202 ± 0.228</td>
<td>0.224 ± 0.246</td>
<td>0.269 ± 0.269</td>
<td>0.333 ± 0.272</td>
</tr>
<tr>
<td>10</td>
<td>0.198 ± 0.178</td>
<td>0.186 ± 0.172</td>
<td>0.186 ± 0.176</td>
<td>0.184 ± 0.183</td>
<td>0.195 ± 0.184</td>
<td>0.213 ± 0.188</td>
</tr>
<tr>
<td>11</td>
<td>0.119 ± 0.146</td>
<td>0.157 ± 0.185</td>
<td>0.196 ± 0.209</td>
<td>0.213 ± 0.214</td>
<td>0.229 ± 0.214</td>
<td>0.279 ± 0.189</td>
</tr>
<tr>
<td>12</td>
<td>0.100 ± 0.106</td>
<td>0.066 ± 0.081</td>
<td>0.050 ± 0.062</td>
<td>0.043 ± 0.055</td>
<td>0.039 ± 0.048</td>
<td>0.042 ± 0.045</td>
</tr>
</tbody>
</table>

| Group mean ± SD | 0.133 ± 0.153 | 0.141 ± 0.178 | 0.154 ± 0.192 | 0.165 ± 0.204 | 0.182 ± 0.219 | 0.205 ± 0.231 |
Across patients, The $R^2$ varied from $0.13 \pm 0.15$ to $0.21 \pm 0.23$ depending on the window length used to complete regression analysis (Figure 2-9).

Figure 2-9: Results of multiple linear regression analysis with MAP and CO2 and independent variables and CBF as a dependent variable. The figure shows changes in coefficient of determination ($R^2$) as a function of window length use for regression analysis.
2.4 Discussion

*Main findings*

Our study shows that in critically ill patients with respiratory failure or shock, CBF\(v\) deviates from its baseline by more than 20-30% for 17-24% of the observation time. There were more CBF\(v\) deviations above than below the baseline (15 ± 31 vs 9 ± 13% of the observation time). These CBF\(v\) deviations occurred both during periods of preserved and impaired dynamic autoregulation, which was impaired 20-35% of the observation time in our cohort, nor were they fully explained by associated variations in MAP and CO\(\text{2}\). Given that CBF thresholds used in our study are similar to those associated with ischemic injury and neurologic symptoms from previous studies in cardiac surgery patients, our findings represent biologically plausible insult that may lead to CBF-mediated brain injury in critically ill patients independently from the state of dynamic autoregulation or changes in MAP and CO\(\text{2}\).

*CBF deviations in healthy subjects and patients with neurologic disorders*

To our knowledge this is the first study to quantify the magnitude and duration of spontaneous CBF\(v\) deviations beyond specific thresholds in patients with respiratory failure or shock. Spontaneous deviations in CBF have been previously described in healthy participants and in patients with neurologic disorders. In one study that recorded CBF over 5-10 minutes, the mean ± standard error range of CBF variations was 11± 4% in healthy participants and 14 ± 13% in neurosurgical population. Five of 11 healthy participants had at least one wave with a range of more than 20% compared to 13 of 22 neurosurgical patients.\(^\text{16}\) In another study that recorded CBF over 2 hours in resting supine healthy participants, the range of CBF variation was 77 ± 8 % and coefficient of variation of 9.3 ± 2%.\(^\text{14}\) Most of these CBF deviations occurred at frequencies lower than 0.1 Hz, where dynamic autoregulation appeared to be most effective.\(^\text{14,15}\)

More recent research in traumatic brain injury suggests that deviation in cerebral perfusion are common and considerable in duration. Davie et al. used cerebral oximetry to show that 12 of 18 patients experience an episode of cerebral desaturation (defined as
regional cerebral oxygen saturation of < 65%, which is ~7-10% reduction from baseline) and that the duration of these desaturations episodes over 72 hours varied from 2.6 to 26% of observation time, with a median of 8.1%. This magnitude and duration of reduction in cerebral perfusion pressure is comparable to our study, where the mean time with CBFv deviation of more than 20% below baseline was 9 ± 13% of total observation time.

**What CBF thresholds are associated with brain injury?**

While much work has been done on ischemic thresholds in animal models and human studies of stroke, information in other clinical populations is less clear. Synaptic failure threshold corresponds to reduction of CBF below 15-20 ml/100g/min, which causes loss of EEG signal in humans, cortical SSEP signals in baboons, and loss of spontaneous neuronal firing in cats. The threshold for membrane failure is lower, reported at 6-7 ml/100g/min. The threshold for infarction is around 10 ml/100g/min, but development of infarction takes time such that low flows of 5 to 8 ml/100g/min can be tolerated of up to 1 hours without resulting in infarction. More recent MRI studies from human stroke suggest higher thresholds for ischemic injury that vary between grey (median 34.6 ml/100g/min) and white (median 20.8 ml/100g/min) matter. In fact, functional brain impairment likely occurs at higher thresholds than are required for infraction. For example, cellular protein synthesis is inhibited at CBF values of 35-55 ml/100g/min, and reduction in CBF below 37 ml/100 g/min causes reversible deterioration in sustained attention in patients undergoing occlusion of the internal carotid artery as part of inoperable cavernous sinus aneurism management. These thresholds represent about 20-30% reduction in global CBF, which is similar to the thresholds used in this study.

More recent clinical studies in cardiac surgery patients suggest that the time below cerebral oxygenation thresholds of only 7-10% from baseline is associated with major clinical complications including stroke and delirium and development of new ischemic lesions on neuroimaging. Interestingly, in the latter study, the majority (70%) of new lesions developed in the watershed areas of the brain, suggesting that sub-cortical white matter tracts are at higher risk of this subclinical ischemic injury. Given high prevalence
of subcortical white matter injury in the critically ill,\textsuperscript{4,5} and its association with the duration of ICU delirium\textsuperscript{41}, the deviations of CBF by 20-30\% from baseline reported in this study may be of clinical significance. Assuming baseline white matter CBF of 20-22 ml/100g/min,\textsuperscript{42} 20-30\% reduction in CBF below the baseline would correspond to a reduction in white matter CBF to ischemic levels of 15-17 ml/100g/min. Since critical illness is associated with the disruption of the brain blood barrier\textsuperscript{18}, hyperemic response may also contribute to injury by increasing intracranial pressure\textsuperscript{43} and contributing to formation of brain edema, especially in settings of disturbed autoregulation.\textsuperscript{44}

\textit{The duration of CBF deviations beyond thresholds – “time is brain”}

In stroke literature, the concept of “time is brain” is well established. Each minute delay without treatment corresponds to 1.9 million neurons, 14 billion synapses, and 12 km (of myelinated fibers being destroyed, which is equivalent to accelerated ageing at a rate of 3.6 per hour of no treatment.\textsuperscript{45} While ischemic injury in stroke may be an extreme case of neuronal injury, similar evidence is evolving for more subtle injury in cardiac surgery patients. In patients undergoing aortic surgery, the duration of time that regional cerebral oxygenation deviates below 65\% (which is \(\sim\)7-10\% below baseline) is associated with greater number of major post-operative clinical complications (including stroke, delirium, respiratory and renal failure) and longer duration of mechanical ventilation, ICU and hospital length of stay.\textsuperscript{40} In another study of elective cardiac surgery patients, the duration of time that regional cerebral oxygenation was 10\% below baseline was associated with development of new ischemic lesions, 70\% of which were in the watershed areas of the brain.\textsuperscript{19} The median time that regional cerebral oxygenation was 10\% below baseline in patients with new ischemic lesions was 11 minutes, which corresponds to \(\sim\)5\% of the total observation time, highlighting that even short cumulative duration of modest impairment in cerebral perfusion can result in subclinical watershed ischemic brain injury. This duration of cerebral perfusion deviation into ischemic zone is comparable to our study, where CBFv deviated by more than 20-30\% below baseline for a mean 5-9\% of the observation time. The importance of time in development of brain dysfunction is further highlighted by a recent study from critically ill patients showing
that the cumulative duration of dysfunctional cerebral autoregulation is associated with the development of ICU delirium.\textsuperscript{32}

\textit{Cerebral autoregulation and deviations in CBF}\textit{v}

In our study, dynamic cerebral autoregulation was disturbed 20-35\% of the observation time, depending on the length of the window used to compute Mxa (Figure 2-6). However, the disturbance in autoregulation had no impact on the duration of CBF\textit{v} deviations above/below thresholds (Figure 2-7). In fact, during periods of preserved autoregulation CBF\textit{v} deviated by 10-20\% above/below baseline for 10-34\% of observation time. These findings suggest that preserved dynamic autoregulation does not prevent substantial variations in CBF\textit{v}.

The prevalence of disturbed dynamic autoregulation and its association with poor outcomes in critically ill patients are well established. In patient with head injury, disturbed dynamic autoregulation is associated with worse neurologic outcomes and higher mortality.\textsuperscript{46} In sepsis, disturbed autoregulation occurs in up to 50\% of patients and is associated with the development of sepsis-associated brain dysfunction.\textsuperscript{29} In patients with respiratory failure or shock who were monitored continuously for 72 hours, dynamic cerebral autoregulation was impaired for a median of 5.2\% of the observation time in never delirious patients and 10.4\% of the observation time in delirious patients, and the duration of time with disturbed autoregulation correlated with the duration of delirium.\textsuperscript{32}

The disturbance of dynamic autoregulation is clearly associated with the brain dysfunction in critically ill patients, likely by making the brain vulnerable to ischemic and hyperemic injury during variations in CBF. While we confirmed long periods of disturbed dynamic autoregulation in our patients, we were surprised to find prolonged and substantial deviations in CBF\textit{v} during periods of preserved autoregulation.

Our findings suggest that in critically ill patients prolonged deviations in CBF\textit{v} from baseline can occur independently of disturbances in dynamic autoregulation. Whether cumulative burden of these CBF\textit{v} deviations is an independent predictor of poor clinical outcomes requires further dedicated studies.
**Association of CBFv deviations with MAP and CO₂**

Arterial blood pressure and CO₂ are important determinants of CBF. Changes in MAP result in changes in cerebral perfusion pressure and CBF, especially if cerebral autoregulation is impaired. CBF is also exquisitely sensitive to arterial CO₂, which can induce changes in CBF by altering cerebrovascular resistance (1 mmHg change in arterial PCO₂ is associated with approximately 2-5% change in CBF in subjects with preserved cerebrovascular reactivity). Given that both MAP and CO₂ are important determinants of CBF, and since both of these variables fluctuate spontaneously in critically ill patients, we used multiple regression analysis to determine whether CBF deviations can be explained by concurrent changes in MAP and CO₂.

Our analysis revealed that across patients variation in MAP and CO₂ explain only 13-21% of the observed variance in CBFv (Figure 2-9). These findings suggest that variables other than MAP and CO₂ are responsible for a large proportion of the observed CBFv deviation. Alternative mechanisms responsible for observed CBFv deviations may include changes in cardiac output, which has been shown to be an important determinant of CBF independent of cerebral autoregulation and MAP, as well as changes in regional cerebral metabolism and cerebrovascular resistance. Our results highlight the complexity of CBF regulation in the critically ill patients and warrant further multimodal studies to delineate the relative contribution of various control mechanisms to observed deviations in CBF.

**Future work**

Future studies should assess whether the cumulative burden of observed deviations in CBFv from baseline is associated with clinically relevant outcomes including delirium and long-term cognitive impairment. Furthermore, given that after accounting for variations in MAP and CO₂, ~80% of variance in CBFv remained unexplained, future work should concurrently assess additional variables that may affect CBF including cardiac output and measures of cerebral metabolism and regional cerebral perfusion. While tomographic imaging modalities such as PET and MRI would be ideal for these measurements, it may not be feasible or safe to transport critically ill patients outside of
ICU for prolonged periods of monitoring using these tomographic modalities. Furthermore, given that assessment of dynamic autoregulation requires high frequency monitoring of CBF and MAP, the lower temporal resolution of MRI and PET may not be ideal for the assessment of dynamic autoregulation in these patients. Multimodal monitoring with transcranial Doppler, near infrared spectroscopy, diffuse correlation spectroscopy and non-invasive continuous cardiac output monitors is likely an optimal compromise to enable simultaneous assessment of global and regional CBF, regional cerebral metabolism, dynamic autoregulation and cardiac output at the bedside of critically ill patients. Our plans are to explore this approach in future studies.

**Limitations**

Our study had several limitations. Due to the pilot nature of our study, we had a relatively small sample size and as a result of consecutive patient enrollment strategy our sample was not equally balanced between females and males. However, we were still able to demonstrate that, similar to patients with traumatic brain injury, critically ill patients experienced 20-30% deviations in CBF from baseline for substantial periods of time. We also showed that our patients experienced substantial periods of disturbed dynamic cerebral autoregulation. Another limitation of our study is that the use of transcranial Doppler limited our assessment of cerebral blood flow velocity to middle cerebral artery, and therefore represent only portion of global cerebral blood flow. However, the portable nature of transcranial Doppler relative to comprehensive tomographic modalities allowed its application at the bedside early in the course of critical illness when these patients are usually very unstable for transfer to neuroimaging department. Furthermore, its high temporal resolution made it an ideal tool for monitoring and discerning high frequency changes in CBFv over prolonged period of observation used in this study. Finally, whether the observed deviations in CBFv are associated with ischemic brain injury and brain dysfunction, or are simply an epiphenomenon, remains unknown. However, our study provides biologic rationale for future studies to establish whether observed deviations in CBF from baseline in this patient population are associated with imaging markers of brain injury or functional brain impairment.
2.5 Conclusions

In critically ill patients with respiratory failure or shock, CBFv deviates by 20-30% from baseline for 17-24% of observation time early in the course of ICU admission. These deviations occurred both during periods of preserved and impaired autoregulation, and were not fully explained by corresponding changes in MAP and CO₂. Future studies should use multimodal neuromonitoring to establish the mechanisms responsible for these CBF deviations, and assess whether cumulative burden of these deviations is associated with imaging markers of brain injury and poor neurologic outcomes.
REFERENCES


Chapter 3

3  Impairment in Baseline Cerebrovascular Function in Patients at High Risk of Critical Illness.

In the previous chapter we showed that critically ill patients experience substantial deviations in cerebral blood flow (CBF) beyond ischemic and hyperemic thresholds early in the course of their critical illness. Such deviations can lead to ischemic or hyperemic injury, especially in patients with impaired cerebrovascular function. However, the functional status of cerebral vasculature in patients who are at high risk of critical illness has not been systematically studied or taken into account when interpreting the effects of ICU exposures and interventions.

Cerebrovascular reactivity to CO₂ (CVR) has emerged as a reliable marker of cerebrovascular function,¹ and impaired CVR is associated with increased risk of stroke² and cognitive impairment.³,⁴ Given that patients with end-stage renal disease receiving hemodialysis (HD) are at higher risk of developing critical illness and requiring admission to the ICU,⁵ we used CVR to assess their cerebrovascular function and compare it to CVR in patients with Stage 4 or 5 chronic kidney disease (CKD, i.e. not requiring dialysis) and healthy participants.

We found that HD patients have impaired CVR compared to CKD patients and healthy participants. We also showed that there was no difference in CVR between CKD patients and healthy participants, suggesting that the impairment in CVR was not simply due to reduction in renal function, but is likely related to the hemodialysis treatment. Our results suggest that certain patient groups may have pre-ICU impairment in cerebrovascular function which can make them vulnerable to ischemic and hyperemic insults during critical illness. Future studies should assess whether pre-ICU impairment in CVR is associated with poor neurocognitive outcomes during and following critical illness.
3.1 Introduction

Critically ill patients suffer from high rates of acute (delirium) and long-term cognitive impairment. The risk for developing delirium and long-term cognitive impairment is thought to be dependent on an interplay between predisposing and precipitating factors. In a recent systematic review of risk factors for ICU delirium, age, hypertension and dementia were identified as predisposing factors, and pre-ICU trauma or emergency surgery, severity of illness score (APACHE II score), mechanical ventilation, metabolic acidosis, delirium on the prior day and coma were identified as precipitating factors. Delirium and delirium duration appear to be the only consistent risk factors for long term cognitive impairment. \(^6\)\(^7\) While these demographic and clinical risk factors are important for identifying at risk patients, the underlying mechanisms responsible for delirium are poorly understood, which impedes development of targeted interventions.

Ischemia has emerged as a plausible mechanism for ICU related brain dysfunction given common occurrence of hemodynamic instability and shock in the critically ill. \(^8\)\(^9\) Data from neuroimaging studies supports the ischemic hypothesis given high prevalence of subcortical white matter injury that is associated with the duration of delirium \(^10\) and septic shock. \(^11\) It remains unknown whether certain patient populations are at higher risk of ischemic or hyperemic injury during critical illness due to baseline impairment in cerebrovascular function.

Patients with end-stage renal disease who require dialysis are at higher risk of requiring hospitalization and admission to the intensive care units, with a 30-fold risk of critical care requirements compared to the general population. \(^5\)\(^12\)\(^-\)\(^14\) While in the ICU, chronic dialysis patients are more critically ill, having higher severity of illness scores, \(^12\) and have more comorbidities that the general population including higher rates of diabetes and peripheral arterial disease. \(^15\) They also have higher ICU mortality rates \(^12\) that are related with physiologic disturbances including hypotension \(^12\) and the need for inotropic support, \(^16\) suggesting impaired physiologic reserve and, potentially, cerebrovascular function.
HD patients also have high prevalence of cognitive impairment, with as many as 70% having moderate to severe cognitive impairment.\textsuperscript{17,18} Unlike ageing or Alzheimer’s disease that predominately affects memory, cognitive impairment in HD patients spans multiple domains including orientation and attention, language, construction and motor function, concept and reasoning, memory, and executive function.\textsuperscript{17,18} The most severe deficits occur in the domains of attention and executive function,\textsuperscript{18} which corresponds to changes seen in patients with vascular\textsuperscript{19} rather than neurodegenerative dementia. The vascular hypothesis for cognitive impairment is supported by a recent findings that cerebral ischemia occurs in almost 25% of hemodialysis sessions\textsuperscript{20} and that global CBF falls by an average of 10%, with concurrent reduction in regional CBF in the frontal, parietal, temporal, and occipital lobes, as well as cerebellum and thalamus.\textsuperscript{21} Furthermore, incident HD patients develop new diffuse subcortical white matter injury that is independent of the traditional cardiovascular risk factors (smoking, diabetes and ischemic heart disease), but is associated with the multi-domain cognitive impairment and with hemodynamic instability during dialysis sessions as measured by the mean arterial pressure (MAP) extrema points.\textsuperscript{22} Interventions to improve hemodynamic stability, such as dialysate cooling, appear to completely protect HD patients from this pattern of brain injury.\textsuperscript{23} While the circulatory stress of hemodialysis is a plausible ischemic insult in HD patients, it may be superimposed on the impaired cerebrovascular function that provides an optimal milieu for development of observed subcortical white matter injury. Whether HD patients have impairment in cerebrovascular function as measured by CVR is unknown.

In this study we measured CVR as a marker of cerebrovascular function in prevalent HD patients and compared it to CVR in stage 4 or 5 CKD patients and healthy participants. We hypothesized that CVR will be impaired in HD patients compared to those in healthy participants and CKD patients. Given that HD patients represent a well-defined group that is at high risk of critical illness, identifying whether they have impaired cerebrovascular function at baseline prior to critical illness will help interpret the effects of ICU exposures such as CBF\textsubscript{v} deviations reported in Chapter 2, and inform future
observational and interventional studies seeking to understand the mechanisms of ICU delirium and long-term cognitive impairment.

3.2 Materials and Methods

**Study design and Participants**

This was a single-centre prospective observational study that was approved by Western University Health Sciences Research Ethics Board (protocol number 109548) and carried out at the Kidney Clinical Research Unit in London, Canada. HD and CKD patients were recruited from the prevalent patient population of the hemodialysis and chronic kidney disease programs at Kidney Care Centre, London Health Sciences Centre. Healthy participants were recruited from the general population using poster advertisements. Inclusion criteria varied by participant group. For healthy participants we included adults (age ≥ 18 years) with no history of cardiovascular disease, cerebrovascular disease, diabetes or CKD. For CKD patients, we included adults (age ≥ 18 years) with a diagnosis of stage 4 or 5 CKD. For HD patients, we included adults (age ≥ 18 years) who were receiving hemodialysis treatment at least 3 times per week at a London Health Sciences Centre facility. Dialysis patients were tested on the day between their dialysis sessions. Exclusion criteria in all participants were: severe chronic obstructive lung disease or asthma, past history of cerebrovascular accident (stroke or transient ischemic attack), carotid stenosis or carotid surgery, prior neurosurgery, history of vasculitis, pregnancy and mental incapacity for consent. All participants signed an informed consent form prior to participation in the study.

**Cerebral blood flow monitoring**

We used transcranial Doppler to measures middle cerebral artery blood flow velocity (CBFv) as an indicator of global cerebral blood flow. We used 2-MHz transcranial Doppler probes (ST3, Spencer Technologies, USA) to insonate one/both middle cerebral arteries through the transtemporal window. The middle cerebral arteries were identified using standard technique described in the literature,\textsuperscript{24,25} and the probes were fixed in
place using provided head frame (Spencer Technologies, Redmond, WA, USA). CBFv was sampled and recorded continuously at 125 Hz on an ST3 device.

**CO₂ changes**

We used an automated gas blender and gas delivery breathing circuit (RA-MR, RespirAct™, Thornhill Medical, Toronto, Canada) to prospectively target and control end-tidal gases. The RespirAct™ is based on theory of sequential gas delivery to provide a quantitative and reproducible CO₂ stimulus that has been previously used to quantify cerebrovascular response to CO₂ in healthy participants and patients. Unlike other vasodilatory stimuli such as transient or pharmacologically induced changes in MAP, administration of acetazolamide, breath holding, or addition of CO₂ to inspired gas, prospective targeting offered by RespirAct™ allows for a non-invasive, rapidly reversible and reproducible stimulus that greatly reduces between subject variability in the CO₂ stimulus, allowing for a more accurate measurement of cerebrovascular response. Methods that use increased inspired fraction of CO₂ often result in unpredictable end-tidal partial pressure of CO₂ (PetCO₂) due to variable ventilatory sensitivity to CO₂ among participants, sometimes resulting in paradoxical reduction in PetCO₂. Furthermore, with inspired CO₂ methods the variable difference between PetCO₂ and arterial PCO₂ (PaCO₂) between participants adds error to estimation of the stimulus magnitude. In contrast, the prospective targeting method used in this study has been shown to accurately reflect changes in PaCO₂ from PetCO₂.

**Hemodynamic monitoring**

We used Finapres NOVA (Finapres, Finapres Medical Systems, Netherlands) to record global hemodynamic parameters non-invasively. The Finapres measures hemodynamics by continuous non-invasive pulse-wave analysis at the digital artery. The Finapres utilizes a finger-cuff with infra-red photoplethysmograph to detect beat-to-beat changes in digital artery blood pressure and calibrates this to oscillometric brachial artery pressure. Heart rate (HR), systolic (SBP), diastolic (DBP) and mean arterial (MAP) blood pressures, and cardiac output (CO) were derived and measured continuously. The finger-cuff was placed on an appropriate finger (preferably the middle finger of the non-fistula
arm) and on the upper arm of the same arm. Non-invasive methods such as Finapres are validated in critical care\textsuperscript{34,35} and hemodialysis\textsuperscript{36,37} settings, and used it prior CVR studies.\textsuperscript{38–40} While its accuracy and precision are not interchangeable with direct intra-arterial measurements,\textsuperscript{41,42} it has become an accepted non-invasive alternative in physiological and clinical studies.\textsuperscript{42–46}

\textit{Study protocol and data collection}

Participants were tested in the Kidney Clinical Research Unit at Victoria Hospital, London Health Sciences Centre. Baseline participant demographic and relevant clinical data for patient participants were recorded in dedicated case report forms. Participants were seated in a comfortable recliner chair for the duration of the study. After application of the transcranial Doppler probes, the non-invasive hemodynamic monitor probe and a RespirAct\textsuperscript{TM} facemask, baseline respiratory and hemodynamic data were acquired after 5 minutes of acclimatization to the experimental apparatus. The CO\textsubscript{2} sequence consisting of three 5-minute stages was then applied: 1) patient’s own resting PetCO\textsubscript{2} (baseline); 2) increase in PetCO\textsubscript{2} by 10 mmHg above baseline (intervention); and 3) return to resting PetCO\textsubscript{2} (recovery) (Figure 3-2). RespirAct\textsuperscript{TM} eliminates the usual end-tidal to arterial difference in PCO\textsubscript{2}, so that changes in PetCO\textsubscript{2} actually reflect changes in PaCO\textsubscript{2}.\textsuperscript{33} End-tidal partial pressure of O\textsubscript{2} (PetO\textsubscript{2}) was kept constant at normoxia. CBFv, hemodynamics and changes in end-tidal gases were recorded continuously and exported as comma-separated values for offline analysis. Data analysis was performed using custom Python software, where CBF, hemodynamic and respiratory data were aligned using time stamps. To allow comparison between participants, CBFv was expressed as percent change from participant’s baseline. The average values for CBFv, hemodynamic variables (MAP, HR, CO), PetCO\textsubscript{2} and PetO\textsubscript{2} for each experimental stage were calculated using data from the last minute of each 5-minute stage. To assess for hysteresis, CVR was calculated as the percent change in CBFv divided by the change in PetCO\textsubscript{2} for both increase in PetCO\textsubscript{2} from baseline to hypercapnia (CVR intervention) and decrease in PetCO\textsubscript{2} from hypercapnia back to baseline (CVR recovery).
**Statistical analysis**

Statistical analysis was performed using the GraphPad Prism software version 8.3 for macOS (GraphPad Software, San Diego, CA, U.S.A.). Continuous data were analyzed for normal distribution using the Shapiro-Wilk normality test. Descriptive statistics were reported as mean and standard deviation for normally distributed data; otherwise, data were summarized using median and interquartile range. To compare differences between participant groups (healthy vs. CKD vs. HD patients), we used one and 2-way ANOVA with Tukey’s multiple comparisons test for normally distributed variables, and Kruskal–Wallis test for non-normally distributed variables. We used Pearson’s correlation or non-parametric (Spearman’s rank) correlation analysis to assess the strength of relationship between CVR and change in MAP, HR, CO, estimated glomerular filtration rate (eGFR, for CKD patients only) and dialysis vintage (length of time on dialysis, for HD patients only) within participant groups. We reported correlation coefficients (r-values) and the significance level of the p-value. A p-value of <0.05 was considered significant.

**3.3 Results**

A total of 24 healthy participants, 12 CKD and 15 HD patients met the inclusion criteria and were enrolled in the study. Of these, 7 healthy participants, 2 CKD patients and 7 HD patients were excluded due to equipment malfunction (5 healthy, 3 HD), poor CO\textsubscript{2} intervention due to leak around facemask (2 healthy, 1 CKD, 2 HD), inability to tolerate intervention (1 CKD, 1 HD) and inability to obtain good quality TCD signals (1 HD). A total of 17 healthy participants, 10 CKD and 8 HD patients completed full protocol and were included in the final analysis (Figure 3-1).
Figure 3-1: Patient enrollment flow diagram.

Participant baseline characteristics are summarized in Table 3-1.
Table 3-1: Participant baseline characteristics.

<table>
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<th>CKD</th>
<th>HD</th>
<th>P-values</th>
</tr>
</thead>
<tbody>
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<td><strong>n</strong></td>
<td>17</td>
<td>10</td>
<td>8</td>
<td>0.0022</td>
</tr>
<tr>
<td><strong>Females, n (%)</strong></td>
<td>8 (47%)</td>
<td>3 (30%)</td>
<td>3 (38%)</td>
<td>0.6735</td>
</tr>
<tr>
<td><strong>Age (yrs)</strong></td>
<td>31 (26, 41)</td>
<td>71 (56, 73)</td>
<td>69 (61, 71)</td>
<td>0.0002</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>68 (64, 85)</td>
<td>94 (84, 102)</td>
<td>91 (85, 105)</td>
<td>0.0077</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>168 (165, 174)</td>
<td>175 (163, 182)</td>
<td>172 (163, 175)</td>
<td>0.5257</td>
</tr>
<tr>
<td><strong>CBFv (cm/s)</strong></td>
<td>52 (43, 60)</td>
<td>48 (46, 56)</td>
<td>45 (21, 58)</td>
<td>0.5956</td>
</tr>
<tr>
<td><strong>PCO2 (mmHg)</strong></td>
<td>38 (35, 42)</td>
<td>36 (34, 38)</td>
<td>42 (37, 46)</td>
<td>0.0400</td>
</tr>
<tr>
<td><strong>PO2 (mmHg)</strong></td>
<td>103 (102, 112)</td>
<td>111 (107, 114)</td>
<td>108 (92, 112)</td>
<td>0.1739</td>
</tr>
<tr>
<td><strong>SBP (mmHg)</strong></td>
<td>129 (119, 137)</td>
<td>136 (116, 145)</td>
<td>127 (107, 178)</td>
<td>0.7120</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>96 (90, 103)</td>
<td>90 (82, 100)</td>
<td>87 (71, 103)</td>
<td>0.4681</td>
</tr>
<tr>
<td><strong>DIA (mmHg)</strong></td>
<td>76 (70, 82)</td>
<td>68 (60, 80)</td>
<td>63 (56, 70)</td>
<td>0.0718</td>
</tr>
<tr>
<td><strong>HR (bpm)</strong></td>
<td>76 (67, 83)</td>
<td>73 (56, 85)</td>
<td>68 (58, 79)</td>
<td>0.6330</td>
</tr>
<tr>
<td><strong>CO (L/min)</strong></td>
<td>5.7 (5.1, 6.4)</td>
<td>5.7 (5.5, 7.4)</td>
<td>7.8 (6.7, 9.8)</td>
<td>0.0625</td>
</tr>
<tr>
<td><strong>eGFR</strong></td>
<td>22 (17, 27)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Dialysis vintage (months)</strong></td>
<td>27 (14, 62)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Values are expressed as medians (interquartile range). Abbreviations: H= Healthy participants, CKD = chronic kidney disease patients, HD = hemodialysis patients, CBFv = mean cerebral blood flow, PCO2 = end-tidal partial pressure of CO2, PO2 = end-tidal partial pressure of O2, SBP = systolic blood pressure, MAP = mean arterial blood pressure, DIA = diastolic blood pressure, HR = heart rate, CO = cardiac output, eGFR = estimated glomerular filtration rate. * p<0.05 values highlighted are in italics.
Healthy participants were younger (median 31.0 years, IQR 26, 41) than CKD patients (median 71 years, IQR 56, 73, \( p = 0.0009 \)) and HD patients (median 69 years, IQR 61, 71, \( p=0.0034 \)). There was no difference in age between CKD and HD patients \( (p>0.9999) \). Healthy participants also had a lower weight (median 68 kg, IQR 64, 85) than CKD (median 94 kg, IQR 84, 102, \( p = 0.0142 \)) and HD (median 91 kg, IQR 85, 105, \( p = 0.0418 \)) patients, with no difference noted between CKD and HD patients \( (p = 0.7227) \). HD patients had a higher baseline PetCO\(_2\) (median 42 mmHg, IQR 37, 46) than CKD patients (median 36 mmHg, IQR 34, 38, \( p = 0.0344 \)), but not healthy participants (median 38 mmHg, IQR 35, 42, \( p = 0.2546 \)). There were no differences between participant groups in terms of sex, height, and baseline CBFv, PetO\(_2\), SBP, MAP, DBP, HR and CO. Figure 3-2 shows experimental data from representative participants from each group.

Table 3-2 shows within group changes in variables across experimental stages. Across all groups, PetCO\(_2\) and CBFv increased from baseline during intervention and returned back to baseline during recovery, with no corresponding changes in PetO\(_2\). In healthy participants and HD patients, MAP increased from baseline during intervention and did not return back to baseline during recovery. In CKD patients, the same trend in MAP was observed, but the difference between baseline and intervention did not reach statistical significance. CKD patients a small increase in HR with intervention that returned back to baseline during recovery, while HR did not change across stages in healthy participants and HD patients. Healthy participants had an increase in CO during intervention that returned back to baseline, while CKD and HD patients had no change in their CO.
Figure 3-2: Sample data from representative healthy (Panel A), chronic kidney disease (Panel B) and hemodialysis (Panel C) participants demonstrating study protocol. Following 5 minutes of baseline, there is an ~10 mmHg square-wave increase in PetCO₂ from baseline (intervention) while PetO₂ is kept constant at normoxia. After 5 minutes of hypercapnia, the PetCO₂ is returned back to baseline (recovery), followed by another 5 minutes of recording. The corresponding change in CBFv and MAP are also shown. Note that most of the response in CBFv is due to change in PetCO₂ rather than modest increase in MAP that continues to rise following return of PetCO₂ to baseline. Red dotted lines represent the 1-min data samples used for each experimental stage (BL= baseline, INT=intervention, REC=recovery). Note reduced CBFv response in hemodialysis patient despite similar PetCO₂ stimulus across patients.
Table 3-2: Within group changes in variables between baseline, intervention and recovery stages.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Healthy</th>
<th>CKD</th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BL</td>
<td>INT</td>
<td>REC</td>
</tr>
<tr>
<td><strong>PetCO₂ (mmHg)</strong></td>
<td>38 (35, 42)</td>
<td>47 (44, 51)*†</td>
<td>38 (35, 42)</td>
</tr>
<tr>
<td><strong>PetO₂ (mmHg)</strong></td>
<td>103 (102, 112)</td>
<td>108 (103, 112)</td>
<td>106 (102, 112)</td>
</tr>
<tr>
<td><strong>CBFv (%)</strong></td>
<td>0 (0, 0)</td>
<td>38 (27.47)*†</td>
<td>-2 (-7, 4)</td>
</tr>
<tr>
<td><strong>MAP (mmHg)</strong></td>
<td>96 (90, 103)</td>
<td>110 (92, 115)*†</td>
<td>99 (89, 108)</td>
</tr>
<tr>
<td><strong>HR (b/min)</strong></td>
<td>76 (67, 83)</td>
<td>78 (67, 88)</td>
<td>79 (67, 88)</td>
</tr>
<tr>
<td><strong>CO (L/min)</strong></td>
<td>5.7 (5.1, 6.4)</td>
<td>6.6 (5.3, 7.4)*†</td>
<td>5.8 (5.6, 8)</td>
</tr>
</tbody>
</table>

|               | BL            | INT            | REC           |               |
|---------------|---------------|----------------|---------------|
| **PetCO₂ (mmHg)** | 38 (34, 39)   | 48 (44, 48)*† | 38 (34, 39)   | <0.0001       |
| **PetO₂ (mmHg)** | 108 (105, 114)| 108 (105, 114)| 110 (105, 114)| 0.4040        |
| **CBFv (%)**  | 0 (0, 0)      | 40 (34, 51)*† | -1 (-3, 2)    | <0.0001       |
| **MAP (mmHg)** | 94 (87, 103)  | 104 (93, 114)  | 103 (91, 108)*| 0.0367        |
| **HR (b/min)** | 69 (56, 81)   | 73 (59, 89)*   | 69 (59, 84)   | 0.0038        |
| **CO (L/min)** | 5.6 (5.5, 6.4)| 6.6 (6, 7.3)   | 5.9 (5.2, 6.9)| 0.5933        |

|               | BL            | INT            | REC           |               |
|---------------|---------------|----------------|---------------|
| **PetCO₂ (mmHg)** | 42 (37, 46)   | 51 (47, 55)*† | 42 (39, 44)   | <0.0001       |
| **PetO₂ (mmHg)** | 108 (92, 112)| 109 (97, 112)  | 108 (98, 112) | 0.3632        |
| **CBFv (%)**  | 0 (0, 0)      | 20 (9, 37)*†  | -2 (-5, 0)    | 0.0039        |
| **MAP (mmHg)** | 87 (71, 103)  | 102 (82, 111)*†| 92 (74, 109)* | 0.0004        |
| **HR (b/min)** | 68 (58, 79)   | 74 (61, 86)    | 70 (59, 78)   | 0.2139        |
| **CO (L/min)** | 7.8 (6.7, 9.8)| 8.4 (7.4, 10.7)| 8.2 (7.1, 10.6)| 0.0901        |

Values are expressed as median (IQR). * p<0.05 vs BL, † p<0.05 vs REC. Abbreviations: BL=baseline, INT=intervention, REC=recovery, CKD=chronic kidney disease patients, HD=hemodialysis patients, PetCO₂=end-tidal PCO₂, PetO₂=end-tidal PO₂, CBFv=cerebral blood flow velocity, MAP=mean arterial pressure, HR=heart rate, CO=cardiac output.
Table 3-3 summarizes the magnitude of change in physiologic parameters across patients groups during intervention and recovery. Hemodialysis patients had a smaller change in CBFv during intervention compared to healthy participants and CKD patients. The same pattern was observed during recovery, but it only reached statistical significance for healthy vs HD patients. There was no difference between groups in any other parameters.

### Table 3-3: Changes in physiologic parameters during intervention and recovery.

<table>
<thead>
<tr>
<th>VARIABLES</th>
<th>INTERVENTION</th>
<th>RECOVERY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H</td>
<td>CKD</td>
</tr>
<tr>
<td>ΔCBFv (%)</td>
<td>38.5 (27, 46.6)</td>
<td>36.8 (29.1, 48.7)</td>
</tr>
<tr>
<td>ΔPetCO2 (mmHg)</td>
<td>9.6 (8.9, 10.1)</td>
<td>9.6 (9.6, 10)</td>
</tr>
<tr>
<td>ΔPetO2 (mmHg)</td>
<td>0 (-0.2, 1)</td>
<td>0.1 (-0.4, 0.5)</td>
</tr>
<tr>
<td>ΔMAP (mmHg)</td>
<td>8.3 (5, 15.5)</td>
<td>9.7 (-0.6, 12.7)</td>
</tr>
<tr>
<td>ΔHR (bpm)</td>
<td>4 (1.6, 6.2)</td>
<td>4.4 (-0.6, 5.9)</td>
</tr>
<tr>
<td>ΔCO (L/min)</td>
<td>0.6 (0.1, 1)</td>
<td>0.7 (-0.2, 0.9)</td>
</tr>
<tr>
<td>CVR (%/mmHg)</td>
<td>4 (2.9, 4.8)</td>
<td>4 (3.4, 5.1)</td>
</tr>
<tr>
<td>ΔCBFv (%)</td>
<td>-37 (-49.5, -30.5)</td>
<td>-40 (-44.8, -28.8)</td>
</tr>
<tr>
<td>ΔPetCO2 (mmHg)</td>
<td>-9.6 (-9.9, -8.8)</td>
<td>-9.7 (-9.8, -9.5)</td>
</tr>
<tr>
<td>ΔPetO2 (mmHg)</td>
<td>0 (-0.4, 0.7)</td>
<td>0.1 (-0.2, 0.3)</td>
</tr>
<tr>
<td>ΔMAP (mmHg)</td>
<td>-7.2 (-11, -2.6)</td>
<td>-3.4 (-6.9, 1.4)</td>
</tr>
<tr>
<td>ΔHR (bpm)</td>
<td>-0.3 (-4.5, 4.4)</td>
<td>-0.5 (-4.3, 0.9)</td>
</tr>
<tr>
<td>ΔCO (L/min)</td>
<td>-0.5 (-1, -0.1)</td>
<td>-0.4 (-0.9, 0.1)</td>
</tr>
<tr>
<td>CVR (%/mmHg)</td>
<td>4.1 (3.1, 5.2)</td>
<td>4.3 (3.6, 5)</td>
</tr>
</tbody>
</table>

Values are expressed as median (IQR). * p<0.05 vs H, † p<0.05 vs CKD. Abbreviations: H= Healthy participants, CKD = chronic kidney disease patients, HD = hemodialysis patients, ΔCBFv = change in cerebral blood flow velocity expressed as percent change from participant baseline, ΔPetCO2 = change in end-tidal PCO2, ΔPetO2 = change in end-tidal PO2, ΔMAP = change in mean arterial blood pressure, ΔHR = change in heart rate, ΔCO = change in cardiac output, CVR = cerebrovascular reactivity calculated as ΔCBFv/ΔPetCO2.
Figure 3-3 shows individual participant changes in CBFv, MAP and PetCO₂ during intervention and recovery across participant groups.

**Figure 3-3: Main results.** Change in cerebral blood flow (ΔCBFv), mean arterial pressure (ΔMAP), and end-tidal PCO₂ (ΔPetCO₂) from baseline during intervention (red lines) and recovery (blue lines) in healthy participants (H), chronic kidney disease (CKD) and hemodialysis (HD) patients. Note variable CBFv and MAP responses across participants despite similar changes in PetCO₂. Only changes in CBFv were statistically significant across participant groups.
Compared to healthy and CKD participants, HD patients had a lower CBFv response to a change in PetCO₂ during intervention (p=0.0258 vs healthy, p=0.0486 vs CKD) and recovery (p=0.0349 vs healthy, p=0.1207 vs CKD). This translated into significantly lower CVR in HD patients compared to healthy and CKD participants during both intervention (p=0.0082 vs healthy, p=0.0041 vs CKD) and recovery (p=0.0162 vs healthy, p=0.0237 vs CKD, Figure 3-4). There were no differences in CVR between healthy and CKD participants during either intervention (p=0.7777) or recovery (p=0.988).

Figure 3-4: Summary of cerebrovascular reactivity across participant group.
Scatter plots of individual (circles) cerebrovascular reactivity (CVR) values in healthy participants (H), chronic kidney disease (CKD) and hemodialysis (HD) patients during intervention (red) and recovery (blue). The median (thick horizontal line), 25th and 75th percentiles (thin horizontal lines) are also shown for each data set. Compared to healthy participants and CKD patients, HD patients had significantly lower CVR both during intervention and recovery stages of the experiment.
Correlation analysis showed that there was no relationship between CVR and change in MAP, HR, CO and PetO\textsubscript{2} during both intervention and recovery within each participant group (Table 3-4). In CKD group, there were no correlations between CVR and eGFR. In HD group, there were no correlations between CVR and dialysis vintage.

### Table 3-4: Correlation analysis between CVR, CBF, end-tidal gases, hemodynamic variables, and dialysis vintage (for HD patients only) across participant groups.

<table>
<thead>
<tr>
<th>Variable 1</th>
<th>Variable 2</th>
<th>Healthy</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Intervention</td>
<td>p-value</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔMAP</td>
<td>0.313</td>
<td>0.221</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔHR</td>
<td>-0.256</td>
<td>0.322</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔCO</td>
<td>0.276</td>
<td>0.284</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔPetO2</td>
<td>-0.237</td>
<td>0.36</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVR</td>
<td>ΔMAP</td>
<td>0.402</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔHR</td>
<td>0.207</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔCO</td>
<td>-0.351</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔPetO2</td>
<td>0.16</td>
</tr>
<tr>
<td>CVR</td>
<td>eGFR</td>
<td>-0.175</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>HD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVR</td>
<td>ΔMAP</td>
<td>-0.102</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔHR</td>
<td>0.275</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔCO</td>
<td>0.116</td>
</tr>
<tr>
<td>CVR</td>
<td>ΔPetO2</td>
<td>-0.397</td>
</tr>
<tr>
<td>CVR</td>
<td>dialysis vintage</td>
<td>-0.112</td>
</tr>
</tbody>
</table>

Abbreviations: CKD = chronic kidney disease patients, HD = hemodialysis patients, CVR = cerebrovascular reactivity, ΔMAP = change in mean arterial blood pressure, ΔHR = change in heart rate, ΔCO = change in cardiac output, ΔPetO2 = change in PO\textsubscript{2}, eGFR = estimated glomerular filtration rate, dialysis vintage = duration of time that the patient has been receiving dialysis.
3.4 Discussion

In this study we showed that HD patients have impaired CVR compared to CKD patients and healthy participants. Given that CVR is an established marker of cerebrovascular function that predicts neurocognitive outcomes, our results suggest that HD patients may be at higher risk of poor neurocognitive outcomes compared to CKD patients and healthy participants at baseline prior to the onset of critical illness. Such functional stratification of baseline cerebrovascular risk is important for interpreting the effects of ICU exposures, such as CBFv deviations described in Chapter 1, on neurocognitive outcomes during and following critical illness.

CVR provides a non-invasive means to quantify cerebrovascular function and has been investigated as a marker of cerebrovascular health in different pathologies. Impaired CVR is associated with increased risk of stroke,\textsuperscript{2} cognitive impairment\textsuperscript{3,4} and cortical thinning.\textsuperscript{47} In concussion, it helps differentiate between concussed and normal patients despite similar anatomic and global resting CBF measurements in both groups.\textsuperscript{48,49} Impaired CVR has also been central to understanding the pathophysiology of leukoaraiosis. Compared to normal appearing white matter, areas with white matter hyperintensities are associated with approximately 10% reduction in resting CBF, 60% reduction in CVR and 45% reduction in fractional anisotropy, the latter being a measure of white matter integrity.\textsuperscript{50} Interestingly, areas of normal white matter that had impaired CVR also showed significant reductions in resting CBF, cerebral blood volume, and impairment in the imaging markers of white matter integrity (fractional anisotropy and mean diffusivity), suggesting that CVR is likely an early functional marker of brain tissue at risk for subsequent injury.\textsuperscript{1} This hypothesis was confirmed in another study, where non-affected white matter that progressed to white matter hyperintensities in one year had significantly lower CVR than preserved non-affected white matter.\textsuperscript{51}

In the previous chapter (Chapter 2), we showed that critically ill patients experience prolonged CBFv deviations beyond ischemic thresholds early in the course of the ICU admission. In patients with preserved CVR, such ischemic episodes would be counteracted by vascular dilation in response to local increase in CO$_2$ in ischemic regions in order to preserve tissue oxygen delivery. In patients with impaired CVR, this
vasodilatory response is attenuated. This would facilitate ischemic injury via two mechanisms. First, failure to vasodilate would prevent local compensatory increase in CBF further worsening ischemia. Second, vasodilation in brain regions with preserved CVR would divert the blood flow from the regions with impaired CVR that are unable to dilate via vascular steal. Interestingly, regional assessment of CVR in healthy participants revealed that such “steal” phenomenon is predominately localized to white matter where elderly patients develop leukoaraiosis (i.e. white matter injury). This may explain why HD patients develop new diffuse subcortical white matter injury that is independent of the traditional cardiovascular risk factors (smoking, diabetes and ischemic heart disease) when they first start receiving dialysis. Whether the same injury occurs in HD patients during hemodynamic stress of critical illness, such as CBFv deviations demonstrated in Chapter 2, should be explored in future studies.

The mechanism of CVR impairment in HD patients is unclear. Preserved CVR in CKD patients that is independent of eGFR suggests that CVR impairment in HD patients is not simply due to reduction in renal function, but is in some way related to the hemodialysis treatment. Prior work suggested that impairment in CVR may be linked to impairment in endothelial function, which is commonly reported in hemodialysis patients. The circulatory stress of hemodialysis can induced direct ischemic brain injury, or results in chronic endotoxemia by inducing repetitive gut ischemia that facilitates bacterial translocation. In fact, HD patients have higher levels of circulating endotoxin than peritoneal dialysis or CKD patients, which can affect cerebrovascular function. Other potential mechanisms for impaired CVR in HD patients could include chronic inflammatory state, increased vascular stiffness, decreased baroreflex sensitivity and chronic uremic stress.

In our study, CVR impairment in HD patients was not associated with dialysis vintage, suggesting that the onset of CVR impairment is not linked to the duration of time that patients have been on dialysis and likely occurs shortly after dialysis initiation. This would be in keeping with previous studies that demonstrated development of white matter injury and cognitive impairment shortly after initiation of dialysis.
Another observation in our study was that CVR responses across participant groups were independent from CO$_2$-induced changes in MAP. This suggests, that CVR assesses aspects of vasomotor control of CBF that are distinct from cerebral autoregulation and therefore provides an additional means of stratifying functional cerebrovascular risk in patients prior to the onset of critical illness. Such functional risk stratification would be important for interpreting the consequences of ICU exposures, such as CBFv deviations described in Chapter 2, and for planning future interventional studies aimed at improving neurocognitive outcomes in critical illness.

**Limitations**

Our study had several limitations. Due to its pilot nature, we had a relatively small sample size. However, our sample size was still sufficient to demonstrate significant difference in CVR between HD patients, CKD patients, and healthy participants, which was the primary objective of our study.

We used transcranial Doppler and CBFv as a marker of global CBF based on prior research showing that CBFv measured in the middle cerebral artery is a reliable and valid index of CBF.$^{65-69}$ However, changes in CBFv are only proportional to changes in CBF as long as the vessel diameter stays constant. In this study, we insonated middle cerebral artery and prior studies have shown that hypercapnia is associated with small dilation of this vessel, which underestimates changes in CBF by about 8%.$^{43}$ Using CBFv to measure CVR may therefore result in underestimated CVR values. However, this does not preclude comparison of relative differences in CVR between participant groups as long as the same CBFv method and magnitude of change in CO$_2$ is used in all groups.

The use of transcranial Doppler limited our results to computation of global CVR from a single major intracranial vessel. Comprehensive evaluation of regional CVR in HD and CKD patients will require tomographic modalities such as magnetic resonance imaging. Nonetheless, our results provide much needed pilot data to support detailed study of CVR in HD and CKD populations using more comprehensive neuroimaging modalities. Furthermore, the relative portability of transcranial Doppler and its ability to identify
CVR impairment in HD patients would make it a practical tool for CVR screening in clinical settings.

CBF responds to changes in PaCO\(_2\). However, in this study we used PetCO\(_2\) as an estimate of PaCO\(_2\). Such approach may present a bias due to end-tidal to arterial PCO\(_2\) difference that occurs as a result of alveolar dead space. However, prospective targeting method that was used to manipulate blood gases in this study (RespirAct\textsuperscript{TM}) practically eliminates alveolar dead space and corresponding end-tidal to arterial PCO\(_2\) difference, such that PetCO\(_2\) actually correspond to PaCO\(_2\).\textsuperscript{33} Unlike other methods that control CO\(_2\), prospective targeting method limits the amount of fresh gas that is delivered into the alveoli, with the balance of the tidal breath made up by previously exhaled gas with a PCO\(_2\) that closely approximates alveolar gas.\textsuperscript{26} This raises the PCO\(_2\) in alveoli with high ventilation to perfusion ratio (i.e. alveoli that make up alveolar dead space) towards the PCO\(_2\) in alveoli with good ventilation-perfusion match, resulting in a more homogenous alveolar PCO\(_2\) throughout the lungs. As a result of this, PaCO\(_2\) is less dependent on the regional inhomogeneities in lung blood flow and that PetCO\(_2\) closely approximated PaCO\(_2\).\textsuperscript{33}

In our study, the starting baseline PetCO\(_2\) was higher in HD patients. As a result, a standard 10 mmHg increase in PetCO\(_2\) in HD group during intervention would result in higher PetCO\(_2\) (and correspondingly PaCO\(_2\)) levels during hypercapnia. With respect to baseline PetCO\(_2\), there are two approaches to assess CVR. In the first approach, you would start CVR assessment at participant’s own resting PetCO\(_2\) prior to induction of hypercapnia. In the second approach, you would start all participants at the same absolute baseline PetCO\(_2\). The benefit of the first approach is that CVR assessment is done relative to participant’s own homeostatic set point. In healthy participants the absolute value of this set point differs between participants but is always in the middle of their individual CBFv-PetCO\(_2\) relationship curve.\textsuperscript{70} The same is likely true in CKD and HD patients. As a result, adopting a second approach (i.e. imposing the same absolute starting PetCO\(_2\) on all participants) may bias CVR assessment. For example, if the baseline PetCO\(_2\) in a given participant is adjusted from 37 to 40 mmHg to ensure that all participants start at 40 mmHg, then this particular participant may have lower CBFv response to the same 10
mmHg increase in PetCO$_2$ by virtue of their starting PetCO$_2$ and corresponding CBFv being closer to the upper limit of their CBFv-PetCO$_2$ curve. Establishing the shape and the limits of the CBFv-PetCO$_2$ relationship in CKD and HD patients requires ramp PetCO$_2$ protocols.$^{31,70}$ While this was beyond the scope of the present study, future studies should explore the shape, limits and PetCO$_2$ set-point of the CBFv-PetCO$_2$ relationship in CKD and HD patients. The higher resting PetCO$_2$ in HD patients is not uncommon and is usually related to high prevalence of obstructive sleep apnea in this patient population.$^{71}$

We did not measure arterial blood gases and corresponding bicarbonate levels in this study. While bicarbonate levels may differ between groups (especially in HD group), they are unlikely to influence the results of this study. While the debate whether CBF responds to changes in PaCO$_2$, brain tissue PCO$_2$ or pH is ongoing, most data support the notion that PaCO$_2$ (and likely brain tissue PCO$_2$) are more important than changes in pH.$^{72}$ Furthermore, the relationship between PaCO$_2$ and bicarbonate in most patients who are not acutely ill is to balance the pH towards normal. Most participants would therefore have normal pH levels at baseline despite different starting PCO$_2$ and bicarbonate levels. Given that PaCO$_2$ changes in this study were rapid, there would not be enough time for compensatory change in bicarbonate irrespective of resting bicarbonate levels. As a result, while difference in resting bicarbonate levels between patients are possible they are unlikely to affect the results of this study.

Finally, since we did not measure imaging markers of ischemia or neurocognitive outcomes in our study, we cannot comment on the clinical relevance of impaired CVR in HD patients. However, future detailed studies can explore whether impaired CVR in HD patients is associated with ischemic injury or worse neurocognitive outcomes as a result of hemodynamic stress of critical illness.

3.5 Conclusion

HD patients have impaired CVR compared to healthy participants and patients with CKD. Given that impaired CVR predicts ischemic injury and worse neurocognitive outcomes, we propose that HD patients would be at higher risk of ischemic injury and
worse neurocognitive outcomes if they are exposed to hemodynamic stressors such as CBFv deviations described in Chapter 2. Impaired CVR may render HD patients vulnerable to ischemia by preventing vasodilatory response to ischemia during spontaneous CBFv deviations and promoting vascular steal in regions with impaired CVR. Future studies should confirm whether impaired CVR in HD patients is associated with subcortical white matter brain injury and worse neurocognitive outcomes during and following critical illness.
REFERENCES


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Chapter 4

4 Optimizing web-based neurocognitive battery for assessment of cognitive outcomes in ICU survivors.


In order to link ischemic insults during critical illness, such as CBFv deviations described in Chapter 2, and impairments in cerebrovascular function, such as impaired CVR in HD patients in Chapter 3, with neurocognitive outcomes we need to establish a clinically feasible and accurate method for detecting cognitive impairment in ICU patients. However, existing cognitive assessment methods are either too simple and fail to detect multi-domain cognitive impairment in ICU patients, or too complex requiring long time and specially trained personnel for completion, rendering them impractical for routine clinical use.\(^1\)

In this study we assessed the feasibility of a comprehensive web-based cognitive battery Cambridge Brain Science (CBS) in detecting multi-domain cognitive impairment in a cohort of ICU survivors. We showed that CBS is both feasible in clinical settings and detected multi-domain impairment in ICU survivors. After identifying battery length as an important feasibility threat, we showed that shortening the battery from 12 to 6 tests yields similar cognitive results and could cut testing time in half.

Our results suggest that the shortened 6-test version of the Cambridge Brain Sciences cognitive battery may be an optimal clinical tool for assessing cognitive outcomes in ICU patients. This new tool fills an important gap in existing cognitive toolset used in critical care by balancing comprehensiveness with brevity and ease of administration. This tool will enable future work exploring links with ischemic insults, such as CBFv deviations described in our first study, and impairments in cerebrovascular function, such as impaired CVR in HD patients in our second study, as well as enable monitoring of cognitive recovery in ICU survivors.
4.1 Introduction

Long-term cognitive impairment is a common complication in critical illness survivors. The mean prevalence of cognitive impairment in ICU survivors varies from 35 to 81% at 3 months following ICU discharge depending on whether subjective or objective cognitive measures are used, the type of cognitive tests used, and the etiology of critical illness. While a recent systematic review attempted to use published cognitive data to describe the natural history of cognitive recovery in ICU survivors, heterogeneity in the types of cognitive batteries used, ICU patient populations studied, and the timing of cognitive testing following ICU discharge made it challenging to meta-analyze these data.

Understanding the natural history of cognitive recovery is critical for identifying associated modifiable risk factors and insults during and following critical illness, selecting therapeutic targets and assessing impact of therapeutic interventions, offering prognosis to patients and their caregivers, and allocating healthcare resources. However, existing neurocognitive assessment tools have a number of limitations that prevent their use for monitoring cognitive recovery in individual patients, as well as in large cohort or interventional studies. Simple cognitive tests or screening cognitive batteries familiar to most clinicians, such as Trails Making Tests A and B, and Mini-Mental State Examination, detect less cognitive impairment in ICU survivors compared to comprehensive cognitive batteries. On the other hand, comprehensive cognitive batteries are able to detect cognitive impairment across multiple cognitive domains, but are too cumbersome, labour intensive and therefore impractical for routine use in clinical settings, which may explain why their use is largely restricted to research studies and no more than 3 time points following ICU discharge.

Additional factors that may contribute to lack of routine monitoring of cognitive outcomes in ICU survivors is that existing comprehensive cognitive batteries are paper-based and require specially trained staff for test administration, take a long time to administer, and necessitate patients to attend testing sessions in person, which often excludes those who have limited mobility, are institutionalized, live far away from the testing centre, or are unwilling to return to the hospital where they were admitted due to
associated traumatic memories. Furthermore, limited number of paper test versions makes them especially prone to floor/ceiling and learning effects with repeated administration.

Cambridge Brain Sciences (CBS) is a web-based cognitive battery that can overcome many of these limitations and offer a paradigm shift in neurocognitive assessment and follow up of ICU survivors. CBS battery can be self-administered by patients using their own computer or a tablet, negating the need to travel to clinic. CBS minimizes floor/ceiling and learning effects by adjusting test difficulty to patient’s performance and randomizing the order of tests. While it has been used in a number of large-scale population-based studies, as well as clinical populations, its feasibility and ability to detect cognitive impairment in ICU survivors is unknown.

In this study, we assessed the feasibility of using CBS to detect cognitive impairment in a cohort of ICU survivors. We hypothesized that the use of CBS would be feasible and that its comprehensive nature would enable detection of cognitive impairment in ICU survivors across multiple cognitive domains.
4.2 Methods

Study design and participants

We conducted a prospective observational study of patients admitted to two adult tertiary care centre intensive care units (ICUs) in London, Canada. The study was approved by Western University Health Sciences Research Ethics Board (protocol number 108156). We enrolled adult patients (18 to 80 years of age) who were mechanically ventilated for a minimum of 24 hours. The latter criterion was added in order to exclude patients who require brief ventilation (e.g. admitted for routine post-operative monitoring or following for acute intoxication). We excluded patients with a pre-existing diagnosis of dementia, new or pre-existing diagnosis of neurological disease known to affect cognitive function (e.g. stroke, head trauma, intracranial hemorrhage, traumatic brain injury, or intracranial malignancy), impaired vision or significant upper extremity weakness precluding use of a computer, inability to communicate in English or were unable to or declined to provide informed consent, or active delirium as determined by the Intensive Care Delirium Screening Checklist (ICDSC).12

Cognitive Testing

To assess cognitive function across multiple domains, we used a web-based computerized cognitive battery Cambridge Brain Sciences (CBS). CBS battery consists of 12 tests that evaluate a broad range of cognitive processes. The individual tests include: Feature Match, Odd One Out, Polygons, Rotations, Spatial Planning, Monkey Ladder, Paired Associates, Spatial Span, Spatial Search, Digit Span, Double Trouble, and Grammatical reasoning. These tests evaluate cognitive performance across major cognitive domains – reasoning skills, planning, short-term memory, and verbal ability, which are considered the main determinants of general intelligence.6 CBS was designed specifically to enable self-administration by individuals without the need for a trained personnel, which enabled its use in large-scale studies enrolling 11,600-44,000 participants5–7 that would otherwise be prohibitively expensive and impractical. Other useful features of this battery include randomization of the order of tests, which minimizes learning effects with repeated administration, and adjustment of test difficulty based on participant performance, which
avoids ceiling or floor effects seen with cognitive testing. CBS battery has been shown to be a very sensitive measure of cognition in various clinical populations including patients with anatomically-specific brain lesions,\textsuperscript{8,9} neurodegenerative disease,\textsuperscript{10,11} in pharmacological intervention studies.\textsuperscript{13,14} CBS neural correlates have been well studied using functional neuroimaging in healthy adults,\textsuperscript{15,16} and in neuropathological populations,\textsuperscript{17,18} and were shown to be highly sensitive to changes in sleeping habits and duration.\textsuperscript{19} With over 7 million users, including a normative database of 75,000 participants, CBS is the largest databases of its kind in the world.

Screening for pre-ICU cognitive impairment

To screen our participants for a previous history of cognitive deficits, we asked a relative or friend who knows the patient well to complete the Informant Questionnaire on Cognitive Decline in Elderly (IQCODE). The IQCODE has been shown to have high reliability in measuring cognitive decline and correlates well with other neurocognitive tests.\textsuperscript{20} Family assessors are presented with 16 specific tasks (e.g., remembering where things are usually kept) and asked to rate the patient’s current status on that task relative to 10 years ago on a scale of 1 (much improved) to 5 (much worst) with a score of 3 indicating “no change”. A cut-off score of 3.44 was used as a positive screen for pre-existing dementia.\textsuperscript{20}

Assessment of Feasibility

Our aim was to assess the feasibility of using a web-based, neurocognitive battery to assess cognition in ICU survivors at the time of ICU discharge. Our primary measure of feasibility was the number of patients who completed the entire 12-test cognitive battery. In addition, we took notes about any issues that arose throughout the administration of the cognitive battery and any concerns that were raised by patients throughout testing so that these challenges could be addressed in future ICU studies using the CBS battery.

Study protocol

We screened patients for eligibility using medical charts and discussion with bedside nurses. We approached eligible patients and obtained written informed consent prior to
commencing the study. Patients were deemed to be adequately alert and capable of providing consent if they were able to participate in the consent discussion.

We recorded demographic and clinical variables including age, sex, admission diagnosis, hospital and ICU admission dates, and Nine Equivalents of Nursing Manpower Use Score (NEMS) as a measure of patients illness severity on the day of testing from each patient’s chart or electronic medical record.

Patients completed cognitive assessment using a laptop computer with an attached computer mouse in their hospital bed in the ICU or shortly after discharge to the ward. Investigators assisted patients by creating a personalized login and password on the CBS study webpage. A standardized set of written and pictorial instructions and a short instructional video preceded each cognitive test. Patients were provided with as much time as they needed to review the instructions prior to beginning each test. Patients completed each of the tests in sequence until the entire battery of 12 tests was completed or they were unable to continue due to testing related fatigue.

**Data analysis**

Demographic and clinical variables were reported using descriptive statistics, expressed as frequency and percentage for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables as applicable.

In keeping with definitions of cognitive impairment in the literature, patients were defined as having cognitive impairment on a given test if their raw test score was ≥ 1.5 SDs below age- and sex-matched controls derived from the CBS normative database. We then compared patients’ cognitive performance with available data from healthy age- and sex-matched control data by converting raw scores into z-scores.

To determine patients’ scores on each of the three cognitive domains (reasoning skills, short-term memory, and verbal processing), the z-score for each individual test was multiplied by a value that reflected the contribution of that test to each cognitive domain (i.e., factor loading) as established by Hampshire and colleagues. Patients’ overall score on each cognitive domain was therefore the sum of the weighted (factor loaded) scores
for that domain across all 12 tests. Data imputation was only used to compare domain scores for patients who completed all 12 tests. The scores are designed such that the healthy population mean on each cognitive domain is 0 and the SD is 1.0.

**Abbreviated 6-test CBS battery**

One of the identified feasibility challenges that our patients identified in this study was the length of time required to complete the 12-test CBS battery. In direct response to this challenge, we explored whether the scores from the abbreviated 6-test battery would yield similar results as the full 12-test battery for our patient cohort. We defined an abbreviated CBS battery that included six of the 12 CBS tests which most strongly reflect one of the three cognitive domains based on previously published data (Reasoning Skills: Odd One Out and Rotations; Short-term Memory: Paired Associates and Monkey Ladder; and Verbal Processing: Digit Span and Verbal Reasoning). We replaced the scores for the omitted tests with their expected values given the six observed test scores and the known correlation structure among the tests in the population. The correlation structure between the 12 tests in the CBS battery was derived from a sample of 44,600. This method has been shown to be most accurate when calculating principle component analysis scores in the presence of missing data. We then calculated a z-score for each patient on each of the three cognitive domains based on the abbreviated 6-test CBS and compared this score to the z-scores calculated based on the complete 12-test CBS battery using simple linear regression.
4.3 Results

Of 45 patients approached, 25 declined to participate in this study, most commonly due to self-reported inability to participate or limited availability due to required clinical care activities (e.g., diagnostic tests). Twenty patients (7 females) were included in the analysis (Figure 4-1).

Patient demographic and clinical characteristics are summarized in Table 4-1. Patients median (interquartile range, IQR) age was 58.5 (41-66) years, our cohort had slightly more males (65%) that were admitted with a range of diagnoses and had median (IQR) duration of ventilation and ICU stay of 2.5 (1-3) and 5 (4-9) days respectively. They also required a substantial amount of ICU nursing workload at the time of enrollment as indicated by a median NEMS score of 18 (full NEMS score ranges from 0-63 points).
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (IQR)</td>
<td>58.5 (41-66)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>13</td>
</tr>
<tr>
<td>Females</td>
<td>7</td>
</tr>
<tr>
<td>Admission Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Respiratory, n</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac, n</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis, n</td>
<td>2</td>
</tr>
<tr>
<td>Cardiac arrest, n</td>
<td>4</td>
</tr>
<tr>
<td>Neurologic, n</td>
<td>1</td>
</tr>
<tr>
<td>Non-head trauma, n</td>
<td>2</td>
</tr>
<tr>
<td>Surgical, n</td>
<td>3</td>
</tr>
<tr>
<td>Other, n</td>
<td>3</td>
</tr>
<tr>
<td>Duration of Mechanical Ventilation, median (IQR)</td>
<td>2.5 (1-3)</td>
</tr>
<tr>
<td>ICU length of stay (days), median (IQR)</td>
<td>5 (4-9)</td>
</tr>
<tr>
<td>Nine equivalents of nursing manpower use score, median (IQR)</td>
<td>18 (18-22)</td>
</tr>
</tbody>
</table>
We reached family members or friends of 15 (75%) of enrolled patients for completion of the IQCODE. None of these patients were found to have pre-morbid dementia as assessed by the IQCODE.

**Cognitive testing**

Thirteen patients were tested in the ICU and seven were tested within one to four days of transfer to the ward. Patients were tested after a median of 4 days (IQR 3.75) following ICU admission. Three patients completed testing on two separate days at the patient’s request. Seventeen of 20 patients completed the full 12-test CBS battery (the other three patients completed four, six and seven tests). Of the three patients who did not complete the full battery, two were tested on the ward and one was tested while still in the ICU. The mean duration for completion of the 12-test CBS battery was 45.5 minutes (SD 11.1) excluding the three patients who did not complete the entire battery and one patient whose testing who had a long break between tests.

All patients were impaired on at least two tests, and 18 were impaired on at least three tests relative to healthy controls. Among the 17 of 20 patients who completed the full CBS battery, patients were impaired on a median of eight tests (IQR 4.5-10, range 2-11).

Individual patient performances as well as cohort means on each of the 12 CBS tests relative to normative data are presented in Figure 4-2. Patients had poorer performance on all CBS tests compared to healthy controls (Table 4-2). Patients also had poorer performance on all three cognitive domains compared to healthy controls (Figure 4-3 and Table 4-2).
Figure 4-2: Patient performance on the 12-test Cambridge Brain Sciences (CBS) neurocognitive battery. Individual patient (circles) and cohort (solid lines) test performance presented as z-scores corrected for age and sex. Cognitive domains that are mostly represented by the individual tests are shown at the top.
Table 4-2: Cognitive performance of ICU survivors relative to healthy controls using CBS 12-test battery.

<table>
<thead>
<tr>
<th>COGNITIVE TEST / DOMAIN</th>
<th>MEAN Z-SCORE (SD)</th>
<th>STATISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBS COGNITIVE TESTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Feature Match</td>
<td>-2.21 (1.16)</td>
<td>t(17) = -8.10, p &lt; 0.0001</td>
</tr>
<tr>
<td>Odd One Out</td>
<td>-2.1 (1.83)</td>
<td>t(19) = -5.14, p &lt; 0.0001</td>
</tr>
<tr>
<td>Polygons</td>
<td>-1.35 (0.67)</td>
<td>t(16) = -8.28, p &lt; 0.0001</td>
</tr>
<tr>
<td>Rotations</td>
<td>-1.58 (0.84)</td>
<td>t(18) = -8.22, p &lt; 0.0001</td>
</tr>
<tr>
<td>Spatial Planning</td>
<td>-1.12 (0.92)</td>
<td>t(16) = -5.04, p &lt; 0.0001</td>
</tr>
<tr>
<td>Monkey Ladder</td>
<td>-2.21 (1.93)</td>
<td>t(19) = -5.13, p &lt; 0.0001</td>
</tr>
<tr>
<td>Paired Associates</td>
<td>-1.42 (1.04)</td>
<td>t(16) = -5.64, p &lt; 0.0001</td>
</tr>
<tr>
<td>Spatial Span</td>
<td>-1.97 (1.56)</td>
<td>t(18) = -5.51, p &lt; 0.0001</td>
</tr>
<tr>
<td>Spatial Search</td>
<td>-1.4 (0.92)</td>
<td>t(16) = -6.30, p &lt; 0.0001</td>
</tr>
<tr>
<td>Digit Span</td>
<td>-1.85 (0.91)</td>
<td>t(16) = -8.40, p &lt; 0.0001</td>
</tr>
<tr>
<td>Double Trouble</td>
<td>-1.43 (0.62)</td>
<td>t(19) = -10.40, p &lt; 0.0001</td>
</tr>
<tr>
<td>Grammatical Reasoning</td>
<td>-2.46 (0.65)</td>
<td>t(19) = -16.89, p &lt; 0.0001</td>
</tr>
<tr>
<td><strong>COGNITIVE DOMAIN</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reasoning Skills</td>
<td>-2.13 (1.45)</td>
<td>t(16) = -6.05, p &lt; 0.0001</td>
</tr>
<tr>
<td>Short-term Memory</td>
<td>-1.92 (1.41)</td>
<td>t(16) = -5.60, p &lt; 0.0001</td>
</tr>
<tr>
<td>Verbal Processing</td>
<td>-1.66 (1.21)</td>
<td>t(16) = -5.65, p &lt; 0.0001</td>
</tr>
</tbody>
</table>
Figure 4-3: Patient performance on the three Cambridge Brain Sciences cognitive domains: reasoning skills, short-term memory, and verbal processing. Individual patient (circles) and cohort (solid lines) test performance on each cognitive domain presented as z-scores.
**Feasibility issues**

We identified two feasibility issues with the web-based CBS platform. First, three of our patients reported testing related fatigue due to battery length and requested to stop the test prior to completion of the entire 12-test battery. Second, one of our patients reported inexperience with use of a computer mouse and had to be instructed on how to use a mouse by one of the investigators.

**Abbreviated 6-test battery**

To address the issue of test fatigue related to battery length, we compared the scores from the full 12-test battery with the scores that would have been obtained if we used abbreviated 6-test battery. The 6-tests in the abbreviated battery were selected empirically so that they would most strongly reflect performance on of the three cognitive domains based on previously published data. Correlation analysis yielded good agreement between 6- and 12-test battery scores in each of the three cognitive domains (Fig 4).

**Figure 4-4:** Scatterplots including a linear fit (solid line) of the abbreviated 6-test vs the full 12-test Cambridge Brain Sciences (CBS) battery on the three CBS cognitive domains. (A) Reasoning ($R^2 = 0.91$), (B) Memory ($R^2 = 0.80$), and (C) Verbal Processing ($R^2 = 0.94$).
4.4 Discussion

Our results confirm that a web-based cognitive battery, CBS, can identify domain-specific cognitive impairment in critical illness survivors. Battery length was identified as an important feasibility risk, as four (20%) of our patients were unable to complete the full 12-test battery in one sitting due to testing-related fatigue and asked to stop. We showed that shortening the battery from 12 to 6 tests would have yielded similar cognitive domain scores while shortening the testing time in half. Given that CBS battery can be self-administered by patients, it represents a paradigm shift in cognitive recovery monitoring in ICU patients by circumventing the needs for ICU survivors to come back to clinic for cognitive assessments. Web-based cognitive batteries like CBS can enable comprehensive cognitive recovery monitoring in ICU survivors. CBS provides an objective patient-centred outcome that can be used to identify associated modifiable risk factors and insults during and following critical illness, select therapeutic targets and assess the impact of therapeutic interventions, offer prognosis to patients and their caregivers, and help allocate healthcare resources.

*Why monitor cognitive recovery in ICU survivors?*

Cognitive function is one of the best predictors of life quality, including academic and work success, levels of happiness and even life expectancy.\(^{23-25}\) ICU survivors suffer from high prevalence of multi-domain cognitive impairment that may impede their functional recovery, return to the workforce, and social functioning.\(^1,2\) This problem is likely to get worse in the coming years due to ageing of global populations\(^26\) and increase in the number of ICU survivors due to projected increase in the incidence of critical illness\(^27\) and reduction in ICU mortality. Furthermore, unlike Alzheimer’s disease that primarily occurs in older adults, ICU-related cognitive impairment affects patients across the age spectrum,\(^2\) which has important healthcare system and societal implications. In summary, ICU-related cognitive impairment represents an important public health problem that requires urgent and innovative solutions. Establishing a clinically feasible, comprehensive and objective outcome measure of cognitive function is an important first step in addressing this public health problem.
What are the advantage of using CBS?

Unlike paper-based cognitive assessment tools, the web-based CBS battery can be self-administered by patients from any location (ward, rehabilitation facility, home) after minimal instructions on logging in and starting the tests, obviating the need for patients to travel to hospital to be tested by specially trained staff. The self-administering nature of web-based battery may enable large-scale studies similar to those completed in other populations,5–7 and provides opportunity for repeated remote monitoring of cognitive recovery in patients who are unable (or unwilling) to return to clinic. Given high prevalence of functional disability, post-traumatic stress disorder, and challenging travel logistics, remote web-based testing of cognition provides a more patient-centred approach to monitoring cognition in ICU survivors.

The majority of previous ICU studies have used traditional paper-based tests.1 These tests range from simple single tests such as Trails Making Test A/B or screening batteries for dementia such as Mini-Mental State Examination, to more comprehensive cognitive batteries such as Repeatable Battery for the Assessment of Neuropsychological Status and Wechsler Adult Intelligence Scale-Fourth Edition.1 Given multi-domain nature of cognitive impairment in ICU survivors, single tests or screening dementia batteries are ineffective at detecting subtle, yet consequential cognitive deficits in critical illness survivors. On the other hand, comprehensive cognitive batteries detect cognitive impairment across multiple domains in a number of studies, but are not practically feasible for routine monitoring of cognitive recovery in the clinic as they require trained personnel, take a long time to complete, have limited number of versions (which makes them prone to learning effects), and do not adjust for individual patient performance (which makes them prone to floor/ceiling effects).

Web-based batteries like CBS offers a compromise to the paper-based approach by enabling comprehensive multi-domain assessment while preserving clinical feasibility through patient self-administration. Furthermore, randomization of the order of tests limits learning effects, while automated adjustment of test difficulty based on patients’ performance avoids floor/ceiling effects. With a normative database of 75,000
participants, and over 7 million users, CBS is the largest databases of its kind in the world. This enables point-of-care benchmarking of patient’s performance against age- and sex-matched data from healthy controls.

**Limitations**

This study has several limitations. First, our sample size was small. While we showed that CBS batter was feasible for use in clinical settings, and that it was able to detect multi-domain cognitive impairment, we cannot make any definitive conclusions regarding its ability to track cognitive recovery in ICU survivors. This will require future dedicated studies. Second, web-based cognitive testing in general is not without limitations. The inability to monitor patients during testing to determine their level of engagement, patients’ access to and inexperience with use of a computer, and attrition in follow-up studies are limitations inherent to the use of web-based (remote) cognitive testing that must be addressed prior to large-scale use of such testing platforms in ICU survivors. Patients’ performance in our study may have been affected by their ability to use a computer mouse to navigate through the tasks. In future studies, we plan to test tablets as an alternative to computer-mouse combination based on patient preference. Finally, in the absence of a “gold standard” test for cognitive impairment in this study, the psychometric characteristics of the CBS could not be assessed, although previous studies in healthy controls \(^6\) and elderly neuropsychiatric patients \(^28\) have confirmed that it is comparable to standard neuropsychological test batteries in terms of its latent structure and relation to age. We identified that the length of the CBS cognitive battery may be one challenge to its feasibility in larger studies. The proposed abbreviated CBS battery is one potential solution to this challenge. Future studies are needed to assess the feasibility of the abbreviated CBS battery.
**Future directions**

By enabling remote monitoring of cognitive recovery in critical illness survivors, web-based cognitive testing using CBS battery represents a new frontier in ICU cognition research. This tool will enable future work exploring links with ischemic insults, such as CBFv deviations described in our first study, and impairments in cerebrovascular function, such as impaired CVR in HD patients in our second study. The web-based nature of this cognitive battery will allow patients to complete cognitive assessments remotely without the need to come to clinic and would make tracking of cognitive recovery economically feasible by obviating the need for specially trained personnel for test administration. Furthermore, since Cambridge Brain Science has neuro-anatomical correlates, it would enable mapping of cognitive outcomes to specific neuroimaging findings in ICU patients, which would allow more precise identification of underlying mechanisms responsible for cognitive dysfunction in this patient population.

In our next study, we aim to assess the feasibility of the abbreviated 6-test CBS battery to monitor cognitive recovery over time in a cohort of ICU survivors (this study is currently enrolling patients). In the future, in order to identify potential therapeutic targets, we plan to correlate cognitive recovery trajectories obtained with the CBS against 1) modifiable risk factors that occur during and following critical illness and 2) neuroanatomical injury patterns using multimodal neuroimaging (CT, MRI, PET). This would enable development of targeted interventions that can be evaluated for effectiveness in properly designed randomized control studies. Finally, we plan to engage patient partners and healthcare services stakeholders in analyzing the burden of cognitive disability in ICU survivors and to help establish care pathways that will support rehabilitation and reintegration of ICU survivors into society.

4.5 Conclusions

We demonstrated that a comprehensive, web-based neurocognitive testing platform is feasible for clinical use in critical illness survivors and detects domain-specific cognitive impairment. We identified battery length as a potential challenge to wider scale use of the CBS battery, and showed that abbreviated version of the CBF tool would be as effective
in detecting cognitive impairment. In future work, we plan to use this tool to explore links with ischemic insults, such as CBFv deviations described in our first study, and impairments in cerebrovascular function, such as impaired CVR in HD patients in our second study. We also plan to explore its utility in monitoring cognitive recovery in ICU survivors over time. Further optimization of this tool for ICU patients will enable identification of therapeutic targets for preventative, therapeutic and rehabilitative interventions, and enable informed planning of healthcare resources for ICU survivors.
REFERENCES


Chapter 5

5 Summary, Limitations, Future Work and Significance.

5.1 Overview and Summary

In our first study, we aimed to determine the proportion of time that CBF deviates spontaneously beyond previously reported ischemic or hyperemic thresholds in critically ill patients with respiratory failure and/or shock within 48 hours of ICU admission, and to establish whether these deviations are associated with impairment in dynamic autoregulation and changes in MAP or \( \text{CO}_2 \). We used transcranial Doppler to measure CBFv as an indicator of global CBF and showed that CBFv deviates by 20-30% from baseline for 17-24% of observation time in a cohort of patients with respiratory failure or shock within 48 hours of an ICU admission. We used transcranial Doppler derived index of dynamic autoregulation Mxa to show that dynamic autoregulation was impaired for 20-35% of observation time in our cohort. However, contrary to our hypothesis, the observed CBFv deviations occurred during periods of both impaired and preserved autoregulation, suggesting that failure of autoregulation alone does not fully explain the observed CBFv deviations. Furthermore, occurrence of CBFv deviations during periods of preserved autoregulation suggest that intact autoregulation does not fully protect the brain from periods of ischemia and hyperemia during early stages of critical illness. In attempt to understand the factors that are responsible for observed CBFv deviations, we used regression analysis to determine the relative contribution of concurrently measured fluctuation of MAP and Pet\( \text{CO}_2 \) to observed CBFv deviations. Again, contrary to our hypothesis, our analysis showed that spontaneous fluctuations in Pet\( \text{CO}_2 \) and MAP explain less than 25% of the observed CBFv deviations, suggesting that other unmeasured factors, such as cardiac output or regional changes in cerebral metabolism and cerebrovascular resistance, may play a role.

Prior studies in cardiac surgery have shown that cumulative duration of CBF deviations beyond ischemic thresholds was associated with major clinical complications including stroke and delirium\(^1\) and development of new ischemic lesions on neuroimaging\(^2\). Our results suggest that critically ill patients with respiratory failure or shock may experience
similar insults during early stages of their critical illness, which may explain high prevalence of ischemic lesions on neuroimaging\textsuperscript{3,4} and histopathology,\textsuperscript{5,6} delirium\textsuperscript{7} and long-term cognitive impairment\textsuperscript{8,9} in ICU patients. Future studies should establish whether the cumulative burden of CBFv deviation reported in this study is associated with imaging markers of ischemia and neurocognitive outcomes in this patient population.

While prior studies suggested that the cumulative duration of impaired autoregulation may be associated with development of delirium in patients with respiratory failure or shock,\textsuperscript{10} our study suggests that ischemic insult in this population can occur even in the settings of preserved autoregulation. This implies that assessment of autoregulation status alone may not be sufficient in predicting neurocognitive outcomes, and future studies should explore whether cumulative duration of CBFv deviations is a better predictor that assessment of autoregulation alone.

Since MAP and PetCO$_2$ are considered important determinants of CBF, we were surprised to find that variation in these variables predicted $<25\%$ of observed CBFv deviations. Other factors, such as cardiac output, have emerged as important determinants of CBF that are independent of changes in MAP\textsuperscript{11} and their relative contribution to observed CBFv deviations should be explored in future work. Additionally, regional changes in cerebral metabolism may play a role and warrant further detailed examination.

In our second study, we aimed to assess whether patients with a high risk of critical illness have impaired cerebrovascular function prior to the ICU admission. We chose to examine HD patients since they are at higher risk of developing critical illness than the general population.\textsuperscript{12} We used cerebrovascular reactivity to CO$_2$ (CVR) to assess cerebrovascular function in HD patients, and compare it to patients with CKD and healthy participants. We showed that HD patients have impaired CVR, while there was no difference in CVR between CKD patients and healthy participants. Our findings suggest that certain patient groups may have pre-ICU impairment in their cerebrovascular function that may render them more susceptible to ischemic injury and worse
neurocognitive outcomes when exposed to hemodynamic stress during critical illness, such as CBFv deviations reported in our first study.

CVR has emerged as a robust marker of cerebrovascular function. Impairment in CVR is associated with increased risk of stroke,\textsuperscript{13} cognitive impairment,\textsuperscript{14,15} cortical thinning,\textsuperscript{16} and leukoaraiosis.\textsuperscript{17} Furthermore, areas of normal white matter that have impaired CVR show significant reductions in resting CBF, cerebral blood volume, and impairment in the imaging markers of white matter integrity (fractional anisotropy and mean diffusivity), suggesting that CVR is likely an early functional marker of white matter at risk for subsequent injury.\textsuperscript{18} These findings may also explain why HD patients are more vulnerable to developing subcortical white matter ischemic injury and associated cognitive impairment when exposed to circulatory stress of hemodialysis.\textsuperscript{19}

Our results suggest that HD patients are less likely to mount an effective compensatory response during critical illness if they experience CBFv deviations seen in our first study. In patients with preserved CVR, reduction in CBFv would lead to compensatory vasodilation to maintain effective cerebral perfusion and oxygen delivery. Patients with impaired CVR would not be able to mount an effective vasodilatory response and would be more likely to experience ischemia. Furthermore, during episodes of global ischemia, brain regions with impaired CVR may suffer worse ischemia than brain regions with preserved CVR, as preserved vasodilation in the latter would divert blood flow from the former by means of vascular steal. This phenomenon would be more pronounced in white matter regions of the brain that are already more susceptible to vascular steal,\textsuperscript{20} and may explain the high burden of white matter injury in critically ill patients (see Table 1-3).\textsuperscript{21,22} Future studies should explore whether impaired CVR in HD patients is associated with higher risk of white matter injury and worse neurocognitive outcomes during critical illness.

By demonstrating that certain patients have different baseline cerebrovascular function prior to the onset of critical illness, we highlight the importance of incorporating such functional assessments into interpretation of the effects of ICU exposures and interventions on neurocognitive outcomes. The value of such functional assessment is
highlighted in our study by the ability of CVR to differentiate cerebrovascular function between CKD and HD patients, despite both groups sharing impaired renal function. Functional stratification of baseline cerebrovascular risk advances this field of research beyond simple assessment of baseline comorbidities and enables a more detailed stratification of the relative risk of ischemic injury due to critical illness in individual patients. Such individualized approach represents a new frontier in this field of research and opens opportunities for identification of individualized therapeutic targets for specific patients or groups of patients (i.e. personalized medicine).

In order to link ischemic insults during critical illness, such as CBFv deviations described in our first study, and impairments in cerebrovascular function, such as impaired CVR in HD patients in our second study, with neurocognitive outcomes we needed to establish a clinically feasible and accurate method for detecting cognitive impairment in ICU patients. However, existing cognitive assessment methods were either too simple and fail to detect multi-domain cognitive impairment in ICU patients, or too complex requiring long time and specially trained personnel for completion, rendering them impractical for routine clinical use. In our third study, we therefore aimed to establish a clinically feasible and accurate method for detecting cognitive impairment in ICU patients. Given that ICU patients suffer from multi-domain cognitive impairment, we thought to use a comprehensive cognitive battery that assesses multiple cognitive domains. However, traditional paper-based comprehensive cognitive batteries are nor practical for routine use in clinical settings as they take long time to administer and require specially trained personnel. Cambridge Brain Sciences, an established and widely used web-based cognitive battery that assess multiple cognitive domains, presented an attractive compromise between comprehensiveness and ease of administration. We thought to establish its clinical feasibility and ability to detect cognitive impairment in ICU patients.

We administered Cambridge Brain Sciences to a cohort of ICU patients prior to or shortly after ICU discharge and showed that this battery was able to detect cognitive impairment across multiple domains in all participants. Since the duration of battery administration was identified as common limiting feasibility factor in our study, we also demonstrated that shortening the battery from 12 to 6 tests would have yielded similar cognitive results.
Our results suggest that the shortened 6-test version of the Cambridge Brain Sciences cognitive battery may be an optimal clinical tool for assessing cognitive outcomes in ICU patients. This new tool fills an important gap in existing cognitive toolset used in critical care. Similar to traditional paper-based comprehensive cognitive batteries, it assesses cognition across multiple domains, but it does not require trained personnel to administer, can be remotely self-administered by patients allowing for remote monitoring of cognitive recovery and saving time during clinical appointments, and avoids learning and floor-ceiling effects by randomizing the order and adjusting the difficulty of individual tests based on patient performance. Similar to simple screening tools like Mini Mental State Examination (MMSE), it is short and easy to administer, while also being able to detect subtle cognitive impairment across multiple domains that is often missed by screening tests like MMSE.8

Given that cognitive health is an important patient-centred outcome that determines the overall function,24–26 our clinical validation of the shortened version of the Cambridge Brain Sciences tool opens a new frontier for monitoring cognitive outcomes in ICU survivors. This tool will enable future work exploring links with ischemic insults, such as CBFv deviations described in our first study, and impairments in cerebrovascular function, such as impaired CVR in HD patients in our second study. The web-based nature of this cognitive battery will allow patients to complete cognitive assessments remotely without the need to come to clinic and would make tracking of cognitive recovery economically feasible by obviating the need for specially trained personnel for test administration. Furthermore, since Cambridge Brain Science has neuro-anatomical correlates, it would enable mapping of cognitive outcomes to specific neuroimaging findings in ICU patients, which would allow more precise identification of underlying mechanisms responsible for cognitive dysfunction in this patient population.

In summary, in this work we demonstrated that critically ill patients experience substantial duration of CBFv deviations beyond previously described ischemic and hyperemic thresholds that occur irrespective of the state of dynamic cerebral autoregulation and are not fully explained by concurrent variations in MAP and CO2. We then showed that HD patients have impaired cerebrovascular function that may render
them more susceptible to ischemic injury during critical illness when exposed to CBFv variations identified in our first study. Finally, we optimized an existing comprehensive web-based cognitive battery for monitoring cognitive outcomes in ICU patients, which should enable linkage between clinical observations (such as CBFv deviations and impaired cerebrovascular function in our first two studies) with an important patient-centred outcome.

Our work highlights the importance of studying the problem of neurocognitive outcomes in ICU patients across the continuum of critical illness framework (Figure 5-1).

**Figure 5-1:** Continuum of Critical Illness Framework for studying the problem of neurocognitive outcomes in ICU patients.

Under this framework, it is important to consider pre-ICU, ICU and post-ICU factors related to neurocognitive health. At the pre-ICU stage, consideration of risk factors should move beyond epidemiologic considerations of traditional comorbidities and incorporate functional assessment of brain health (e.g. cerebrovascular function as assessed by CVR), especially in patient populations that are at high risk of critical illness (e.g. HD patients). Such functional stratification would help stratify patients in future observational and interventional trials assessing ICU exposures and interventions. During ICU-stage, we should employ modern multimodal neuromonitoring methods to better
delineate biologically plausible insults (e.g. CBFv deviations beyond ischemic and hyperemic thresholds), and utilize these methods over prolonged observations periods to quantify the burden of such insults (e.g. the cumulative time of CBFv deviations). Combining different monitoring modalities (e.g. transcranial Doppler with invasive MAP and exhaled PetCO2 monitoring) can help explore mechanisms behind identified insults (e.g autoregulation), while adding novel monitors (e.g. diffuse correlation spectroscopy) in future studies can provide a more in-depth assessment of the various contributing factors (e.g. cerebral metabolism and oxygen delivery). At the post-ICU stage it is critical to establish clinically feasible yet comprehensive tools for detecting relevant patient-centred outcomes (e.g. cognitive function). Such tools will enable linkage of patient-centred outcomes with pre-ICU functional risk factors (e.g. CVR) and ICU exposures (e.g. CBFv deviations) and interventions. They will also enable longitudinal studies to better understand the natural history of cognitive recovery in ICU patients, identify optimal time windows for interventions, and assess outcomes of targeted therapeutic interventions.

5.2 Limitations of current work

There were several limitations in our studies. First, our sample sizes were relatively small. However, all three studies were of pilot nature and aimed to: 1) explore the potential burden of CBFv deviations beyond ischemic/hyperemic thresholds in the early stages critical illness, 2) assess whether certain patients at high risk of critical illness may have impaired cerebrovascular function that can render them more susceptible to ischemic injury during critical illness, and 3) develop clinically feasible yet comprehensive method for monitoring cognitive outcomes in ICU patients following resolution of critical illness.

Another limitation is that we used transcranial Doppler to monitor CBFv velocity in the middle cerebral artery as an indicator of global CBF. This method, while having excellent temporal resolution, lacks in spatial resolution. Given that CVR differs between gray and white matter,27 we cannot conclude whether CVR impairments in HD patients was secondary to impaired gray or white matter CVR, or both. Furthermore, subtle changes and CVR in specific brain regions may have been missed.
Lastly, CBF velocity is proportional to CBF as long as the diameter of insonated vessel remains the same. One recent study reported that hypercapnia dilates middle cerebral artery, which would cause CBF velocity to underestimate CBF.\textsuperscript{28} Another study suggested that middle cerebral artery diameter stays relatively constant at modest elevations of CO\textsubscript{2}.\textsuperscript{29} The reason for difference between these studies remains unclear, but may be related to different magnetic resonance imaging protocols, and the relationship between MCA diameter and PCO\textsubscript{2} may in fact be sigmoid based on main published studies in this area.\textsuperscript{30} Since we did not measure middle cerebral artery diameter during this study we cannot comment whether our results have been affected by its changes. Either way, despite the uncertainties regarding the changes in middle cerebral artery diameter during CO\textsubscript{2} challenges, transcranial Doppler has been previously used to study CVR in the middle cerebral artery,\textsuperscript{31–33} and impaired CVR has been associated with pathologies such as hypertension and vascular disease,\textsuperscript{34} as well as increased risk of death.\textsuperscript{35} Furthermore, in our first study the changes in CO\textsubscript{2} were equivalent between the three patient groups, so differences in CVR are likely representative of difference in global CBF. However, this would need to be confirmed with more accurate CBF measures such as magnetic resonance imaging.

In our first two studies, we did not link observed changes in CVR and CBF with imaging markers of ischemia or cognitive outcomes. Such linkage would require larger sample size studies that control for important covariates and the use tomographic imaging modalities such as magnetic resonance imaging, which would be make pilot study complex and expensive. As a result, we chose to first determine whether our hypotheses were supported by plausible physiologic data prior to embarking on large scale clinical studies. Our results from the first two studies provide important empiric rationale for design of larger scale studies that should explore potential associations of impaired CVR and CBFv deviations beyond ischemic thresholds with imaging markers of ischemia and clinical outcomes. Furthermore, results of our third study provide a feasible and objective outcome measure that can be utilized in these future studies.
5.3 Future work

In the future, we plan to further characterize impairment in CVR in HD patients. First, we will use tomographic imaging methods such as MRI to better delineate whether the impairment occurs in gray or white matter, and whether it is associated with imaging markers of ischemic injury. Given that CVR was preserved in CKD group, we will test the hypothesis that transition of CKD to hemodialysis is associated with the development of impaired CVR. Finally, we would like to determine the functional consequences of decreased CVR by establishing whether it is associated with cognitive impairment in the settings of hemodialysis and critical illness. From epidemiological perspective, we would like to determine if HD patients have a higher risk of developing ICU-related delirium and long-term cognitive impairment compared to CKD patients and non-CKD controls.

In the ICU settings, we plan to determine if the cumulative burden of observed deviations in CBFv is associated with the imaging markers of ischemia and cognitive impairment. We will also determine if this phenomenon occurs in other critically ill populations including those with acquired brain injury. Given that patients with ARDS have higher prevalence of cognitive impairment and are also exposed to higher PaCO₂ due to permissive hypercapnia, we would like to explore whether permissive hypercapnia contributes to cognitive impairment in these patients by impairing cerebrovascular function and facilitating ischemic brain injury. Finally, if we confirm that CBFv deviations are associated with ischemic injury and cognitive impairment using Cambridge Brain Sciences battery that we developed in our third study, we will plan interventional trials to reduce such injury, perhaps by improving cerebrovascular function through optimization of PaCO₂.

Finally, we plan to use the 6-test version of Cambridge Brain Sciences cognitive battery from our last study to describe the natural history of cognitive recovery following resolution of critical illness. Specifically, our aim would be to determine if there are different cognitive recovery phenotypes (Figure 5-2), and utilize neuroimaging modalities to assess whether such phenotypes are associated with different patterns of brain injury. We will also 6-test version of Cambridge Brain Sciences as a feasible outcome measure in both pre-ICU and ICU studies proposed early.
Figure 5-2: Hypothetical Cognitive Recovery Phenotypes in ICU Survivors. Regular follow-up testing of individual ICU survivors using Cambridge Brain Sciences (CBS) battery may identify different trajectories of cognitive recovery phenotypes among patients.
5.4 Significance

While cognitive impairment in ICU patient is very common,\textsuperscript{7,8} and associated demographic and clinical risk factors have been identified,\textsuperscript{37,38} the underlying biologic mechanisms responsible for these functional impairments remain elusive. This lack of knowledge of underlying pathophysiologic mechanisms prevents development of targeted interventions and limits therapeutic options. In this body of work, we identified previously under-appreciated insult (i.e. CBFv deviations) that is not fully counteracted by a known homeostatic mechanism (i.e. cerebral autoregulation) and is not fully explained by two established physiologic variables (i.e. fluctuations in MAP and PetCO\textsubscript{2}). We then showed that for the first time that certain patients at high risk of critical illness have impaired in cerebrovascular function that may render them more susceptible to ischemic injury when exposed to insults such as the one identified in the first study. Finally, we developed a clinically feasible outcome measure for detecting and tracking the functional consequences of pre-ICU impairments in cerebrovascular function and ICU insults, such as CBFv deviations reported in the first study.

Our approach is a paradigm shift in this area of research by refocusing efforts from ongoing description of association between cognitive impairment and clinical risk factors, to in depth discovery of the underlying biologic mechanisms and insults grounded in established models of ischemic injury in other clinical populations, such as CKD and HD patients. We demonstrate that similar processes may be at play during circulatory stress of critical illness. As a result, our work provides much needed pilot data and substantiates the rationale for further detailed enquiry into the mechanisms of brain injury in this patient populations using state of the art neuroimaging techniques, functional assessment of cerebrovascular function, and the newly developed cognitive outcome measure. By focusing on understanding the underlying mechanisms and linking them to imaging and functional markers of injury, we should be able to discover new therapeutic targets and position this field of research for designing targeted interventional trials to improve neurocognitive outcomes in ICU patients.
REFERENCES


6 Appendices

Appendix A: Within patient analysis of the time that CBFv deviated above or below CBFv thresholds.

Table 6-1: Within patient analysis of the proportion of the observation time that CBFv was above or below CBFv thresholds

<table>
<thead>
<tr>
<th>Patient</th>
<th>Proportion of observation time CBFv was above threshold</th>
<th>Proportion of observation time CBFv was below threshold</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CBF threshold (% above baseline)</td>
<td>CBF threshold (% below baseline)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>1</td>
<td>0.429</td>
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</tr>
<tr>
<td>2</td>
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<td>0.198</td>
</tr>
<tr>
<td>3</td>
<td>0.334</td>
<td>0.204</td>
</tr>
<tr>
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<td>0.043</td>
</tr>
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<td>0.191</td>
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</tr>
<tr>
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</tr>
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<td>7</td>
<td>0.966</td>
<td>0.966</td>
</tr>
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<td>0.469</td>
<td>0.236</td>
</tr>
<tr>
<td>9</td>
<td>0.133</td>
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</tr>
<tr>
<td>10</td>
<td>0.901</td>
<td>0.79</td>
</tr>
<tr>
<td>11</td>
<td>0.259</td>
<td>0.165</td>
</tr>
<tr>
<td>12</td>
<td>0.297</td>
<td>0.076</td>
</tr>
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</table>
Appendix B: Within patient analysis of the relationship between CBFv deviations and state of dynamic autoregulation.

Figure 6-1, Figure 6-2 and Table 6-2 below provide within patient data on the relationship between CBFv deviations above/below thresholds and state of dynamic cerebral autoregulation (preserved/impaired).
Figure 6-1: Relationship between CBFv deviations above/below thresholds and state of dynamic autoregulation (patients 1-6)
Figure 6-2: Relationship between CBFv deviations above/below thresholds and state of dynamic autoregulation (patients 7-12)
Table 6-2: Within patient comparison of the duration that CBFv deviated above/below CBF thresholds between windows with preserved versus impaired autoregulation (AR).

<table>
<thead>
<tr>
<th>Subject</th>
<th>CBF threshold</th>
<th>Time CBFv ABOVE threshold (fraction of 5-min window time)</th>
<th>Time CBFv BELOW threshold (fraction of 5-min window time)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AR Preserved mean ± SD AR Impaired mean ± SD p-value</td>
<td>AR Preserved mean ± SD AR Impaired mean ± SD p-value</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>0.416 ± 0.345 0.595 ± 0.346 &lt;0.0001 0.352 ± 0.017 0.236 ± 0.041 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>10</td>
<td>0.233 ± 0.264 0.381 ± 0.325 0.0006 0.29 ± 0.014 0.175 ± 0.031 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>15</td>
<td>0.092 ± 0.191 0.206 ± 0.281 0.0155 0.181 ± 0.009 0.126 ± 0.022 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>0.04 ± 0.158 0.078 ± 0.184 0.8975 0.107 ± 0.005 0.059 ± 0.01 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>1</td>
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<td>0.017 ± 0.086 0.019 ± 0.061 &gt;0.9999 0.036 ± 0.002 0.014 ± 0.002 &lt;0.0001</td>
<td></td>
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<tr>
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<td>0 ± 0.004 0 ± 0 &gt;0.9999 0.004 ± 0 0.003 ± 0.001 0.9656</td>
<td></td>
</tr>
<tr>
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<tr>
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<tr>
<td>2</td>
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<td>0.145 ± 0.304 0.245 ± 0.408 0.0495 0.149 ± 0.275 0.183 ± 0.328 0.912</td>
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</tr>
<tr>
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<td>Time CBFv ABOVE threshold (fraction of 5-min window time)</td>
<td>Time CBFv BELOW threshold (fraction of 5-min window time)</td>
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<td>Time CBFv BELOW threshold (fraction of 5-min window time)</td>
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<td>----------------------------------------------------------</td>
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</tr>
<tr>
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<td></td>
<td>AR Preserved mean ± SD</td>
<td>AR Impaired mean ± SD</td>
</tr>
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<td>10</td>
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<td>0.67 ± 0.458</td>
<td>0.472 ± 0.487</td>
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<td>0.614 ± 0.466</td>
<td>0.4 ± 0.473</td>
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<td>0.56 ± 0.467</td>
<td>0.334 ± 0.444</td>
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<tr>
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<td>0.26 ± 0.368</td>
<td>0.192 ± 0.266</td>
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<td>0.17 ± 0.284</td>
<td>0.104 ± 0.174</td>
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<tr>
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<td>15</td>
<td>0.075 ± 0.162</td>
<td>0.049 ± 0.104</td>
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<tr>
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<td>0.028 ± 0.094</td>
<td>0.026 ± 0.071</td>
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<td>0.01 ± 0.06</td>
<td>0.011 ± 0.04</td>
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<td>0.004 ± 0.038</td>
<td>0.005 ± 0.021</td>
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<tr>
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<td>0.286 ± 0.298</td>
<td>0.326 ± 0.291</td>
</tr>
<tr>
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<td>0.08 ± 0.161</td>
<td>0.115 ± 0.174</td>
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<tr>
<td>12</td>
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<td>0.022 ± 0.085</td>
<td>0.036 ± 0.083</td>
</tr>
<tr>
<td>12</td>
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<td>0.007 ± 0.039</td>
<td>0.009 ± 0.03</td>
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<tr>
<td>12</td>
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<td>0.002 ± 0.01</td>
<td>0.003 ± 0.017</td>
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<tr>
<td>12</td>
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<td>0 ± 0</td>
<td>0 ± 0</td>
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</tbody>
</table>
**Curriculum Vitae**

**Name:** Marat Slessarev  

**Post-secondary Education and Degrees:**  
University of Toronto  
Toronto, Ontario, Canada  
2000-2003 Hon.B.Sc.  
University of Toronto  
Toronto, Ontario, Canada  
2003-2006 M.Sc.  
University of Toronto  
Toronto, Ontario, Canada  
2003-2006 M.D.  
Western University  
London, Ontario, Canada  
2015-2020 Ph.D. Candidate

**Honours and Awards:**  
Critical Care Western Leadership Award  
2017  
Vanier Canada Graduate Scholarship,  
The Government of Canada  
2017-2020  
Queen Elizabeth II Scholarship (Ontario Graduate Scholarship)  
2016-2017  
Resident Research Career Development Award,  
Schulich School of Medicine & Dentistry, Western University  
2015-2017  
London Health Research Day Feature Presentation Winner  
2015  
Canadian Critical Care Trials Group Education Travel Award  
2015
Honorable mention, (top 20 student presentation award finalist), International 2009 Hypoxia Symposia, Lake Louise, Alberta, Canada

CREMS distinction in research program, University of Toronto 2007-2008
Ontario Thoracic Society Summer Student Fellowship
Ontario Thoracic Society 2003

University of Toronto and New College Entrance Scholarships 2000

**Related Work Experience**

- Post-Graduate Doctor of Medicine – Internal Medicine
  University of Toronto
  2010-2013

- Post-Graduate Doctor of Medicine – Critical Care Medicine
  Western University
  2013-2015

- Clinical Scholar/ Attending Physician– Critical Care Medicine
  Western University
  2015-2017

- Assistant Professor of Medicine – Critical Care Medicine
  Western University
  2017-2020

**Publications:**


5. Jennifer L. Chen, Claudio Martin, Christopher W. McIntyre, Ian Ball, James Duffin, **Marat Slessarev**. Impact of graded passive cycling on hemodynamics, brain and heart perfusion in healthy adults. Frontiers in Medicine, 2019 Jul 8, **Senior Responsible Author**, Available from: www.frontiersin.org


12. Razik R, Slessarev M. Resident work hours: why keeping the status quo may not be such a bad thing. Can Med Educ J, 2013 Jan 1; 4 (2): e56-62, Senior Responsible Author


