AGE AND SEX-RELATED DIFFERENCES IN CEREBROVASCULAR RESPONSE IN TRAUMATIC BRAIN INJURY (TBI)

by

Carleen Batson

A Thesis Submitted to the Faculty of Graduate Studies of
The University of Manitoba
in Partial Fulfillment of the Requirements of the Degree of

MASTER OF SCIENCE

Department of Human Anatomy and Cell Science
University of Manitoba
Winnipeg



Copyright © 2022 by Carleen Batson

Acknowledgments

Firstly, thank you to the University of Manitoba for awarding me with the Centre on Aging Fellowship and the Research Completion Scholarship which provided the financial means to complete this project.

I would like to thank all the TBI patients for allowing their data to be collected and analysed making this project possible.

I wish to extend special thanks to my supervisor, Dr. Frederick Zeiler for accepting me as his student, his teaching, wisdom, guidance, unwavering support, patience and understanding on this life-changing journey. I am forever grateful and look forward to future mentorship and collaboration.

I wish to show my appreciation to my advisory committee members: Dr. Bertram Unger, Dr. Colin Kazina and Dr. Ji Hyun Ko for agreeing to be an integral part of my journey and providing guidance and support.

Thank you to my lab mates at the Winnipeg Acute TBI Laboratories: Logan Froese for your expert help with data analysis and teaching; Alwyn Gomez for teaching in the ICU and outpatient clinic; Kevin Stein for being a great reviewer on my scoping review; Amanjyot Sainbhi for your input on reviewing my manuscripts; Arsalan Alizadeh for your expert input on my manuscripts and for imparting wisdom from your experiences to guide me on my journey. I wish to extend a heartfelt thank you for all your invaluable support.

I would like to thank the members of the CAHR-TBI Research Collaborative for all their hard work, dedication and input to making my multicenter study a success.

I would like to express sincere gratitude to my parents; Cuthbert and Evelyn Batson, Clayton and Craig Batson, Randy and Barbara Panchoo, Sean and Ezra Lucas, Jody Daniel, Dr. Devon Francis, Dr. Dolland Noel and Dr. Linwald Fleary for your unwavering support on this journey.

Dedication

“In Loving Memory of My Uncle, Leonder Panchoo, Forever in My Heart”

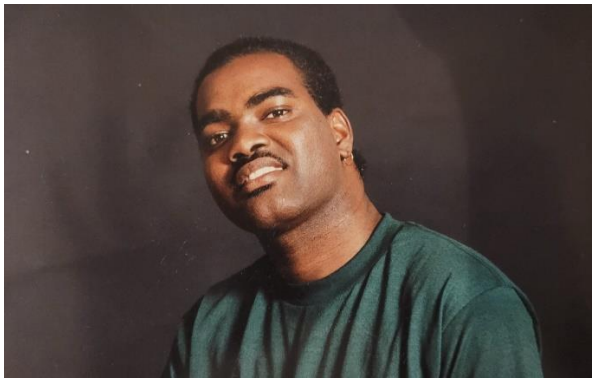


TABLE OF CONTENTS **PAGE #**

LIST OF TABLES vii

LIST OF FIGURES viii

LIST OF FORMULAE ix

LIST OF ABBREVIATIONS x

ABSTRACT 1

CHAPTER 1: INTRODUCTION 2

1.1 Aims and Hypotheses 3

1.2 Overview of Thesis 5

CHAPTER 2: REVIEW OF LITERATURE 6

2.1 Advance Neuromonitoring 6

2.2 Acute Neuromonitoring Techniques in Moderate/Severe TBI 7

2.3 Advanced Invasive Techniques for Early Multi-Modal Monitoring of Cerebral Physiology 9

2.4 Advanced Non-Invasive Techniques for Early Multi-Modal Monitoring of Cerebral Physiology 12

2.5 Derived Metrics for Continuous Physiologic Assessment 14

2.6 Advanced Age as a Biological Consideration 17

2.7 Sex as a Biological Consideration 18

2.8 Potential Mixed Biological Effects of Aging and Sex 20

2.9 Review of Literature on Age and Biological Sex Associations 21

2.10 Association with ICP-Derived Cerebrovascular Reactivity Indices 26

2.11 Limitations of the Literature 31

CHAPTER 3: IMPACT OF AGE AND SEX ON CEREBROVASCULAR REACTIVITY IN ADULT MODERATE/SEVERE TBI: AN EXPLORATORY ANALYSIS 33

3.1 Introduction 33

3.2 Methods 35

3.3 Results 40
3.4 Discussion 48
3.5 Limitations 51
3.6 Conclusion 52
CHAPTER 4: IMPACT OF CHRONOLOGICAL AGE AND BIOLOGICAL SEX ON CEREBROVASCULAR REACTIVITY IN MODERATE/SEVERE TRAUMATIC BRAIN INJURY: A CANADIAN HIGH-RESOLUTION TBI (CAHR-TBI) STUDY 54
4.1 Introduction 54
4.2 Methods 55
4.3 Results 59
4.4 Discussion 71
4.5 Limitations 73
CHAPTER 5: OVERALL THESIS CONCLUSION 75
CHAPTER 6: FUTURE DIRECTIONS 77
REFERENCES 81
APPENDICES 99
Appendix A: Cerebral Physiology Based on Biological Sex: Medians/IQRs and Mann-Whitney-U Testing of the Entire Recording Period 99
Appendix B: Scatterplots with 95% confidence interval between age and % time ICP > 22 mm Hg, mean CPP, % time PRx > 0.25 and % time PAx > 0.25 of the Entire Recording Period 101
Appendix C: Cerebral Physiology Association with Trichotomized Age (Age < 40, Age 40 – 60, Age > 60): Medians/IQRs and Kruskal-Wallis Testing of the Entire Recording Period 103
Appendix D: Entire Recording Period 104
Table D.1 Cerebral Physiology Based on Biological Sex: Medians/IQRs, Mann-Whitney-U and FDR Testing 104

Figure D.1 Scatterplots and Linear Regression % Time ICP > 22 mm Hg vs. Age, Mean CPP vs. Age, % Time PRx > +0.25 vs. Age, and % Time PAx > +0.25 vs. Age 106
Table D.2 Cerebral Physiology Association with Trichotomized Age (Age < 40, Age 40 – 60, Age > 60): Medians/IQRs, Kruskal-Wallis and FDR Testing 107
Table D.3 Cerebral Physiology Association with Decades of Age Subgroups (Age < 30, Age 30 – 39, Age 40 – 49, Age 50 – 59, Age 60 – 69, Age > 69): Medians/IQRs, Kruskal-Wallis and FDR Testing for the Entire Recording Period 109

Appendix E: 111
Figure E.1 Agglomerative Hierarchical of Male and Female Physiology During the 1st 72 Hours of Recording 112
Figure E.2 Agglomerative Hierarchical Clustering of Physiology for Trichotomized Age Groups During the 1st 72 Hours of Recording 113
Figure E.3 Agglomerative Hierarchical Clustering Based on Biological Sex – Entire Recording Period 114
Figure E.4 Agglomerative Hierarchical Clustering Based on Trichotomized Age Subgroups – Entire Recording Period 115

Appendix F 116
Figure F.1.1 Principal Component Analysis Based on Biological Sex – 1st 72 Hours 117
Figure F.3.1 Principal Component Analysis Based on Trichotomized Age Subgroups – 1st 72 Hours 119
Figure F.6.1 Principal Component Analysis Based on Biological Sex – Entire Recording Period 122
Figure F.8.1 Principal Component Analysis Based on Trichotomized Age Subgroups – Entire Recording Period 124

List of Tables

Page #

Table 2.1: Findings Regarding an Association Between ICP-derived Continuous Cerebrovascular Reactivity Measures and Age 28

Table 2.2: Findings Regarding an Association Between ICP-derived Continuous Cerebrovascular Reactivity Measures and Sex 30

Table 3.1: Patients' Demographic Information 40

Table 3.2: Cerebral Physiology for the 1st 72 Hours and Entire Recording Period 41

Table 3.3: Cerebral Physiology Based on Biological Sex: Medians/IQRs and Mann-Whitney-U Testing of the 1st 72 Hours of Recording 44

Table 3.4: Cerebral Physiology Association with Trichotomized Age (Age < 40, Age 40 – 60, Age > 60): Medians/IQRs and Kruskal-Wallis Testing of the 1st 72 Hours of Recording 47

Table 4.1: Patients' Demographic Information 60

Table 4.2: Cerebral Physiology for the 1st 72 hours and Entire Recording Period 61

Table 4.3: Cerebral Physiology Based on Biological Sex: Medians/IQRs and Mann-Whitney-U Testing: 1st 72 Hours of Recording 63

Table 4.4: Cerebral Physiology Association with Trichotomized Age (Age < 40, Age 40 – 60, Age > 60): Medians/IQRs, Kruskal-Wallis and FDR Testing for the 1st 72 Hours of Recording 67

Table 4.5: Cerebral Physiology Association with Decades of Age Subgroups (Age < 30, Age 30 – 39, Age 40 – 49, Age 50 – 59, Age 60 – 69, Age > 69): Medians/IQRs, Kruskal-Wallis and FDR Testing for the 1st 72 Hours of Recording 69

List of Figures

Page #

Figure 3.1: Multi-Device Setup at The Patient Bedside in the ICU 36

Figure 3.2: ICM+ Signal Recording and Artifact Clearing 38

Figure 3.3: Boxplots of Daily Recordings of the 1st 7 days 43

Figure 3.4: Scatterplots and Linear Regression (1st 72 Hours of Recording) 46

Figure 4.1: Boxplots of Daily Recordings of the 1st 7 days 62

Figure 4.2: Scatterplots and Linear Regression (1st 72 Hours of Recording) 65

List of Formulae

1. CPP calculation:
   CPP = MAP – ICP.
   CPP = cerebral perfusion pressure (mm Hg), ICP = intracranial pressure (mmHg), MAP = mean arterial pressure (mm Hg)

2. PRx calculation:
   Pearson correlation between slow waves of MAP and ICP.

3. PAx calculation:
   Pearson correlation between slow waves of MAP and AMP.
   AMP = pulse amplitude of ICP (mm Hg)

4. RAC calculation:
   Pearson correlation (R) between slow waves of AMP (A) and CPP (C).

5. RAP calculation:
   Pearson correlation (R) between slow waves of AMP (A) and ICP (P).

List of Abbreviations

1st – first
ABP – arterial blood pressure
ADC – analogue-to-digital converter
AGT – angiotensinogen
AHC – agglomerative hierarchical clustering
AMP – pulse amplitude of ICP
ARDS – acute respiratory distress syndrome
ARIMA – autoregressive integrated moving average
a.u. – arbitrary units
BDNF – brain-derived neurotrophic factor
BK-B1 – large potassium channel beta-1 subunit
BTF – Brain Trauma Foundation
CA – cerebral autoregulation
CAHR-TBI – CAnadian High Resolution Traumatic Brain Injury Research Collaborative
CBF – cerebral blood flow
CBFV – cerebral blood flow velocity
CBV – cerebral blood volume
cEEG – continuous electroencephalography
CENTER-TBI – Collaborative European NeuroTrauma Effectiveness Research in TBI
CI – confidence interval
CMD – cerebral microdialysis
cm/s – centimeter per second
CO_2 – carbon dioxide
COX – cyclooxygenase
CPP – cerebral perfusion pressure
CPP_{opt} – optimal cerebral perfusion pressure
CSF – cerebrospinal fluid
CSV – comma-separated values
CT – computed tomography
DAI – diffuse axonal injury
DNA – deoxyribonucleic acid
EDH – epidural hemorrhage
eNOS – endothelial nitric oxide synthase
etc. – et cetera
EVDs – external ventricular drains
FDR – false discovery rate
g – gram
g/min – grams per minute
GCS – Glasgow Coma Scale
GCS-M – Glasgow Coma Scale - Motor
HbO – oxygenated hemoglobin
HHb – deoxygenated hemoglobin
ICM+ – intensive care monitoring "plus" software
ICP – intracranial pressure
ICU – intensive care unit
IL – interleukin
iNOS – inducible nitric oxide synthase
IQR – interquartile range
KMCA – k-means cluster analysis
LLA – lower limit of autoregulation
LPR – lactate: pyruvate ratio
MAP – mean arterial pressure
MCA – middle cerebral artery
min – minute
mL – milliliter
mm – millimeter
mm Hg – millimeter of Mercury
MMM – multimodal monitoring
MRI – magnetic resonance imaging
MVAs – motor vehicle accidents
nABP – non-invasive arterial blood pressure
NICU – neuro-intensive care unit
NIR – near infrared
NIRS – near infrared spectroscopy
nm – nanometer
NO – nitric oxide
O_2 - oxygen
ONSD – optic nerve sheath diameter
PAM – partitioning around medoids
PAx – pulse amplitude index
$PbtO_2$ – brain tissue oxygen
PCA – principal component analysis
pCO_2 – partial pressure of carbon dioxide
PG – prostaglandin
PI – pulsatility index
ProTECT – Progesterone for Traumatic Brain Injury, Experimental Clinical Treatment
PRx – pressure reactivity index
PRx_{24} – PRx for the 1st 24 hours of monitoring
R – correlation

RAC – correlation between AMP and CPP
RAP – correlation between AMP and ICP
rCBF – regional cerebral blood flow
ROS – reactive oxygen species
rSO_2 – regional cerebral oxygen saturation
sec – seconds
SIBICC – the Seattle International Severe Traumatic Brain Injury Consensus Conference
SICU – surgical intensive care unit
SNP – single nucleotide polymorphism
SyNAPSe - Efficacy and Safety Study of Intravenous Progesterone in Patients with Severe Traumatic Brain Injury Trial
TBI – traumatic brain injury
TDF – thermal diffusion flowmetry
TCD – transcranial Doppler
THI – total hemoglobin index
TOI – tissue oxygen index
tSAH – traumatic subarachnoid hemorrhage
TX – thromboxane
UK – United Kingdom
ULA – upper limit of autoregulation
ULR – univariate logistic regression
US – United States
VARIMA – vector autoregressive moving average
vs. – versus
Xe-CT – Xenon CT

Abstract

Secondary insults post traumatic brain injury (TBI) entail a deadly disease process, with impaired cerebrovascular reactivity dominating the landscape of cerebral physiologic insult burden during the acute phase post-injury. Age and biological sex are potential modifiers of this process. Through this thesis, age and biological sex subgroup differences and impacts on insult burden of cerebral physiology was investigated, with the hypotheses that advancing age, and not sex, would be associated with worse cerebrovascular function post-TBI. Two separate cohorts of TBI patients were evaluated, totalling 42 males, 7 females and 224 males, 59 females, respectively. The following measures of cerebrovascular reactivity were studied: Pressure reactivity index (PRx), pulse amplitude index (PAx) and RAC. Statistically significant results were found where impaired cerebrovascular reactivity (PAx and RAC not PRx) was seen with advancing age but unclear results with sex. These interesting findings require further investigation to ascertain the true utility of these indices in neurotrauma care.

Chapter 1: Introduction

Traumatic brain injury (TBI) is damage sustained to the brain from external forces causing disturbance in its normal functioning, with severity defined by clinical neurological examination on presentation and occurring across a spectrum of mild, moderate and severe. Some of the key causes of this injury are falls mainly in the elderly, assaults mainly amongst young people and motor vehicle accidents (MVAs), just to name a few [1,2]. TBI is one of the most expensive diseases worldwide with staggering costs (US $400 billion per year), morbidity and mortality (~ 35% in severe TBI patients) [3–5].

Moderate and severe TBI is defined by both primary and secondary injury processes. Primary injury is the genesis of this deadly disease from exterior forces causing structural damage to the cranium and brain [5]. Whereas, secondary brain injury refers to the milieu of host injury responses that lead to alterations in blood flow, nutrient delivery, changes in metabolism and neuroinflammation, which exposes the brain to ongoing damage over the minutes, hours and days after injury. Impaired cerebrovascular reactivity, which is really impaired cerebral blood flow (CBF) regulation/cerebral autoregulation (CA), is a major cause of ongoing secondary brain injury after TBI, leading to hypo- or hyper-perfusion [1,6–8]. The derangement in CA is responsible for many physiologic, metabolic, cellular and molecular changes that occur during the acute phase after TBI, which leads to ongoing neural injury and cell death [9,10]. These downstream consequences of impaired CA can manifest as (but are not limited to): impaired extracellular fluid homeostasis leading to elevated intracranial pressure, disrupted CA, activation of pro-inflammatory cascades, generation of reactive oxygen species (ROS), shift to anaerobic metabolism, mitochondrial failure and activation of cell death pathways [10–12].

A major challenge is understanding what exactly drives this impaired cerebrovascular reactivity. Age and biological sex are important known modifiers of global outcome in moderate/severe TBI, however, their roles in various secondary injury pathways, including autoregulatory dysfunction remains unclear and requires more research to fully understand their effects.

The goal of this thesis is to improve our understanding of subgroup differences in physiologic phenotype based on age and biological sex. This will be done with the use of bedside multimodal monitoring (MMM) techniques and continuous high-frequency data examining age and biological sex insult burden and subgroup differences. This will aid in creating management guidelines, anticipation of secondary insults, development of therapeutics to reduce morbidity/mortality, creation of accurate prognostic models, transitioning to personalized medicine approaches in neurocritical/neurotrauma care, all of which may help to alleviate financial and family-related burdens.

1.1 Aims and Hypotheses

1.1.1 Overriding Hypothesis

The overriding hypothesis of this thesis is that: *Cerebrovascular reactivity of medium-sized vessels is a function of an age-related maturation process, which begins in the immature form, matures and then degenerates in advanced age. Whereas, sex does not impact cerebrovascular responses.*

1.1.2 Age-Related Variations in Cerebrovascular Reactivity in TBI

Czosnyka and colleagues showed from preliminary work on a small retrospective cohort of severe TBI patients using gross summary metrics, that advanced age is likely associated with worse cerebrovascular reactivity [13]. Also, reviewing the literature revealed limited studies in existence which actually looked at the impact of age on cerebrovascular reactivity post-TBI using gross averages over varying periods of time and were conducted by mainly one center.

Some questions come to mind:

Would there be cerebrovascular reactivity derangements with increasing age?

Which indices would prove significant?

The first step of this thesis involves directly measuring and characterizing variations in age-related cerebrovascular reactivity in a TBI population. For the first time intracranial pressure (ICP) and

arterial blood pressure (ABP) monitoring would be used to derive continuous measures of cerebrovascular reactivity. These measures would then be used to characterize age-related differences, across the spectrum of late pediatric to the elderly, in moderate to severe TBI.

<u>Hypothesis I:</u> Cerebrovascular reactivity as assessed through ICP and ABP will be more impaired in TBI patients with advanced age, compared to the younger cohorts.

1.1.3 Sex-Related Variations in Cerebrovascular Reactivity in TBI

Currently, there is no data to support *in vivo* sex-related differences in cerebrovascular response post-TBI [14,15]. Biological sex subgroup studies will help shed some light on this very important topic.

Therefore, the second objective of this thesis was to directly measure and characterize sex-related cerebrovascular reactivity in a TBI population. For the first time ICP and ABP monitoring would be used to derive continuous cerebrovascular reactivity measures. These measures would then be used to characterize sex-related differences, across the spectrum of age, in moderate to severe TBI.

<u>Hypothesis II:</u> Cerebrovascular reactivity will not be related to biological sex in TBI cohorts, regardless of method of assessment and age category.

1.2 Overview of Thesis

Chapter 2 provides an extensive review of the relevant literature involving neuromonitoring and age and biological sex associations with cerebrovascular reactivity indices in TBI. This review is based on a textbook chapter (in press), a narrative overview and a scoping review published as part of this thesis. The chapter will summarize neuromonitoring techniques, age and biological sex-related findings and their relationship to various high-frequency MMM and ICP-based cerebrovascular reactivity physiological measures in TBI.

Chapter 3 presents findings from the first original work performed in this thesis (published). The preliminary findings of an exploratory analysis into the impact of age and biological sex on cerebrovascular reactivity in adult moderate/severe TBI are presented. This study sought to address both hypotheses of this thesis.

Chapter 4 reports the findings of the second original work performed in this thesis (under review). It is an expanded analysis on age and sex impacts on cerebrovascular reactivity of a multi-center data set exploring a larger cohort of patients with the aim of validating findings from the exploratory analysis in chapter 3. This study sought to address both hypotheses in this thesis.

Chapter 5 concludes this thesis by highlighting the main findings in context of the initial hypotheses.

Chapter 6 discusses possible future approaches involving studies into the impact of age and biological sex relationships on cerebrovascular reactivity in TBI.

Chapter 2: Review of Literature

The following review of literature chapter is based on the findings from the following works conducted as part of this thesis - textbook chapter (in press), a narrative overview (published) and a scoping review (published). Please refer to the references below.

1. **Batson C**, Froese L, Gomez A, Sainbhi AS, Zeiler FA. Advanced Neuromonitoring in Trauma, in: Trauma Team Dynamics. 2nd ed. Springer: USA; 2020: In Press.

2. **Batson C**, Gomez A, Sainbhi AS, et al. Association of Age and Sex with Multi-Modal Cerebral Physiology in Adult Moderate/Severe Traumatic Brain Injury: A Narrative Overview and Future Avenues for Personalized Approaches. Front Pharmacol 2021;12:676154; doi:10.3389/fphar.2021.676154.

3. **Batson C**, Stein KY, Gomez A, et al. Intracranial Pressure–Derived Cerebrovascular Reactivity Indices, Chronological Age, and Biological Sex in Traumatic Brain Injury: A Scoping Review. Neurotrauma Rep 2022;3(1):44–56; doi: 10.1089/neur.2021.0054.

2.1 Advance Neuromonitoring

Early and rapid intervention is critical to mitigate secondary brain injury after moderate and severe TBI. In order to facilitate rapid and pointed intervention directed at these secondary brain injury mechanisms, we have seen the development of guideline-based therapeutic approaches, such as those supported by the Brain Trauma Foundation (BTF) [16,17]. Therapeutic intervention is further supported by continuous multi-modal assessments of various aspects of cerebral physiology at the bedside. Such advanced monitoring allows for early rapid detection of secondary brain insult, with continuous feedback regarding therapeutic efficacy of interventions [16,17]. This monitoring has advanced TBI care in recent years from guideline physiologic therapies towards personalized medicine approaches in the intensive care unit (ICU) [1,18,19].

1. Contemporary TBI Guideline-Based Care

BTF guidelines state that "in general a TBI patient with a poor neurological exam, abnormal CT of the brain and risk factors for secondary injury should be monitored" [20]. Invasive ICP monitoring is done for TBI patients within the intensive care unit (ICU); prolonged elevations are associated with poor patient outcome [20]. Threshold for ICP treatment is 22 mm Hg, with sustained periods of time spent above this threshold associated with poor global outcome [20]. More recently, the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) guidelines comprises tier zero to tier three management algorithms for severe TBI [21]. Tier zero comprises basic care for a severe TBI patient admitted to the ICU with an ICP monitor in place [21]. The aim is to stabilize the patient neurologically e.g. manage intracranial hypertension, as the minimal cerebral perfusion pressure (CPP) threshold is 60 mm Hg and initial ICP threshold is 22 mm Hg [21]. Tier 1-3 steps up management based on severity of the situation [21].

The BTF and SIBICC guidelines are referenced for more details surrounding tiered management approaches for secondary brain injury mitigation [17,20–22].

2.2 Acute Neuromonitoring Techniques in Moderate/Severe TBI

1. ICP and CPP – Invasive Monitoring and the Basics

The foundation of acute monitoring in moderate/severe TBI is ICP and CPP, as previously mentioned. ICP is the pressure exerted by the contents of an intact calvarium i.e., brain tissue volume, blood, CSF and any space occupying lesion. ICP can be monitored invasively and non-invasively, with invasive techniques and External Ventricular Drains (EVDs) considered the "gold standard". The zero-reference point for ICP is considered the foramen of Monro. The origins of ICP monitoring trace back to times when computed tomography (CT) and magnetic resonance imaging (MRI) were inaccessible. It aided with the detection of hematomas in post-operative patients, and the potential need for intervention could be signaled by increased values in post-op recovery [23,24]. Since then, ICP monitoring has been adopted for continuous bedside assessment in TBI care within the ICU, with the majority of current guideline targets and therapies based on ICP values, or derived measures such as CPP. BTF guidelines recommend ICP monitoring of patients

admitted to the ICU with TBI, and state that an ICP of ≥22 mm Hg requires management [21,23], as extensive literature documented the association between time spent above this ICP value and unfavorable outcome at 6-months following injury [23,25]. Invasive methods for ICP monitoring include parenchymal devices (strain gauge monitors and fiber-optic-based pressure sensors) which can in theory be inserted anyplace in the cranial cavity (typically right frontal lobe), and EVDs inserted in the ventricular system, all used to assess liquid or tissue pressure within the cranium [23,26]. Such techniques are considered the standard for ICP monitoring in TBI care.

Aside from targeting ICP thresholds, we are also interested in maintaining CBF in TBI. Currently, we lack effective continuous bedside methods for objective CBF measurement. As such, we rely on potential surrogate metrics for CBF, with one such measure being CPP. CPP is thought to be the pressure within the brain that maintains CBF. In its simplistic form, CPP is defined as the difference between mean arterial pressure (MAP) and ICP. It is believed that low CPP causes low CBF which can cause harmful effects (ischemia and/or infarction) of the brain parenchyma as less oxygen and nutrients will reach the tissues [23]. Equally, persistently high CPP is believed to be associated with cerebral hyperemia, break-down of the blood-brain-barrier, and potentially intracerebral hemorrhage. The gold standard for CPP measurement requires both invasive ABP and ICP measures [23,25]. BTF guidelines recommend that CPP should be maintained between 60 mm Hg and 70 mm Hg, but some research work suggests a threshold of 70 mm Hg and report poor outcomes noted in patients with values below this number over time [23,25]. Some debate exists surrounding maintaining CPP above 70 mm Hg, as historically literature has linked this to unfavorable outcomes as a result of increased precapillary arteriolar pressure, capillary bed filtration pressures, cerebral edema and even acute respiratory distress syndrome (ARDS) [23,27]. However, recent literature suggests with advances in general cardiopulmonary care in the ICU, systemic complications of elevated CPP targets may not remain a significant concern [27].

2. Non-Invasive ICP/CPP Determination Methods

Recent advances in transcranial ultrasonic techniques have led to the development of non-invasive methods including optic nerve sheath diameter (ONSD) ultrasound and Transcranial Doppler (TCD) ICP estimations. Of note, these are not widely adopted or considered standard of care.

First, for ONSD, it is thought that the subarachnoid space enclosing the optic nerve is continuous with the intracranial subarachnoid space, with pressure changes in the cranium causing similar changes in the optic nerve diameter due to stretching of the dural-based sheath [23]. The measured diameter is believed to estimate ICP [23]. Most studies have not clearly outlined what normal readings are, they suggest a cut-off of approximately 5 mm or less with readings exceeding that considered pathologic [23].

TCD was developed as a method of interrogating CBF through the basal cerebral arteries non-invasively [28]. By measuring cerebral blood flow velocity (CBFV) through these vessels, using the Doppler effect, CBF can be inferred so long as vessel caliber remains relatively constant. Shortly after its development, invasive studies in a non-TBI population found relatively good concordance with invasive CPP and those estimated by TCD [29]. This led to interest in developing TCD-based estimates of ICP and CPP in TBI patients [30–34]. Ultimately their conclusions were all similar. TCD was somewhat effective at identifying episodes of low CPP and high ICP but, regardless of the methodology used, estimates of ICP and CPP had too large a margin of error to effectively eliminate the need for invasive monitoring [33–35].
TCD then, like ONSD, may have a place in guiding management of TBI patients prior to the availability of invasive monitoring, such as in the pre-hospital settings [36].

2.3 Advanced Invasive Techniques for Early Multi-Modal Monitoring of Cerebral Physiology

In the following sub-sections is a brief overview of common advanced invasive cerebral physiologic monitoring devices employed in TBI care within the acute phase. Such devices overviewed include: brain tissue oxygen monitoring ($PbtO_2$), thermal diffusion CBF monitoring,

and extracellular fluid chemistry through cerebral microdialysis (CMD). As these sub-sections only briefly introduce the techniques, more information can be garnered from the referenced literature.

1. $PbtO_2$

$PbtO_2$ was introduced as a means to possibly provide information regarding end-organ oxygen delivery in the brain. It is assessed by inserting an invasive parenchymal $PbtO_2$ probe, which analyzes the extracellular partial pressure of oxygen using a Clark electrode [20,33]. This device provides continuous bedside extracellular oxygen values, updated every minute [37]. Normal threshold for intervention in TBI is considered 20 mm Hg [23]. Recent literature supports a strong association between time spent below $PbtO_2$ of 20 mm Hg and poor outcome at 6-months post-TBI [37]. Similarly, high $PbtO_2$ has been associated with poor outcome in patients where mitochondrial failure is suspected, through CMD analysis, where high $PbtO_2$ with corresponding elevations in extracellular lactate: pyruvate ratios (LPR) suggest failure of oxidative metabolism [23,38].

2. Thermal Diffusion CBF Monitoring

In an attempt to avoid proxy measures of CBF, thermal diffusion flowmetry (TDF) probes have been developed to facilitate continuous bedside assessments of CBF. Such monitoring provides absolute measurements with a high temporal resolution, and can aid in detection and prevention of secondary injury [39]. Probe placement can be on the cortical surface of interest (Saber) or placed in the brain tissue (Bowman Perfusion Monitor), classically right frontal lobe concurrent with ICP monitor placement [39].

Although this method has been used for years in trial models, and there is potential for it to be included into a MMM regimen, there is no threshold agreed upon for this technique or an understanding of how to apply this device for monitoring of TBI patients [40].

Further, the consensus summary by the International Multidisciplinary Consensus Conference on Multimodality Monitoring provides little additional guidance regarding this matter [40].
Furthermore, some of the commercially available TDF probes are thought to assess blood flow "continuously", but in fact they require regular recalibration periods every 30 minutes to 2 hours which takes about 2-5 minutes to complete and interrupts the recordings. CBF ranges considered normal by the TDF method range from 20–40 mL/100 g/min (lower threshold) to 70-100 mL/100 g/min (upper threshold), depending on if the TDF measurement was cortical or parenchymal [39,41].

In theory, increasing CBF could be achieved by expanding plasma volume, inotropic support, and osmotic agents and lowering CBF achieved by hyperventilation and barbiturate coma [41].
Based on several small studies in adult TBI cohorts, it was noted that CBF continuously below 20 mL/100 g/min (ischemic levels) and above 80–100 mL/100 g/min (hyperemia) was linked to poor outcomes [39]. Some probe related complications that arose in some studies were cerebrospinal fluid (CSF) leak around the probe, meningitis, intracerebral abscess and superficial soft tissue infection [41,42]. Of note, the literature supports a positive correlation between changes in regional cerebral blood flow (rCBF) measured by Xenon CT (Xe-CT) and $PbtO_2$, which is consistent with Xe-CT findings showing a positive correlation between brain tissue oxygen and regional blood flow [43]. Despite these promising findings, widespread adoption of this monitoring modality remains limited to leading academic neurotrauma centers globally.

3. Extracellular Brain Chemistry – CMD

CMD done at the bedside serves as a means of invasively monitoring metabolites in the extracellular space via a semi permeable intraparenchymal catheter which aids in avoiding metabolic derangements in TBI patients [44,45]. Extracellular dialysate fluid is captured in microvials and processed typically hourly at the bedside for a panel of common analytes. This method has largely been described within the TBI population, and the information gained can be useful in guiding clinical therapy [12]. Main analytes processed at the bedside include: glucose, lactate, pyruvate, glutamate, and glycerol. Decreased levels of brain glucose and an increased LPR can provide information on aerobic/anaerobic metabolism and oxidative mitochondrial function, with derangements in adult TBI patients linked to poor patient outcomes [12,44,46–48]. Glutamate, an

excitatory neurotransmitter, provides information regarding potential excitotoxicity post-injury [11]. While glycerol provides information regarding the degree of neural injury [12]. Given cost and complexity of interpretation, CMD is another monitored modality in TBI relegated to leading academic neurotrauma units. However, with improvements in microfluidic chips, self-contained bedside microanalyzers are on the horizon, set to improve accessibility and cost associated with the technique [49].

2.4 Advanced Non-Invasive Techniques for Early Multi-Modal Monitoring of Cerebral Physiology

In the following sub-sections is a brief overview of common advanced non-invasive cerebral physiologic monitoring devices employed in TBI care within the acute phase. Three such devices will be highlighted: TCD, near infrared spectroscopy (NIRS) and continuous electroencephalogram (cEEG). As these sub-sections only briefly introduce the techniques, more information can be garnered from the referenced literature.

1. TCD

As mentioned earlier, TCD is a method of noninvasively measuring CBFV in the basal cerebral arteries [28]. In recent years, its adoption into neurointensive care units (NICUs) has increased dramatically with one recent European study finding it to be the second most common form of bedside intracranial monitoring behind only ICP monitoring [50]. Direct parameters measured by TCD include CBFV and the pulsatility index (PI) and have been found to be associated with global outcomes following TBI [51–55]. There has also been evidence linking episodes of reduced CBFV as measured with TCD and reduced $PbtO_2$ as measured by invasive monitors [56]. TCD has also been used as a robust method of identifying post-traumatic vasospasm at the bedside, which has independently been linked to poor outcomes [57]. Ultimately, TCD is limited by its need for expertise in order to both acquire consistent signals and interpret the data obtained.

2. NIRS

NIRS is a non-invasive technique utilized to monitor frontal cerebral oxygen hemoglobin concentration in TBI patients as a way of identifying brain tissue at risk for potential secondary injury [45]. It is used as a marker for pulsatile cerebral blood volume (CBV) [26]. Near-infrared (NIR) involves use of wavelengths between 700 and 1000 nm on the electromagnetic spectrum, a range that allows signal penetration through tissues [45]. In neurocritical care, these spectrometers are usually used to measure the concentration of oxygenated hemoglobin (HbO) and deoxygenated hemoglobin (HHb) within the target tissue, to gain information on blood and oxygen supply [58]. Simpler NIRS equipment utilizes constant wave technology whilst newer versions utilize multi-distance techniques. They assess cerebral oxygenation status and newer versions are able to refine hemoglobin signals by removing interferences and thus purer results like total oxygen index (TOI) and total hemoglobin index (THI) are gained [58].

As opposed to other non-invasive neuromonitoring techniques e.g. TCD-based methods, NIRS is not significantly impacted by interoperator variability [59], and can provide continuous multi-channel (typically bifrontal) assessments of regional cerebral oxygen saturations (rSO_2) and oxy-/deoxyhemoglobin concentrations in the TBI patient. NIRS use in the TBI population can be challenged by signal issues related to injured extracranial tissue and intracranial lesions but there has been improvement in the signal-to-noise ratio with newer multi-distance methods [45]. This technology is reasonably expensive, but can provide long durations of uninterrupted intracranial oxygenated/deoxygenated CBFV surrogate measures, which can be used in concert with non-invasive arterial blood pressure (nABP) devices like the Finapres [26], to derive entirely non-invasive metrics of cerebrovascular reactivity. However, it must be acknowledged that arterial, venous and capillary blood are assessed by NIRS in a portion of the cortex (typically frontal lobes) and recordings are affected by the degree of oxygen extraction [26].

Adult TBI literature for NIRS based regional oxygen saturation supports an association between low regional saturations in the frontal lobes and poor functional outcome after TBI [60]. Similarly, preliminary work with NIRS-based cerebrovascular reactivity metrics supports an association between impaired NIRS-derived cerebrovascular reactivity and poor outcome in moderate/severe

TBI [58]. Similarly, in theory, the device could be used for long-term follow-up, providing information on persistent cerebral physiologic dysfunction and long-term functional outcomes in TBI. It is expected that NIRS monitoring will become more standard in TBI bedside monitoring in the near future.

3. cEEG

cEEG is a non-invasive means of monitoring the brain's electrical activity via superficial scalp electrodes. Though, it must be recognized, the practice of placing the electrodes internally exists, where subdural paddles or parenchymal depth monitors can be inserted (epilepsy monitoring and surgical intervention). Two types of cEEG existing for use with TBI patients in the NICU are the standard multi-channel and focal reduced channel [23]. In cases where regular epileptic specialists are unable to interpret the results there are automatic signal detection algorithms accessible [61]. cEEG has been used in seizure detection, prognostication post-TBI, detection of ischemia, detection of spreading cortical depolarisations and vasospasm post aneurysmal subarachnoid hemorrhage [23]. Seizures after TBI are common, early detection and treatment can prevent secondary brain injury [9]. This method has been used as an auxiliary test to assess brain death as it provides comprehensive analysis of regional and global electrical activity [23,62].

2.5 Derived Metrics for Continuous Physiologic Assessment

Aside from the raw physiologic measures provided by the above-mentioned core and advanced monitoring devices, much more can be obtained from the signal information provided. Advances in bedside data acquisition platforms and real-time signal processing, has allowed us to derive additional continuously updating cerebral physiologic metrics in moderate/severe TBI care. In the sub-sections below, outlined are some of the main derived metrics that have demonstrated strong association with outcome in TBI, including cerebrovascular reactivity monitoring and cerebral compensatory reserve measures.

1. Cerebrovascular Reactivity Monitoring – Pressure Reactivity Index (PRx)

Aside from derangements in ICP and CPP, recent work in bedside signal processing has afforded the treating clinicians the ability to continuously measure aspects of CA. CA is defined as the innate ability of the cerebral vessels to maintain constant CBF over a wide range of MAP or CPP, ensuring a steady state of oxygen and nutrient delivery to the brain [63]. In the injured state, CA is known to be disrupted, leading to impaired or even absent autoregulation of CBF altogether [64,65].

By evaluating the relationship between slow-wave fluctuations in ICP (a surrogate for pulsatile CBV) and MAP (a driver for blood flow), one can provide some information regarding cerebrovascular responsiveness or reactivity [66]. This concept has led to the derivation of the PRx from the Pearson correlation between slow-wave vasogenic fluctuations in ICP and MAP [8]. This index is then updated every minute, providing real-time information regarding cerebrovascular reactivity, and potentially CA. PRx has received validation as a measure of the autoregulatory curve in experimental animal models of intracranial hypertension and systemic arterial hypotension [67–69]. In its most simplistic interpretation, positive values of PRx indicate impaired autoregulation, while negative values denote intact autoregulation [70].

In the adult TBI literature, there exists numerous retrospective and prospective studies linking derangements in PRx and increased mortality and morbidity post-TBI [8,70–73]. Thresholds for morbidity and mortality have been defined in multiple TBI populations with values above a PRx of +0.20 equating to deranged cerebrovascular reactivity [70,72]. In addition, recent literature supports an association between impaired cerebrovascular reactivity and CT-based contusion progression in the acute phase after TBI [74]. Further, evaluating burden of physiologic derangements in TBI, recent work suggests that in the era of current guideline-based therapeutics, the majority of the acute phase physiology in moderate/severe TBI is dominated by impaired autoregulation, and not ICP, CPP or $PbtO_2$ issues [75,76]. These findings suggest that cerebrovascular reactivity monitoring may play a crucial future role in the monitoring and therapeutic intervention for the TBI patient.

2. Pulse Amplitude Index (PAx)

PAx is also an ICP-derived measure of cerebrovascular reactivity. It is the pulse amplitude index and is derived from the moving Pearson correlation coefficient between slow waves of pulse amplitude of ICP (AMP) and MAP [6,72,77]. It has received validation against the lower limit of autoregulation (LLA) for intracranial hypertension and pure arterial hypotension [67–69]. It performs superiorly at detecting impaired cerebrovascular reactivity in cases where ICP is low [77]. Literature on this index is sparse and requires more research to determine its true utility.

3. RAC

RAC is yet another ICP-derived measure of cerebrovascular reactivity. It is the moving Pearson correlation coefficient (R) between slow waves of AMP and CPP [72,78]. It has received validation against the LLA for pure arterial hypotension [67–69]. It tends to reveal similar results to PRx regarding mortality and six-month outcome after TBI [7,72,73]. It also appears to provide useful information regarding cerebral compensatory reserve (RAP) [79]. Currently, work with RAC is quite experimental, limited in the literature and requires more research into its usefulness in neurotrauma care [78].

4. Additional Measure – Cerebral Compensatory Reserve (RAP)

ICP alone provides only a small amount of information regarding the intracranial pressure dynamics after TBI. In an attempt to improve our ability to estimate how "tight" or "relaxed" the brain might be after injury; cerebral compensatory reserve metrics have been developed. By assessing the correlation between slow-wave vasogenic fluctuations in ICP and AMP, one in theory can produce an index of compliance or compensatory reserve [80]. The RAP (R – correlation, A – pulse amplitude of ICP, P – intracranial pressure) is derived through the moving Pearson correlation between slow-waves of ICP and AMP, updated every minute [24,80–82]. This RAP measure varies from -1 to +1, and provides a continuous bedside assessment of cerebral compensatory reserve. Similarly, impaired RAP values have been linked to diffuse intracranial injury patterns present on admission CT scans of the brain [80].

However, despite from initial promising results, much further work is required on RAP, with studies validating it as a true measure of compliance on the horizon. Though its use is not widespread, preliminary work supports its association with patient outcome in TBI, with impaired compensatory reserve associated with increased mortality [24,80–82].

2.6 Advanced Age as a Biological Consideration

Advanced age is known to be associated with impaired cerebrovascular response through cerebrovascular reactivity testing in healthy populations during partial pressure of carbon dioxide (pCO_2) challenges in concert with advanced functional neuroimaging [83–85] and TCD assessments of middle cerebral artery (MCA) CBFV [86–89]. This has been confirmed in both populations of awake and anesthetized patients. It is also seen that advanced age is associated with worse cerebrovascular reactivity in moderate/severe TBI patients from previous studies [7,13,73].

There are a variety of pathological changes that could be associated with impaired cerebral vascular performance during the aging process [90]. First, accumulation of amyloid protein precursor and beta amyloid in the wall of cerebral vessels has long been known to occur with advancing age, as seen in both human literature and experimental models [91–93]. Such accumulation has been linked to reduced endothelial nitric oxide (NO) activity secondary to shuttling to the formation of peroxynitrite and an increase in ROS [94,95]. This leads to impaired resting tone, as well as attenuated vasodilatory responses of the cerebral vessels. In addition, the general response of the cerebral vasculature to free radicals and ROS becomes impaired. The angiotensin II (AGT) pathway is known to be involved in ROS vascular responses. With advanced aging, it appears that there is an uninhibited angiotensin II mediated generation of ROS, further potentiating the impacts on the NO vasodilatory pathways [90,94–96].

Aside from NO/ROS mediated changes seen with aging, chronic inflammation has also emerged as a potentially important pathological driver of cerebrovascular dysfunction [97–99]. Advanced age has demonstrated increased expression of various systemic pro-inflammatory cytokines, such as interleukin (IL)-1B and IL-6, in both experimental and human literature [97]. This response is believed to be a maladaptive autoimmune action to cellular breakdown products found during the

normal aging process. Furthermore, recent literature also suggests some of the chronic cerebral vascular changes seen with aging, such as amyloid deposition, lead to increased leukocyte adhesion, further potentiating the immune response [97–99]. This chronic immune response may be linked to ongoing dysfunction in the central nervous system, and degeneration. Increased circulating IL-6 levels have even been associated with MRI defined white matter ischemic volumes in elderly populations [97,98]. The exact mechanism of cerebrovascular dysfunction related to chronic neuroinflammation remains unclear at this time. However, of interest, the acute TBI literature has also found strong associations between serum and CSF pro-inflammatory cytokines, such as IL-6, with poor long-term outcome [10,100,101]. Furthermore, the impact of the immune response post-TBI has also been supported by the association between various single nucleotide polymorphisms (SNPs) in genes regulating pro-inflammatory cytokines, and patient outcomes [1]. Genetic variation in immune response has also been highlighted as an important consideration in the genetics of biological aging, where SNPs in IL-6 has been underlined as an important future area to consider in aging research [102].

Finally, neural modulation and repair mechanisms are also impaired as a result of aging. Decreased expression of brain derived neurotropic factor (BDNF) has been recently associated with advancing age. SNPs in BDNF have also received note as potential areas of importance for future research in aging [102]. Of note, BDNF SNPs have also been linked to long-term outcomes in adult TBI literature [1,18]. It may be that specific BDNF SNPs potentiate impaired BDNF expression associated with aging, which leads to reduction in downstream regenerative mechanisms post-injury. Such impaired recovery mechanisms in the central nervous system may lead to increase in the pro-inflammatory process described previously, leading to worse cerebral vascular function.

2.7 Sex as a Biological Consideration

As an additional layer of complexity, biological sex has some potentially major roles to play in cerebral vascular responses both in healthy and disease states. It impacts cerebrovascular responses both independent of, but also potentially mixed effects with, advancing age. With respect to moderate/severe TBI, the incidence of such injury overwhelmingly favors males. The majority of studies to date on TBI have had male predominance in their cohorts, limiting proper assessment

of the impact of sex on secondary injury patterns and outcome [103,104]. This is also the case with all of the above-mentioned studies on MMM and their association with biological sex. However, biologically, sex differences leave important considerations regarding disparities in treatment responses, secondary injury severity, and outcomes [105].

With regards to progesterone in moderate/severe TBI, substantial prior work has been conducted. Pre-clinical models of TBI have provided evidence that progesterone carries a neuroprotective effect, with exogenous supplementation in animals leading to reduced neural loss, improved neurophysiologic and functional outcomes [106,107]. In humans, sex-related disparities in outcome after moderate/severe TBI have been well documented, despite the overwhelming majority of patients being male [103–105]. Supplementation with progesterone has been explored in such TBI cohorts in numerous randomized control trials evaluating the impact on long-term global outcomes, including the Progesterone for Traumatic Brain Injury, Experimental Clinical Treatment (ProTECT) [108] and Efficacy and Safety Study of Intravenous Progesterone in Patients With Severe Traumatic Brain Injury (SyNAPSe) Trials [109]. However, despite early evidence suggesting a potential impact on mortality and functional outcome [110], all trials have failed to demonstrate long-term impacts on mortality and morbidity [111–114]. Though, functional outcomes assessments in trials were limited to coarse outcomes metrics standard in moderate/severe TBI, such as the Glasgow Outcome Scale [111–114]. Similarly, progesterone supplementation has also failed to lead to reproducibly measurable differences in biomarkers of neural injury in such populations [115]. To date no assessments of sex steroid supplementation and its impact on high-frequency cerebral physiology in adult moderate/severe TBI have been conducted.

Aside from progesterone, circulating estrogen levels have a well-documented impact on cerebral vasculature [116]. Estrogen is known to promote prostaglandin I2 (PGI2) release, an important vasodilator [116,117]. Similarly, in males, or instances of low estrogen production, thromboxane A2 (TXA2) predominates, leading to cerebral vasoconstriction and impaired vasodilatory responses of the cerebral vessels [117]. Furthermore, in young female mice with higher circulating estrogen levels, there appears to be an attenuated angiotensin II/ROS response, with reduced vasoconstriction responses seen in female models to ROS exposures [118]. Finally, experimental literature points to high endothelial nitric oxide synthase (eNOS) vasodilation in female vs. male

rats, under exercise conditions [119]. Aside from the endothelial and myogenic impacts of estrogen on the cerebral vasculature, there is a known anti-inflammatory effect. Data suggests that higher circulating estrogen levels are linked to decrease in leukocyte adhesion to the cerebral vasculature [116]. Furthermore, estrogen has been shown to decrease inducible nitric oxide synthase (iNOS) in response to IL-1B, which is linked to upregulation of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2). As COX-2 and PGE2 are known cerebral vasoconstrictors, circulating estrogen levels subsequently attenuate their responses in the setting of injury [116]. These anti-inflammatory properties of estrogen have triggered neuroprotective studies in both experimental and human settings [120–123]. However, their impact on global outcome post-TBI in humans is still uncertain.

Finally, aside from estrogenic endothelial/myogenic and anti-inflammatory effects, there have been documented differences in potassium channel expression in males vs. females, with a direct link to estrogen levels [124]. In rats, large potassium channel beta-1 subunit (BK-B1) displays decreased expression in both males and female rats with removed ovaries. This BK-B1 reduction leads to increased MCA reactivity, as the large potassium channels are known to regulate cerebrovascular myogenic activity. This has yet to be substantiated in humans, but carries potential to explain discrepancies in cerebrovascular physiology seen in health and disease.

2.8 Potential Mixed Biological Effects of Aging and Sex

Accounting of the biological impacts of aging and sex highlighted in sections 2.6 and 2.7, it's clear that there is a potential for interaction on cerebrovascular function in the setting of TBI. This is particularly the case for aging females [116]. During youth, females do benefit from the protective effects of higher circulating estrogen on cerebral vasculature. However, during menopause or post oophorectomy the risk profile may change. Menopause in particular, occurring with advancing age may now dramatically increase the risk of abnormal vascular responses in the setting of TBI. Such changes may be reflected in the emerging literature suggesting worse long-term outcomes for females suffering from TBI. Future work in this area will need to evaluate such age/sex interactions in a more comprehensive manner.

2.9 Review of Literature on Age and Biological Sex Associations

A Narrative Overview and a Scoping Review were conducted as part of the literature review for this thesis. The narrative overview focused on age and biological sex relationships with MMM cerebral physiology and the scoping review focused on age and biological sex relationship with the ICP-based cerebrovascular reactivity indices. The narrative overview was conducted solely by the author of this thesis. For the scoping review, in keeping with the standard guidelines outlined by the Cochrane Handbook for Systematic Reviews [125], Kevin Stein (undergraduate student) was the second reviewer/filterer of the articles and Frederick A. Zeiler (thesis supervisor) was the third reviewer to resolve any discrepancies. Otherwise, all other processes involved in completing the reviews were conducted by the author of this thesis. Findings from these reviews will be presented in the following subsections. Refer to the referenced publications for more information [14,15].

2.9.1 Association with MMM Cerebral Physiology

A Narrative Overview of the literature on age and biological sex associations with MMM cerebral physiology in adult moderate/severe TBI was conducted. The goal was to outline some of the major selected studies pertaining to the topic, explore some of the potential biological explanations for discrepancies seen in such physiological measures and provide some suggestions for future directions. Refer to the full review in Batson et al [14].

To start, this was presented by highlighting the major representative available literature on high-frequency data from ICP, CPP, $PbtO_2$, rSO_2, CBF, CBFV, Cerebrovascular Reactivity, RAP, common CMD analytes and their correlation to age and sex in moderate/severe TBI cohorts. One example each of the findings on age and sex associations (where available) will be presented in the following subsections.

1. ICP and CPP

Five large studies with patient numbers ranging from 355 – 556 were examined [13,70,126–128]. The data showed that older patients tended to have high ICPs and low CPPs and suffered undesirable

outcomes [13,126]. Males were predominant in these studies therefore leading in numbers for fatal outcomes. Exploring age and ICP/CPP in more detail, it is clear that MMM based high-frequency ICP and CPP have not been directly evaluated in association with age and biological sex. One example from Adams et al compared the mean ICP and CPP of patients in functional survivors and fatal outcome groups [127]. Patients in the functional survivors group were younger with a mean age of 38 +/- 16 years vs. 45 +/- 18 years ($p < 0.001$) for patients in fatal outcomes group [127]. Patients in the functional survivors group compared to the fatal outcome group, had lower mean ICP and higher mean CPP (15.1 +/- 8.2 mm Hg vs. 21.0 +/- 10.2 mm Hg ($p < 0.001$); and 78.5 +/- 8.0 mm Hg vs. 75.9 +/-8.3 mm Hg ($p = 0.009$), respectively) [127]. In the study by Sorrentino et al, it is seen that ICP threshold for survival was lower in males compared to females at 22 mm Hg vs. 23 mm Hg ($p < 0.001$), and lower in patients > 55 years of age compared to younger patients, at 21 mm Hg vs. 23 mm Hg respectively ($p = 0.018$) [70]. Furthermore, the CPP threshold for survival in that study was higher in older patients (> 55 years) at 75 mm Hg vs. 70 mm Hg in young patients ($p = 0.047$), regardless of sex [70].

2. $PbtO_2$

Three large studies with patient numbers ranging from 47 – 629 were examined [76,129,130]. The data showed that older patients trended towards having lower $PbtO_2$ and tended to suffer undesirable outcomes [76,129,130]. Males were predominant in these studies, but no major association was documented between the sexes. It must be highlighted that all of the relationships in these studies failed to reach statistical significance and only showed a potential relationship based on raw differences in mean/median magnitudes. This lack of significance occurred in the absence of adjusting for multiple comparisons, highlighting that no definitive comments on the associations can truly be made. One example is the Zeiler et al study where it can be seen that older patients were part of the group with high ICP and low $PbtO_2$ [76]. In this study, median age for patients in the group with mean ICP below 15 mm Hg was 51 (IQR: 31-62.3 years) vs. 54 (IQR: 35.3-68.3 years) ($p = 0.311$) in the group with mean ICP above 20 mm Hg, though this failed to reach significance [76]. Those patients in the group with mean ICP above 20 mm Hg had lower median $PbtO_2$ of 22.1 (IQR: 18.2-26.2 mm Hg) vs. 27 (IQR: 23.2-33.1 mm Hg) ($p = 0.183$) in those with mean ICP below 15 mm Hg, though this failed to reach significance [76].

3. rSO_2 - NIRS

Two studies with patient numbers 16 and 104 were examined [131,132]. The data showed that older patients tended to have low rSO_2 and suffered undesirable outcomes, though this was only a trend which failed to reach statistical significance [131,132]. There was not a clear breakdown of male vs. females. Example, Adatia et al showed that the younger patients, with a median age of 54 (IQR: 31) years vs. 61 (IQR: 21) years (p = 0.38), had the highest mean rSO_2 of 66 (IQR: 12%) vs. 63 (IQR: 8%) (p = 0.13) [131]. While in follow-up, Adatia et al demonstrated that patients without midline shift were older, with mean age of 62 +/- 16 years vs. 59 +/- 15 years (p = 0.36) [132]. In this follow-up work, older patients had lower median rSO_2 of 60.5 (IQR: 45.1-65.2%) compared to younger patients with rSO_2 values of 64.7 (IQR: 52.0-68.1%) (p = 0.39) [132]. The role of age and biological sex in cerebral oxygen saturation, as measured by NIRS, has been more extensively examined outside the context of TBI.

4. CBF and CBFV – TDF and TCD

Two studies, patient numbers 12 and 18 were examined in relation to CBF [41,133] and four studies, patient numbers ranging from 30 – 237 were examined in relation to CBFV [13,134–136]. The data showed that older patients tended to have low CBF and CBFV and suffered undesirable outcomes [13,41,133–136]. No major association was made between the sexes. One example of CBF is by Dias et al who showed that patients with preserved cerebrovascular reactivity (measured through pressure reactivity index value of < 0.25) were younger with mean age of 40 +/- 16 years vs. 52 +/- 11 years (p = 0.173) in those with impaired cerebrovascular reactivity [133]. In this study, older patients in the impaired cerebrovascular reactivity group had lower mean CBF of 36.3 +/- 22.2 ml/100 g/min, compared to 39.0 +/- 20.9 ml/100 g/min (p = 0.953) in the younger group of patients, though this failed to reach significance [133]. One example of CBFV is by Bouzat et al, where older vs. younger patients (median age of 46 (IQR: 20-80 years) vs. 34 (IQR: 15-84 years), p = 0.04) had lower mean CBFV of 31 (range: 18-60 cm/s) vs. 49 (range: 31-80 cm/s) (p < 0.01), respectively [134].

5. PRx

Five large studies with patient numbers ranging from 358 – 556 were examined [13,70,126,127,137]. The data showed that older patients tended to suffer undesirable outcomes, with trends towards worse cerebrovascular reactivity metrics [13,70,126,127,137]. There were varying results regarding sex. One example, in the Adams et al study, mean PRx of patients in the Functional Survivors group was lower compared to patients in the Fatal Outcome group, with results of 0.05 +/- 0.15 a.u. vs. 0.16 +/- 0.21 a.u. ($p < 0.001$), respectively [127]. In this study, patients in the Functional Survivors group were younger with a mean age of 38 +/- 16 years vs. patients in the Fatal Outcome group who were older at 45 +/- 18 years ($p < 0.001$) [127]. It is seen that most studies on PRx do not comment directly on the association between cerebrovascular reactivity and age/biological sex.

6. RAP

Three large studies with patient numbers ranging from 56 – 358 were examined [24,80,81]. The data showed older patients tended to have undesirable outcomes [24,80,81]. Males were predominant in these studies and no major association was made between the sexes. One example, by Zeiler et al had showed no difference in mean RAP values between males and females ($p > 0.05$) and no relationship with age ($p > 0.05$) [80]. There exists a limited literature body documenting the association between RAP and age/biological sex in moderate/severe TBI, further work is needed [24,80,81].

7. CMD – Standard Analytes

Five large studies with patient numbers ranging from 46 – 165 were examined [47,138–141]. The data showed that older patients tended to have undesirable outcomes along with those who had low glucose, low pyruvate, high glycerol, high glutamate and high lactate levels, though many of the relationships failed to reach statistical significance [47,138–141]. Males were predominant in most studies but no comparisons were made between the biological sex categories and CMD analytes. One example, by Stein et al showed that older patients compared to younger patients (median age 50.5 (IQR: 38.3-62.0) vs. 32.5 (IQR: 26.3-45.0 years), respectively; $p = 0.008$) with lower glucose

(p = 0.061), lower glycerol (p = 0.998), higher glutamate (p = 0.027), higher lactate (p = 0.132) and lower pyruvate (p = 0.978) suffered poor outcomes [47]. It must be acknowledged that to date CMD use has been limited to a few specialized centers globally with limited published literature on the topic [38].

2.9.2 Conclusion

The current literature body on the association between age and sex with high-frequency continuous MMM based cerebral physiological measures in moderate/severe TBI is lacking. Most studies use coarse summary metrics, documenting association between physiology and chronological age and/or binary sex designations. Few studies to date account for biological processes of aging and sex, and their impact on MMM physiology. Future work on the impact of aging and sex on MMM physiology in TBI will require advanced signal analytic techniques, with integrated proteomic and genomic data, while accounting for biological age using epigenetics.

2.10 Association with ICP-Derived Cerebrovascular Reactivity Indices

A Scoping Review of the literature on the association between age and biological sex with ICP-derived cerebrovascular reactivity indices in moderate/severe TBI was conducted. The goal was to find studies highlighting this relationship. Refer to the full review in Batson et al [15].

To gather the necessary articles, MEDLINE, BIOSIS, EMBASE, SCOPUS, Global Health and Cochrane library were searched from inception to June 2021 using relevant search variables.

A total of 10 original studies fulfilled our inclusion criteria [4,13,77,79,126,137,142–145]. Nine of the articles documented a correlation between advanced age and worse cerebrovascular reactivity, with eight using PRx [4,13,77,79,137,142–144], three using PAx [77,137,145] and one using RAC [137] ($p < 0.05$; for all indices across all studies). Three articles displayed a correlation between biological sex and PRx, with females trending towards higher PRx values ($p < 0.05$) in the limited available literature [126,137,143]. However, no literature exists comparing PAx or RAC with biological sex. Findings showed that aging was associated with impaired cerebrovascular reactivity. We observed a trend between female sex and worse PRx values, but the literature was limited and statistical significance was borderline.

2.10.1 Indices and their Statistical Correlation to Age

As seen in Table 2.1, an association between the ICP-derived indices and age was made in nine of the ten selected studies. Eight of these studies referred to PRx, three to PAx and one to RAC. Generally, it was noted that there was a significant correlation between advanced age and PRx, PAx and RAC. Three of the most robust examples involving PRx, the three involving PAx and the one involving RAC will be highlighted. Liu et al. compared PRx to age using a multivariable binary logistic regression model showing a relationship of $R = 0.24$, $p < 0.001$ [142]. Czosnyka et al. did their comparison using correlation expressing the relationship as $R = 0.24$, $p = 0.003$ [143]. And the final example by Aries et al. involved the use of the Spearman partial rank correlation to represent the relationship between PRx and age which was found to be $R = 0.17$, $p = 0.004$ [77]. PAx was compared to age by Aries et al. using the Spearman partial rank correlation, which showed

the following relationship, $R = 0.35$, $p < 0.001$ [77]. The next study done by Zeiler et al. used Spearman Correlation Matrix to compare PAx and age, showing a relationship where $R = 0.495$, $p < 0.05$ [137]. Radolovich et al. used *T*-tests and ANOVA to analyze the relationship between these two variables resulting in $R^2 = 0.18$, $p < 0.05$ [145]. The last highlighted study done by Zeiler et al. used Spearman Correlation Matrix to compare RAC and age, showing a relationship where $R = 0.390$, $p < 0.05$ [137]. All mentioned studies displayed a weak-to-moderate positive correlation between age and worse cerebrovascular reactivity as measured through PRx, PAx or RAC.

TABLE 2.1 Findings Regarding an Association Between ICP-derived Continuous Cerebrovascular Reactivity Measures and Age

Source (authors)	Sample size (TBI patients)	Measure(s) correlated with age	Findings
Czosnyka et al. [13]	348 (only 158 used in analysis of age and PRx)	PRx	- There was a significant correlation between PRx and age ($R = 0.24$, $p = 0.003$), indicating a deterioration in cerebrovascular control with advanced age. - Multiple comparisons were not corrected for.
Liu et al. [142]	515	PRx	- There was a significant correlation between PRx and age ($R = 0.24$, $p < 0.001$), indicating a deterioration in cerebrovascular control with advanced age. - Multiple comparisons were not corrected for.
Steiner et al. [4]	114	PRx	- There was a significant correlation between PRx and age ($R = 0.358$, $p = 0.0001$), indicating a deterioration in cerebrovascular control with advanced age. - Multiple comparisons were not corrected for.
Aries et al. [77]	327	PRx and PAx	- There was a significant correlation between PRx and age ($R = 0.17$, $p = 0.004$) as well as PAx and age ($R = 0.35$, $p < 0.001$), indicating a deterioration in cerebrovascular control with advanced age. - Multiple comparisons were not corrected for.
Zeiler et al. [79]	165	PRx	- Mean PRx values above the threshold were associated with advanced age (for a threshold of 0, mean age above = 51.4 years vs. mean age below = 41.4 years, $p = 0.0007$). - Multiple comparisons were corrected for using Bonferroni's method.
Zeiler et al. [137]	358	PRx, PAx, and RAC	- Age was associated with PRx ($R = 0.235$, $p < 0.05$), PAx ($R = 0.495$, $p < 0.05$), and RAC ($R = 0.390$, $p < 0.05$). Advanced age was also associated with increased % time spent above index thresholds. - Multiple comparisons were corrected for using Bonferroni's method.
Czosnyka et al. [143]	429	PRx	- There was a significant correlation between PRx and age ($R = 0.24$, $p = 0.003$), indicating a deterioration in cerebrovascular control with advanced age. - Multiple comparisons were not corrected for.

Hiler et al. [144]	126	PRx_{24}	- Patients with disturbed pressure reactivity had a significantly greater mean age than those with intact pressure reactivity (patients with $PRx_{24} > 0$, mean age = 44; patients with $PRx_{24} < 0$, mean age = 33 years; p = 0.0004). - Multiple comparisons were not corrected for.
Radolovich et al. [145]	293	PAx	- There was a significant correlation between PAx and age (R = 0.424, $p < 0.05$), indicating a deterioration in cerebrovascular control with advanced age. - Multiple comparisons were not corrected for.

p = p-value, PAx = pulse-amplitude index, PRx = pressure reactivity index, PRx_{24} = pressure reactivity index for the first 24 hours of monitoring, R = correlation coefficient, RAC = correlation between AMP and CPP, < = less than, > = greater than, % = percentage.

2.10.2 Indices and their Statistical Correlation to Biological Sex

As seen in Table 2.2, the only ICP-based index that was found to be correlated with biological sex was PRx in three of the ten selected studies. None of the other indices were correlated with sex in any of the included papers. The 2008 study by Czosnyka et al. showed that for patients < 50 years, PRx was found to be worse in females compared to males (females 0.11 ± 0.047, males 0.044 ± 0.031; $p < 0.05$). The study by Zeiler et al. showed that sex was associated with impaired cerebrovascular reactivity for those in the category PRx > 0.25, p = 0.040 using Univariate Logistic Regression (ULR). The final study by Czosnyka et al. (2006) demonstrated that females had worse mean PRx (females 0.1 vs. males 0.04, p = 0.022). However, from these results, it can be seen that the p values barely reached the threshold for statistical significance.

TABLE 2.2 Findings Regarding an Association Between ICP-Derived Continuous Cerebrovascular Reactivity Measures and Sex

Source (authors)	Sample size (TBI patients)	Measure(s) correlated with sex	Findings
Czosnyka et al. [126]	469	PRx	- PRx was found to be worse in females than in males in the age group < 50 years (males: 0.044 ± 0.031, females: 0.11 ± 0.047, $p < 0.05$), no such change was noted in patients > 50 years. - Multiple comparisons were not corrected for.
Zeiler et al. [137]	358	PRx	- Sex was associated with impaired cerebrovascular reactivity in patients in the category PRx > 0.25, $p = 0.040$. - Multiple comparisons were corrected for using the Bonferroni's method.
Czosnyka et al. [143]	429	PRx	- PRx was found to be worse in females than in males (males: 0.04, females: 0.1, $p = 0.022$). - Multiple comparisons were not corrected for.

AUC = area under the receiver operating curve, PRx = pressure reactivity index, < = less than, > = more than.

2.10.3 Conclusion

From the few studies identified, it was noted that with advancing age, PRx (with PAx and RAC to a lesser extent) becomes increasingly impaired. Furthermore, preliminary data suggest that potentially females suffered worse cerebrovascular reactivity, compared to their male counterparts, during the acute phase of their ICU stay. However, all studies suffered from significant limitations, including small heterogeneous populations, small number of female patients and grand averaging of large epochs of cerebral physiologic data. Future multicenter studies on the impact of age and biological sex on continuously assessed cerebrovascular physiology are required, as there still exists a substantial knowledge gap.

2.11 Limitations of the Literature

The literature was searched in order to address the aims and hypotheses of this thesis outlined in Chapter 1. In this chapter, the results of the narrative overview and scoping review into age and biological sex associations were presented albeit many limitations.

First, a small number of representative studies were found to address the topics and all contained a small number of females (menopausal status unknown) which is usually the case in TBI studies. Small numbers affect the power of these studies. Another issue here is that male predominance in these studies can give the false notion that males are suffering worse outcomes.

Second, all studies mainly included gross averaging of data to obtain results which had unclear associations, borderline statistical significance or in some cases failed to reach statistical significance and had no correction for multiple comparisons. Insult burden was not looked at in any great detail to ascertain the relationship between different thresholds of the indices and how various patients are affected based on their age group or sex designation.

Next, patient populations from these studies were very heterogeneous with regards to demographics, injury pattern, duration of monitoring, comorbidities, variance in received therapies between patients and centers, etc., which may create confounding bias.

Fourth, the methods of quantifying age and biological sex in the selected studies could be considered crude and may not be sufficient in the assessment of their impact on cerebrovascular reactivity. Biological age as estimated through emerging epigenetic techniques may provide a quantified way in the future to determine age [146,147]. Linking such data with high-frequency physiology in TBI patients may provide a superior assessment of the link between age and cerebrovascular reactivity. Biological sex as measured through a binary designation (i.e., male vs. female) may be too crude to properly assess the link between sex and cerebrovascular reactivity [116,117,126,148]. Also, there appears to be a discrepancy and intersectional nature between sex and age, regarding the menopausal status [116,117,126,148].

Finally, most studies were conducted involving the same European hospital/cohort of patients. This poses a potential issue as this population is mainly Caucasian. Other potential issues involve the geographic location, genetics and biological differences of the people which will vary to other populations (e.g., immigrants, Africans, etc.). Things to take into consideration are that treatment practices may vary in other parts of the world, for example, Asia, Africa, and South America do not follow BTF guidelines. Also, genetic differences amongst persons of different races could play a part in cerebrovascular response and host response to injury and advancing age [137].

From these significant limitations and the importance of understanding age and sex relationships with cerebrovascular reactivity in TBI it is deemed necessary for research into these to continue in order to advance neurotrauma care. Therefore, the original works in Chapters 3 and 4 were conducted to address the hypotheses in Chapter 1 and overcome some of the limitations discussed here.

Chapter 3: Impact of Age and Biological Sex on Cerebrovascular Reactivity in Adult Moderate/Severe TBI: An Exploratory Analysis

*For a full review of this study please refer to the following publication:

Batson C, Froese L, Gomez A, et al. Impact of Age and Biological Sex on Cerebrovascular Reactivity in Adult Moderate/Severe Traumatic Brain Injury: An Exploratory Analysis. Neurotrauma Reports 2021;2(1):488–501; doi: 10.1089/neur.2021.0039.

3.1 Introduction

It is now well understood that TBI effects on cerebrovascular reactivity accounts for much cost, morbidity and mortality as a result of the primary and secondary injury processes that ensue. Direct continuous bedside assessment of CA is complex. Recent advances in biomedical signal processing of data from MMM in moderate/severe TBI have facilitated the development of surrogate measures, some of which are referred to as cerebrovascular reactivity metrics. It must be acknowledged, however, that these derived metrics encompass additional cerebral physiological information beyond that of pure cerebrovascular reactivity.

PRx is the exemplar and is a continuous derived metric of cerebrovascular reactivity derived from the moving Pearson correlation coefficient between slow waves of ICP and MAP [70]. Impaired cerebrovascular reactivity, as measured through PRx, in moderate/severe TBI has emerged as one of the most prevalent forms of impaired cerebral physiology during the acute phase after injury, leading to ongoing secondary insults [1,8]. Further, current guideline-based therapeutic strategies have failed to impact the incidence and duration of impaired cerebrovascular reactivity after moderate/severe TBI [71,149–152]. As such, more work needs to be done to truly understand the drivers of impaired cerebrovascular reactivity and potential pathways for therapeutic intervention [40].

Central to our current knowledge gap relating to cerebrovascular reactivity in moderate/severe TBI and its drivers are the impact of age and biological sex. These are critical factors regarding overall outcome of patients with TBI. Age alone is one of the major drivers of prognosis and is a crucial component of existing standard prognostic models in moderate/severe TBI. Evidence of the impact

of age on cerebrovascular reactivity is limited, but it does suggest worse cerebrovascular reactivity in older patients after a TBI [13,126]. The older we get, the more our arterial functions deteriorate and the literature has shown that older persons tend to have the worst outcomes [13,126].

And too, biological sex is a known modulator of secondary injury responses, specifically regarding the presence of female sex hormones and their downstream effects on neural injury mitigation and repair. This is despite males dominating the TBI cohorts in terms of overall incidence. Females in their young years benefit from estrogen's protective vasodilatory and anti-inflammatory effects on the neurovasculature but lose this once menopausal [116,117,148]. Finally, an interplay between age and sex can be possible as seen in older females with decreased estrogen and more deranged cerebrovascular reactivity [116].

Our understanding of the role that age and sex play on continuous MMM cerebral physiology, including cerebrovascular reactivity metrics, however, is still in its infancy with very few focused studies to date [13,126]. Further, earlier work has been centered on using grand averages of data instead of insult burden metrics. Insult burden metrics are emerging as superior assessments for cerebral physiological dysfunction, where the amount of time spent above known physiological thresholds (example: BTF-based and literature-defined critical threshold for ICP of 20 mm Hg) display stronger associations with global outcomes, compared with grand averaged values over large epochs of recorded physiology [73,153,154]. Consequently, having a clear understanding of insult burden is crucial if we are to transition toward personalized precision medicine in moderate/severe TBI care.

From the review of literature in Chapter 2, it is seen that a few large studies were found regarding impact of age and biological sex on continuously assessed cerebrovascular reactivity post moderate/severe TBI. These studies examined overall grand averages of data collected over extended periods and lacked a more detailed analysis of age subgroups. Due to the limited available literature, this study aimed to explore the association between various age groups and biological sex and how these separately impact continuously measured cerebrovascular reactivity in adult patients with moderate/severe TBI during the acute phase of their ICU stay.

The working hypothesis is that CA is an age-related process that begins in its immaturity during youth, matures in function and then deteriorates with age. As such, it should naturally follow that such age-related variations would be seen in patients with moderate/severe TBI, where continuous cerebrovascular reactivity measures can be derived based on available invasive intracranial monitoring. A further hypothesis here is that younger females would have a slight degree of improved cerebrovascular reactivity versus younger males that would disappear after menopause in moderate/severe TBI.

3.2 Methods

3.2.1 Study Type

This study was a local retrospective evaluation of a prospectively maintained approved database of moderate to severe TBI patients. This database contains demographic, injury, treatment, outcome information and high-frequency physiological signals from various MMM devices. Local research ethics board approval at the University of Manitoba was approved for all aspects of this database (H2017:181 and H2017:188). Similarly, ethics approval was obtained for retrospective access to this database for this project (H2020:118).

3.2.2 Patient Population

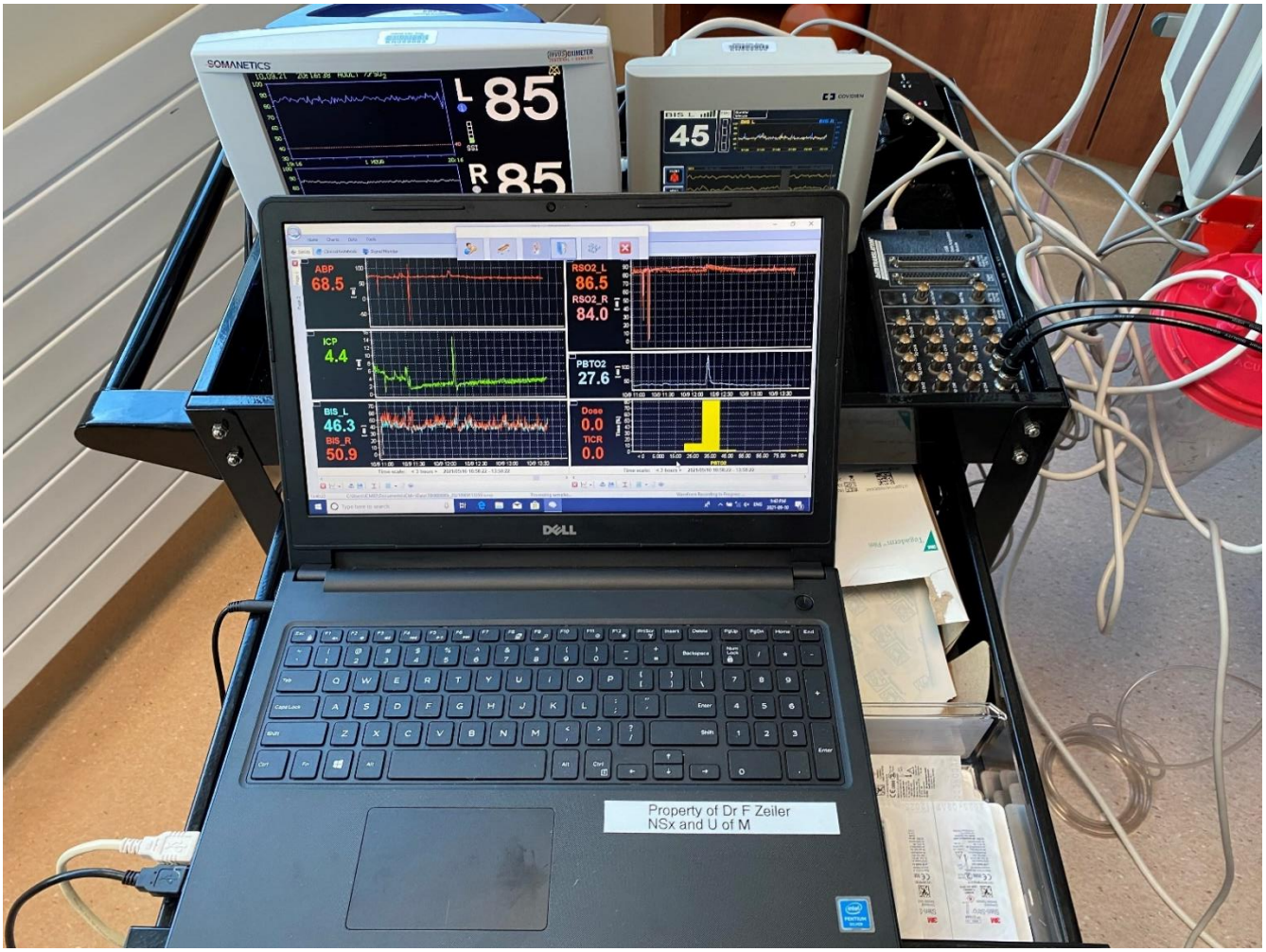
Patient data was entered into the database from January 2019 to December 2020. Inclusion criteria for this study were patients 16 years and older who suffered moderate to severe TBI with invasive ICP and ABP monitoring, who were admitted to Health Sciences Centre Winnipeg – Surgical Intensive Care Unit (SICU). Patients who were younger than 16 years, those who suffered mild TBI and those without invasive ICP monitoring were excluded from this study.

3.2.3 Physiologic Data Acquisition

In keeping with standard BTF guidelines, critically ill moderate/severe TBI patients have ABP and ICP monitoring placed as part of the standard of care locally. Monitoring of ABP was done via

radial arterial lines (zeroed at the level of the tragus) and monitoring of ICP was done via intraparenchymal strain gauge monitors (Codman ICP Microsensor; Codman & Shurtleff Inc., Raynham, MA). All physiology data was recorded in digital high-frequency time series (i.e., 100 Hertz) using analogue-to-digital signal converters (ADC) (Data Translations, DT9804 or DT9826), where applicable. This data was linked and stored in time series using Intensive Care Monitoring "plus" (ICM+) software (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk). An example of the multi-device setup at the patients' bedside can be seen in Figure 3.1 below.

Figure 3.1 Multi-Device Setup at The Patient Bedside in the ICU

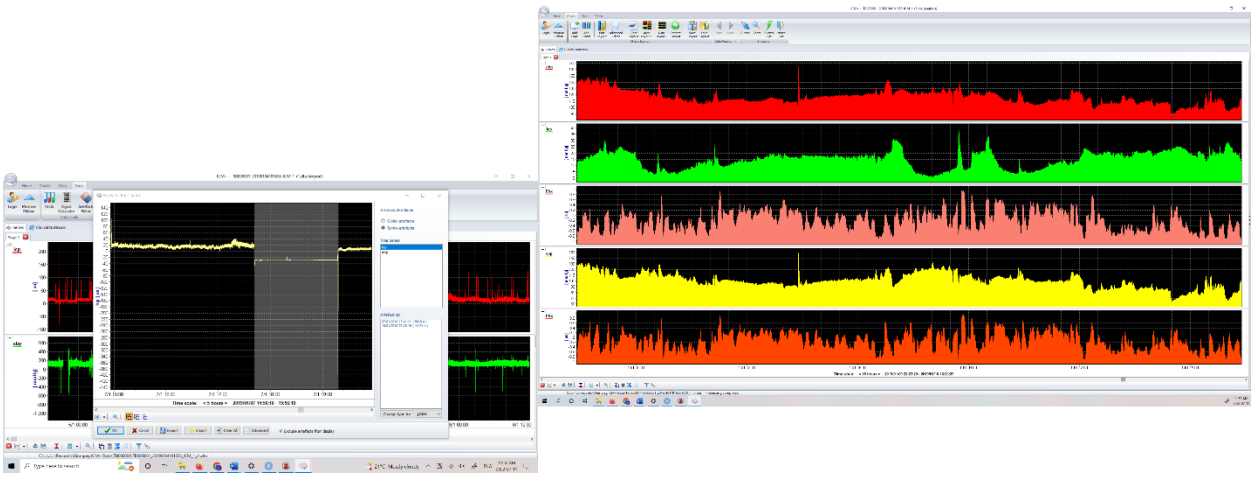


Right: Data going into ADC, back right: BIS monitor, back left: NIRS monitor, front: laptop with multiple devices simultaneously recorded on ICM+ software. ADC = analogue-to-digital converter, BIS = bispectral index, ICM+ = intensive care monitoring "plus", NIRS = near infrared spectroscopy.

3.2.4 Physiologic Signal Processing

The archived high-frequency physiologic patient data had to be processed before statistical analysis could be conducted. First, was the process of artifact clearing which was done manually using ICM+ software. An example of ICM+ signal recording and the tedious artifact clearing process can be seen in Figure 3.2 below. CPP was calculated as MAP minus ICP. Next, AMP was derived using wavelet analysis of the ICP pulse waveform [25,77]. Subsequently, the full waveform data for all physiology was decimated using a non-overlapping moving average filter of 10-sec duration that facilitated focusing on the slow-wave frequency range associated with CA. This facilitates focusing on the slow-wave frequency range associated with CA interference with ventilation induced changes [155,156]. This 10-sec by 10-sec data were then used to derive continuously updated cerebrovascular reactivity and compensatory reserve measures. As an example, PRx is calculated as the moving Pearson correlation coefficient between 30 consecutive 10-sec mean paired values of ICP and MAP. An identical process is used to calculate the other indices. The following cerebrovascular reactivity indices were derived: PRx – correlation between slow waves of MAP and ICP [157], pulse amplitude index (PAx) – correlation between slow waves of AMP and MAP [25], and RAC (correlation [R] between slow waves of AMP [A] and CPP [C] [78]. Finally, the compensatory reserve index RAP (correlation between slow waves of AMP and ICP) [24], was also derived to facilitate surrogate evaluation of brain compliance. All recorded and derived signals were output in minute averages into comma-separated values (CSV) datasets for further analysis. Such minute by minute data update frequency for further analytics, using high-frequency cerebral physiological signals in moderate/severe TBI [158].

Figure 3.2 ICM+ Signal Recording and Artifact Clearing



Right: various signals recorded by ICM+ software, left: isolated signal showing a highlighted area of artifact to be cleared. ICM+ = intensive care monitoring software "plus".

3.2.5 Physiologic Data Post-Processing

Two main datasheets were created from the data, namely, the first (1st) 72 hours of recording and the entire recording period. The 1st 72 hours is a crucial period where most acute physiology changes tend to occur and where aggressive treatment occurs post-TBI [73,159,160]. In addition, this is the window where autoregulation is impaired and blood flow is affected by various external and internal mechanisms causing the cerebrovasculature to be vulnerable to ischemia [161].

Therefore, a comparison was done to see if the "acute" period and entire recording period would yield different results. Such analytic strategies, utilizing the 1st 72 hours of data, have been employed in various other studies pertaining to cerebral physiological dysfunction in moderate/severe TBI [7,72,79,160,162]. Similar strategies were used in this study to evaluate the two datasheets; the acute physiology versus the entire recording period. This was done along with deriving insult burden metrics for key physiological measures in both datasheets so as to avoid the pitfalls of previous literature regarding the use of grand averages of cerebrovascular reactivity metrics. Also, this helps in cases where withdrawal of treatment due to refractory hypertension occurs with monitoring devices still in situ. Such insult burden metrics were defined as the percent time spent above literature-defined thresholds for ICP, CPP, PRx, PAx and RAC. These derived variables included:

1. % time with ICP above 20 and 22 mm Hg. These are BTF-based ICP treatment thresholds [21].
2. % time with CPP below 60 mm Hg and above 70 mm Hg. These are BTF-based CPP thresholds [70,153].
3. % time with PRx above 0, +0.25 and +0.35. These are literature-defined critical thresholds associated with outcomes in TBI [70,72].
4. % time with PAx above 0 and +0.25. These are literature-defined critical thresholds associated with outcomes in TBI [72].
5. % time with RAC above -0.10 and -0.05. These are literature-defined critical thresholds associated with outcomes in TBI [72].

3.2.6 Statistical Analysis

Statistical analysis was performed using the R statistical software (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Descriptive statistics (mean/standard deviation [SD] and median/IQR) was used to summarize patient demographics and physiology variables for both datasheets. Boxplots were used to visualize the 1st 7 days of recorded data. Shapiro-Wilks test revealed a non-parametric nature of the physiology from the two data sets upon testing for normality. Alpha for all statistical testing described was set at 0.001 for significance after correction for multiple comparisons was done using the Bonferroni method.

To test for significance of the relationship between biological sex (males and females) and the continuously measured metrics (ICP, MAP, CPP, PRx, PAx, RAC and RAP) Mann-Whitney U testing was conducted. To test for significance of the relationship between age and the continuously measured metrics three methods were used, namely, linear regression, age dichotomization and age trichotomization. To begin, using age as a continuous variable, it was compared with the physiology variables using both Pearson and Kendall Tau correlation, with linear regression modelling. Data visualization was aided using scatterplots, linear regression plotting (95% confidence interval [CI]). Next, the patient cohort was split using an age dichotomization (i.e., age < 60 vs. age ≥ 60) and age trichotomization (i.e., age < 40, age 40 – 60

and age > 60 years) scheme. The trichotomization scheme for age was to assess the hypothesis of age-related maturation of cerebrovascular function in this cohort. Age 40 was used as a cut-off because it was noted in the literature that there is potentially more unfavorable outcomes across age groups centered on 40 years with persons < 40 years likely to experience good recovery unlike persons > 40 years [163–165]. Age 60 is a common cut-off for outcomes in various neuropathological and critical care states, with patients older than 60 years suffering unfavorable long-term outcomes [103,104,153,166]. Significance of the age dichotomization and age trichotomization physiology comparisons were assessed using Mann-Whitney U and Kruskal-Wallis testing, respectively. Age dichotomization revealed no statistically significant relationships with cerebral physiology metrics. Therefore, categorical age analysis reporting in the results will focus mainly on the trichotomization categorical analysis.

3.3 Results

3.3.1 Patient Demographics

Patient data was entered into the database from January 2019 to December 2020. A total of 49 patients were identified as eligible for the study, with 42 males and 7 females having a median age of 42 (IQR: 24.0-54.0). All patients sustained moderate (Glasgow Coma Scale [GCS] 9-12) to severe TBI (GCS < 9) requiring ICU admission, with a median GCS of 7 (IQR: 5.0-9.0). General patient demographics, summarized in means/medians, can be found in Table 3.1. Equally, recorded cerebral physiologic variables, summarized in medians and IQRs, can be found in Table 3.2 for both the 1st 72 hours of physiology (the acute phase) and the entire recording period. The median duration of recorded physiology was 2.67 days (IQR: 1.49-4.96). All physiology variables were non-parametric.

Table 3.1 Patients Demographic Information

Demographic Information				
	Mean	**SD**	**Median**	**IQR**
Age (years)	41.6	17.0	42.0	24.0 – 54.0
Best Admission GCS	7.2	3.0	7.0	5.0 – 9.0
Best Admission GCS – Motor	4.0	1.7	5.0	3.0 – 5.0

	Unilateral Reactive	Unilateral Unreactive	Bilateral Reactive	Bilateral Unreactive
Pupils	0	10	31	8
	Males		**Females**	
Sex	42		7	
Admission Marshall CT Grade:	Males		Females	
II	2		-	
III	11		3	
IV	9		1	
V	15		3	
VI	5		-	
ROTTERDAM CT Grade:	Males		Females	
I	1		-	
II	3		-	
III	5		1	
IV	12		2	
V	11		2	
VI	10		2	
	Yes		**No**	
Pre – Hospital Hypoxia	23		26	
Admission CT – tSAH	47		2	
Admission CT – EDH	5		44	

CT = computed tomography, EDH = epidural hematoma, GCS = Glasgow Coma Scale, IQR = interquartile range, SD = standard deviation, tSAH = traumatic subarachnoid hemorrhage.

Table 3.2 Cerebral Physiology for the 1st 72 hours and Entire Recording Period

Physiologic Variables	**1st 72 Hours of Data**		**Entire Recording Period**	
	Median	**IQR**	**Median**	**IQR**
ICP (mm Hg)	10.7	7.3 – 13.3	10.9	7.2 – 13.6
% Time ICP > 20 mm Hg	2.3	0.9 – 7.3	2.8	0.9 – 10.5
% Time ICP > 22 mm Hg	1.7	0.3 – 3.8	1.7	0.3 – 5.4
MAP (mm Hg)	81.1	77.5 – 88.3	81.7	77.5 – 86.8
CPP (mm Hg)	71.6	64.4 – 76.4	70.9	64.4 – 74.6
% Time CPP > 70 mm Hg	57.4	40.8 – 73.6	56.4	42.2 – 73.4
% Time CPP < 60 mm Hg	8.6	2.9 – 19.1	10.8	3.2 – 21.2
PRx (a.u.)	0.143	0.057 – 0.343	0.147	0.030 – 0.329
% Time PRx > 0	67.0	51.8 – 82.9	68.4	51.0 – 83.2
% Time PRx > 0.25	41.1	28.7 – 64.3	41.2	24.9 – 61.8
% Time PRx > 0.35	31.2	18.6 – 52.4	31.2	17.4 – 50.4
PAx (a.u.)	0.001	-0.077 – 0.243	0.018	-0.073 – 0.221
% Time PAx > 0	50.6	38.1 – 76.7	51.6	37.6 – 73.8
% Time PAx > 0.25	24.1	16.2 – 53.0	24.8	16.2 – 51.0
RAC (a.u.)	-0.161	-0.309 – 0.020	-0.191	(-0.317) – (-0.019)
% Time RAC > -0.10	44.3	27.5 – 67.4	40.5	26.7 – 63.3
% Time RAC > -0.05	38.6	24.2 – 63.3	36.3	23.0 – 57.7
RAP (a.u.)	0.595	0.411 – 0.740	0.595	0.411 – 0.746

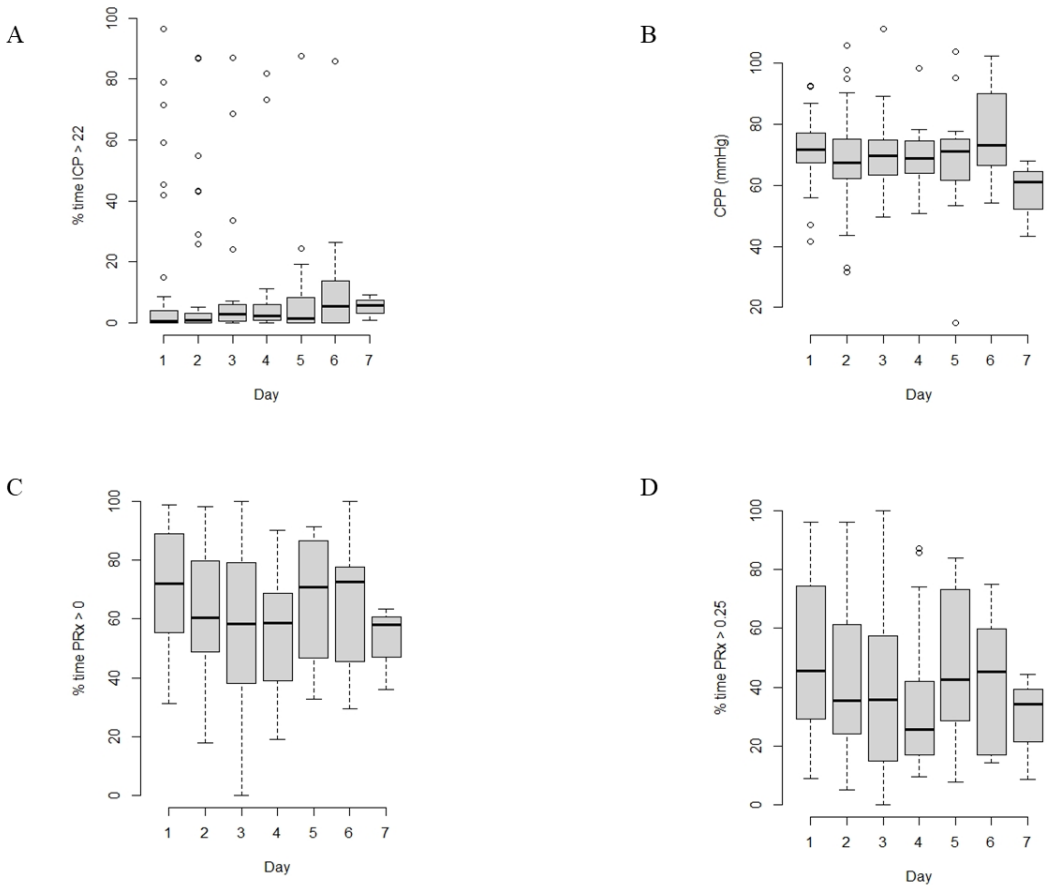
% Time RAP > 0.4	76.5	57.6 – 86.3	76.5	57.4 – 86.3

a.u. = arbitrary units, AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage.

3.3.2 Daily Insult Burden of Impaired Cerebrovascular Reactivity

To aid with understanding the degree of impaired cerebrovascular reactivity seen in this cohort, the % time of index impairment over the 1st 7 days of their ICU stay was analyzed. Generally, during the 1st 7 days, ICP and CPP were well controlled, with limited time spent with ICP above 22 mm Hg and CPP well maintained within the guideline suggested range of 60 to 70 mm Hg. Nevertheless, most patients spent the 1st week of their ICU stay with a daily PRx value above 0 and +0.25 for the majority of each day. Kruskal-Wallis testing, assessing for differences between days for cerebral physiology, failed to demonstrate a significant difference ($p > 0.05$ for all), confirming that the median daily values remained relatively constant. Figure 3.1 displays box-plots for the first 7 days, highlighting % time with ICP > 22 mm Hg (Figure 1A), mean CPP (Figure 1B), % time with PRx > 0 (Figure 1C) and % time with PRx > +0.25 (Figure 1D).

Figure 3.3 Boxplots of Daily Recordings of the first 7 days



Panel A - % time intracranial pressure (ICP) > 22 mm Hg, Panel B - mean cerebral perfusion pressure (CPP), Panel C - % time pressure reactivity index (PRx) > 0 and Panel D - % time PRx > +0.25. Using a Kruskal-Wallis test to compare the different days, we found no statistically significant difference between days for any of the physiology displayed. The number of patient data for each day: day 1 has 49, day 2 has 42, day 3 has 32, day 4 has 21, day 5 has 18, day 6 has 9 and day 7 has 4.

3.3.3 Sex Analysis

Difference in physiologic responses based on biological sex, was assessed by comparing male and female patients. Data presented in Table 3.3 displays medians/IQRs and the Mann-Whitney-U Test p-values for the comparison of the median physiologic variables between males and females for the 1st 72 hours of data. Appendix A shows a similar table for the entire recording period, with similar findings displayed. Within the 1st 72 hours data set, a statistically significant difference was found for mean ICP, % time ICP > 20 mm Hg, % time ICP > 22 mm Hg, mean CPP and %

time CPP > 70 mm Hg, where females showed higher ICP (p = 0.007), % time ICP > 20 mm Hg (p = 0.012), % time ICP > 22 mm Hg (p = 0.010) and lower mean CPP (p = 0.016) and % time with CPP > 70 mm Hg (p = 0.007). Of note, all relationships were statistically insignificant when adjusting for multiple comparisons. All other variables yielded insignificant statistical findings in both datasheets. This includes cerebrovascular reactivity indices, where none of PRx, PAx or RAC demonstrated a significant difference based on biological sex.

Table 3.3 Cerebral Physiology Based on Biological Sex: Medians/IQRs and Mann-Whitney-U Testing of the 1st 72 Hours of Recording

Physiological Variable	Males (n = 42)		Females (n = 7)		Mann-Whitney U-Test p-value
	Median	IQR	Median	IQR	
ICP (mm Hg)	9.1	6.9 – 12.7	17.7	12.3 – 25.3	**0.007**
% Time ICP > 20 mm Hg	2.3	0.4 – 6.1	38.5	6.4 – 84.3	**0.012**
% Time ICP > 22 mm Hg	1.5	0.2 – 2.7	31.8	3.6 – 78.2	**0.010**
MAP (mm Hg)	81.0	77.5 – 89.4	81.9	77.5 – 85.4	0.834
CPP (mm Hg)	71.7	67.5 – 77.0	62.3	57.5 – 66.0	**0.016**
% Time CPP > 70 mm Hg	57.9	44.5 – 74.5	29.9	20.6 – 39.6	**0.007**
% Time CPP < 60 mm Hg	7.2	2.6 – 17.0	18.6	12.9 – 50.9	0.055
PRx (a.u.)	0.143	0.058 – 0.278	0.073	-0.014 – 0.664	1.000
% Time PRx > 0	68.3	52.4 – 82.8	58.2	45.4 – 86.0	0.710
% Time PRx > 0.25	41.4	29.1 – 57.3	35.9	23.3 – 82.8	0.977
% Time PRx > 0.35	31.9	18.8 – 45.1	25.9	16.6 – 80.2	0.932
PAx (a.u.)	0.005	-0.065 – 0.220	-0.008	-0.078 – 0.495	0.753
% Time PAx > 0	50.7	38.1 – 75.7	47.9	41.4 – 82.9	0.932
% Time PAx > 0.25	24.4	16.5 – 51.0	23.8	17.9 – 75.5	0.627
RAC (a.u.)	-0.160	(-0.287) – (-0.017)	-0.192	-0.420 – 0.309	0.932
% Time RAC > -0.10	45.3	29.5 – 62.0	38.5	21.2 – 78.5	0.886
% Time RAC > -0.05	38.8	26.5 – 55.8	33.9	19.4 – 76.1	0.954
RAP (a.u.)	0.583	0.406 – 0.717	0.658	0.615 – 0.801	0.084
% Time RAP > 0.4	75.1	57.5 – 83.3	85.1	79.2 – 94.1	0.069
Age (years)	44.5	27.5 – 54.8	24.0	23.0 – 34.0	0.092

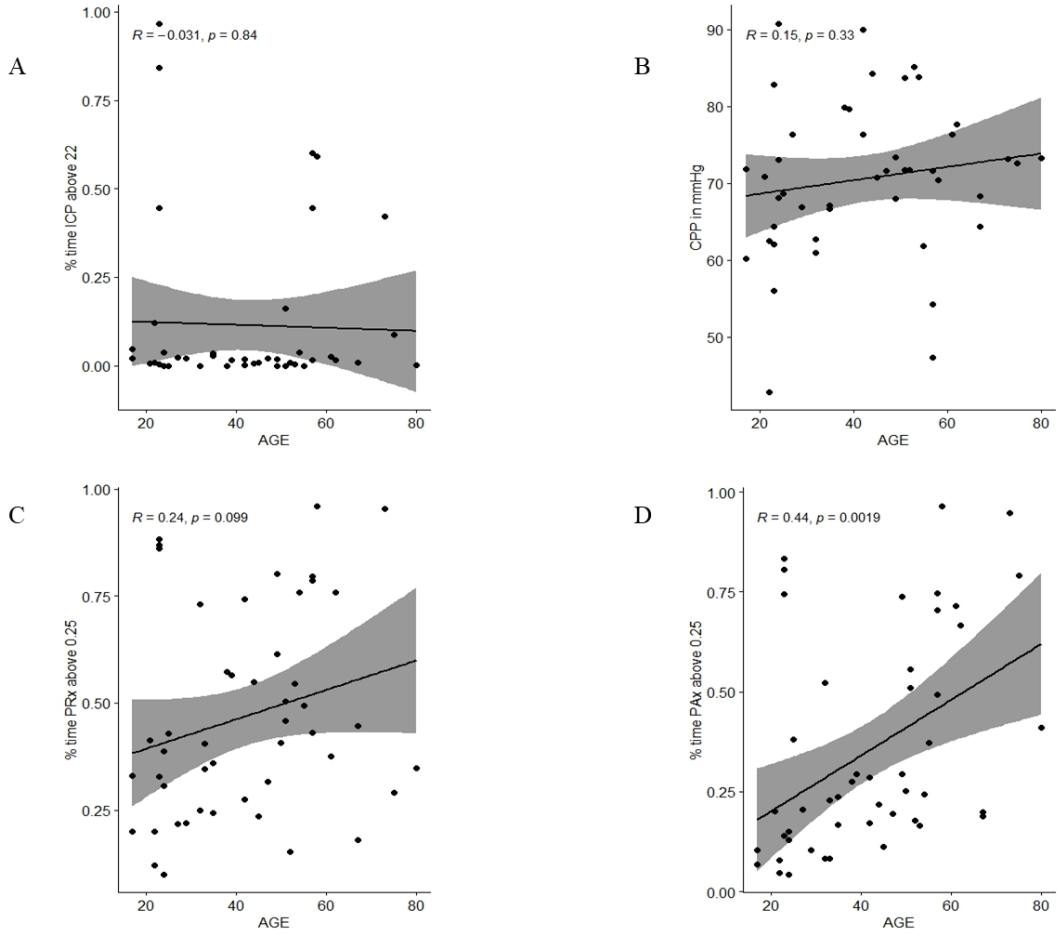
Best Admission GCS	7.0	5.3 – 9.0	7.0	3.0 – 7.5	0.267
Best Admission GCS – Motor	5.0	3.0 – 5.0	5.0	1.0 – 5.0	0.572
Rotterdam CT Grade	4.5	4.0 – 5.0	5.0	4.0 – 5.5	0.638

a.u. = arbitrary units, AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, CT = computed tomography, GCS = Glasgow Coma Scale, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values are those reaching statistical significance of 0.05 on Mann-Whitney-U Testing.

3.3.4 Age as a Continuous Variable – Regression Analysis

Next, the relationship between cerebrovascular reactivity and age were evaluated using linear regression techniques. Findings here suggested that PRx variables demonstrated no relationship with age in our cohort while AMP-derived metrics, such as PAx and RAC demonstrated a statistically significant linear relationship with age. As an example, Figure 3.2 displays the scatterplots and linear regressions presented with 95% CI for the 1st 72 hours of recording, with similar findings for the entire recording period displayed in Appendix B. Figure 3.2 displays age relationship to % time ICP > 22 mm Hg, mean CPP, % time PRx > 0.25 and % time PAx > 0.25. Figures 2A, B and C show no statistically significant change in the physiology variables with increasing age, with relatively unchanged ICP, CPP or PRx across the age range using Pearson correlation. By Kendall's tau correlation, Appendix B, Figure C shows a statistically positive linear relationship between % time PRx > 0.25 and age (R = 0.2, p = 0.04). Figure 2D shows a statistically positive linear relationship between % time with PAx > +0.25 and age (Pearson correlation = 0.4; p = 0.002, Kendall's tau correlation = 0.4; p = 0.0002).

Figure 3.4 Scatterplots and Linear Regression (1st 72 Hours of Recording)



Panel A - % Time with intracranial pressure (ICP) >22 mm Hg vs. Age; Panel B – Mean cerebral perfusion pressure (CPP) vs. Age; Panel C - % Time with pressure reactivity index (PRx) >+0.25 vs. Age; Panel D - % Time with pulse amplitude index (PAx) >+0.25 vs. Age. R = Pearson correlation coefficient. P-values recorded are for the Pearson correlation coefficient.

3.3.5 Age Categorical Analysis

The interesting results of the linear regression analysis with respect to PRx, PAx and RAC, sparked the decision to explore the relationship between age and cerebrovascular reactivity through the categorical organization of age. To assess the relationship between age categories and cerebral physiologic response, a dichotomization and trichotomization of age analysis were conducted, as detailed in the methods section. Using dichotomized age categories (Age < 60 and Age ≥ 60), there was no reproducibly significant relationship between any of the cerebral physiologic variables and age categories apparent in both data sheets. Table 4 provides the trichotomization analysis for the

1st 72 hours of recording, highlighting medians/IQRs across each age group and the Kruskal-Wallis p-values. Data for the trichotomization analysis for the entire recording period can be found in Appendix C, with similar findings for both the 1st 72 hours and entire recording periods.

When age was trichotomized (i.e., Age < 40, Age 40 – 60, and Age > 60), both data sheets demonstrated a statistically significant worsening of cerebrovascular reactivity, as assessed by PAx and RAC, with increasing age category, as assessed through Kruskal-Wallis testing. It was the case for mean PAx ($p = 0.042$), % time PAx > 0 ($p = 0.015$), % time PAx > +0.25 ($p = 0.013$), mean RAC ($p = 0.029$) and % time RAC > -0.10 ($p = 0.047$), in the 1st 72 hours recording sheet. When multiple comparisons were corrected for ($p < 0.001$), however, no values were statistically significant.

Table 3.4 Cerebral Physiology Association with Trichotomized Age (Age < 40, Age 40 – 60, Age > 60): Medians/IQRs and Kruskal-Wallis Testing of the 1st 72 Hours of Recording

Physiological Variable	Age < 40 years (n = 24)		Age 40 – 60 years (n = 18)		Age > 60 years (n = 7)		Kruskal-Wallis Test p-value
	Median	IQR	Median	IQR	Median	IQR	
ICP (mm Hg)	11.9	8.8 – 13.3	9.8	7.1 – 12.6	7.9	6.7 – 12.1	0.487
% Time ICP > 20 mm Hg	5.3	0.0 – 7.3	1.9	0.9 – 4.8	2.3	1.8 – 8.5	0.824
% Time ICP > 22 mm Hg	2.1	0.0 – 3.7	1.5	0.4 – 3.8	1.6	0.9 – 5.6	0.915
MAP (mm Hg)	81.4	76.1 – 87.1	83.0	79.2 – 90.5	78.3	76.9 – 83.5	0.411
CPP (mm Hg)	67.1	62.6 – 73.1	71.7	70.4 – 83.8	73.2	70.5 – 74.8	0.196
% Time CPP > 70 mm Hg	42.2	33.8 – 64.6	65.2	52.7 – 74.7	71.7	54.4 – 77.0	0.102
% Time CPP < 60 mm Hg	11.8	7.1 – 19.1	6.0	2.3 – 13.7	64.6	2.6 – 19.8	0.328
PRx (a.u.)	0.107	0.042 – 0.215	0.241	0.127 – 0.424	0.135	0.075 – 0.301	0.264
% Time PRx > 0	58.2	49.4 – 78.7	74.3	63.9 – 82.6	63.8	57.0 – 80.6	0.283
% Time PRx > 0.25	34.5	23.1 – 49.7	52.5	41.4 – 75.4	37.6	31.9 – 60.3	0.122
% Time PRx > 0.35	25.9	16.1 – 36.3	39.0	32.4 – 65.6	23.8	20.4 – 52.5	0.128
PAx (a.u.)	-0.040	-0.116 -0.052	0.051	-0.040 – 0.265	0.370	0.058 – 0.458	**0.042**
% Time PAx > 0	44.3	33.3 – 57.8	53.5	44.8 – 78.1	87.0	57.1 – 94.1	**0.015**
% Time PAx > 0.25	16.8	9.4 – 28.5	29.0	20.0 – 54.5	66.7	30.5 – 75.3	**0.013**

RAC (a.u.)	-0.264	(-0.406) – (-0.103)	-0.157	-0.241 – 0.123	-0.017	-0.063 – 0.388	**0.029**
% Time RAC > -0.10	35.3	15.3 – 50.1	45.3	33.2 – 72.9	57.4	52.4 – 88.9	**0.047**
% Time RAC > -0.05	32.8	14.0 – 43.3	39.4	28.4 – 69.1	53.4	45.4 – 87.0	0.054
RAP (a.u.)	0.525	0.390 -0.676	0.646	0.517 – 0.745	56.4	0.342 – 0.736	0.428
% Time RAP > 0.4	70.2	57.0 – 85.4	79.2	66.7 – 86.8	75.3	41.7 – 87.4	0.583
Best Admission GCS	7.0	5.0 – 8.5	8.0	4.5 – 8.0	8.0	6.0 – 11.0	0.550
Best Admission GCS – Motor	5.0	3.0 – 5.0	5.0	2.5 – 5.0	5.0	2.5 – 5.5	0.921
Rotterdam CT Grade	5.0	4.0 – 6.0	4.0	3.3 – 5.0	5.0	4.0 – 5.0	0.652

a.u. = arbitrary units, AMP = pulse amplitude ICP, CPP = cerebral perfusion pressure, CT = computed tomography, GCS = Glasgow Coma Scale, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values indicate those reaching statistical significance of 0.05 on Kruskal-Wallis Testing. There were no statistically significant p-values after Bonferroni correction for multiple comparisons (alpha 0.001).

3.4 Discussion

Age and sex analysis in this cohort of patients revealed some interesting findings. Overall, physiology results shown in table 3.2 were fairly similar for both data sheets indicating that patients maintained relatively stable levels without major fluctuations during their ICU stay. In addition, from the boxplots in Figure 3.1, ICP and CPP acute management were satisfactory and in accordance with the BTF guideline-based ranges [153]. Lastly, the data demonstrated that PRx insult burden was substantial over the course of the first few days of ICU stay and remained relatively independent to ongoing active treatment, which validates previous findings from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) study [76,149]. These findings were indeed promising but there were some additional findings of interest worth highlighting.

To begin, biological sex-based analysis failed to demonstrate statistically significant differences between males and females with respect to impaired cerebrovascular reactivity, which was demonstrated through analysis of PRx, PAx and RAC-based measures. Nevertheless, results from biological sex analysis did show statistical significance where females had higher mean ICP, % time ICP > 20 mm Hg, % time ICP > 22 mm Hg and lower mean CPP and % time CPP > 70 mm

Hg. The previous was noted despite females displaying similar admission CT injury burden scores as males. These findings make sense, as per the literature, it is known that in the face of high ICPs, we tend to see low CPPs (CPP = MAP – ICP) and it stands out as significant in this patient population [76,117]. Thus, the high ICP and low CPP values in our cohort were seen among the females who are younger instead of the older male patients, which is similar with a single study on sex-based analysis of high-frequency cerebral physiology in moderate/severe TBI [126]. Our results differ, however, because cerebrovascular reactivity metrics do not appear to be different between males versus females, as seen in this previous work [126]. The findings here do deserve more detailed exploration in larger multicenter cohorts with high-frequency cerebral physiological data because this study was based on a small population of seven females. Consequently, no absolute conclusions can be made from this analysis with regards to the relationship between biological sex and cerebrovascular reactivity. Therefore, this area in the literature remains unclear [105] and is the focus of ongoing large multicenter collaboratives [167,168].

Second, this analysis of the impact of age on cerebrovascular reactivity has led to important insights into differences between ICP-derived index measures. In support of the hypothesis of a maturation-degenerative process of the cerebral vessels, it is seen that AMP-derived cerebrovascular reactivity metrics PAx and RAC worsen with increasing age [13,72,169]. Regression analysis and trichotomization of age analysis, revealed a statistically significant relationship whereby cerebrovascular reactivity worsened with increasing age, while PRx and acute management indices did not reflect this [77]. This is in contrast to previous work in the area, demonstrating advanced age leading to worse PRx [126].

Although it must be acknowledged that ICP/CPP derangements in the historical cohort of these previous publications were much more prevalent than in this cohort [126], potentially driving the PRx derangements seen [76,154,170,171]. The poor performance of the "standard" PRx metric in detecting impaired cerebrovascular reactivity in this cohort raises important questions regarding optimal cerebrovascular reactivity indices for subpopulations of TBI patients. PRx performed poorly in detecting deranged cerebrovascular reactivity in older persons, with none of the PRx metrics displaying statistically significant relationships with age, while PAx and RAC displayed this relationship. It can likely be attributed to brain volume loss at advanced ages, as brain atrophy does

not allow for adequate swelling and generation of critical ICPs, which is a known driver of autoregulation failure in moderate/severe TBI [76,154,170,171]. Further, it is supported by our cohort having aggressive ICP/CPP-directed therapy, as mentioned above. Therefore, other metrics like PAx might be better at detecting impaired cerebrovascular reactivity in these situations, as suggested by the limited previous literature on PAx [25,77,78], and now further supported for PAx and RAC based on this study's findings. This is an important and novel finding, because it suggests that continuous bedside cerebrovascular reactivity monitoring in TBI may necessitate the use of specific indices for certain subpopulations. The findings within this study do remain preliminary and exploratory, requiring validation in larger multi-center cohorts.

All in all, some quite useful preliminary information has emerged from our analysis thus far surrounding age and sex effects. With more research on this topic and index-specific subgroup utility, more valuable information will become available to aid with improving neurotrauma management and facilitate the ongoing transition towards individualized precision medicine in moderate/severe TBI. Future work in this area will necessitate larger multi-center high-frequency physiologic data sets from moderate/severe TBI patients [168,169]. Further, a more detailed analytics methods, evaluating sex and age subgroups, using machine learning techniques, may shed further light on nuanced subgroup differences [172,173].

Furthermore, such data sets will require integrating pediatric high-frequency physiologic data to confirm the overall hypothesis of cerebrovascular control displaying an age-related maturation phenomenon. Acquiring pediatric data sets are difficult but it can be made possible by coordination between specialized centers of excellence in pediatric head trauma care [174–177]. Moreover, epigenomics, when linked with such cerebral physiology, may demonstrate the true link between biological age, as highlighted through methylation profiles, and impaired cerebrovascular reactivity in moderate/severe TBI.

Lastly, collecting high-frequency cerebral physiology with other "omics" data, such as serial proteomics, metabolomics, neuroimaging and genotyping, may aid uncovering molecular pathways leading the cerebrovascular dysfunction in subgroups based on age and biological sex [1,103,178]. If such molecular pathways are uncovered, they are poised to produce precision therapeutic

targets aimed at the prevention and treatment of impaired cerebrovascular reactivity in moderate/severe TBI.

3.5 Limitations

In spite of the interesting and novel findings of this analysis, there are some important limitations of this investigative work that must be highlighted. Foremost, age and biological sex analysis in patients with moderate to severe TBI have not been studied in great detail across the literature but rather glossed over providing gross averages of data across extended periods of recordings [71,159]. This has been confirmed by a narrative review I conducted (discussed in Chapter 2), because it is related to all multimodal cerebral physiology in moderate/severe TBI [14]. Even though this work advances our understanding of the impact of age on cerebrovascular reactivity, utilizing different periods of analysis and insult burden metrics for impaired cerebrovascular reactivity, they too are quite preliminary and require much further validation.

Another limitation to mention is that the sample size for this study is small, which indicates low statistical power and can affect discovery rates and estimations of various effects noted in the work. This is despite the study cohort size being above the bare minimum for such high-frequency cerebrovascular physiologic work [179]. This is further underscored by a loss of statistical significance of the findings, when adjusting for multiple comparisons using Bonferroni methodology. Further, comparing the duration of recording time between the 1st 72 hours and the entire recording periods, this small cohort did not display considerable differences. As such, definitive comments on whether there is a true difference between "acute" (i.e., 1st 72 hours) physiology versus the entire period are limited at this time, with findings in this study to be considered as investigative at this time. Moving forward, a larger sample size will help in rectifying these and other issues and is the focus of future works from the Winnipeg Acute TBI Laboratories. Further, such large multi-center data sets will facilitate more detailed subgroup analysis.

Next, it is important to note the heterogeneous population demographics. As moderate/severe TBI is a well-known heterogeneous entity and the patients in this study were actively treated, the results of this study should be taken as purely investigative. Variation in patient demographics, injury

patterns and treatments received could drive changes in the recorded cerebral physiology, and thus the relationships documented between sex and age in this work.

We must recognise, however, that cerebrovascular reactivity monitoring has failed to demonstrate any significant responses to active treatment in moderate/severe TBI [71,149–152]. Similarly, although intracranial injury burden and pattern appear to drive impaired cerebrovascular reactivity in these patients [79,137,144,160], this cohort did not display significant differences in admission CT injury scores between subgroups analyzed. A consideration with future plans, however, to mitigate such confounders, much larger data sets with multivariable modelling of the relationships between cerebrovascular reactivity and age/sex will be required.

Finally, another potential issue to note is the consistently smaller number of females with moderate to severe TBI across the literature [13,70,72,126,127]. Because males are predominant in this group of patients, they tend to dominate most sub-analyses of patients in studies which can give the impression that males have more unfavourable outcomes or are numerous in various categories [13,70,72,126,127]. Our results, which remain exploratory, indicate a potential signal towards differences in biological sex and cerebral physiologic responses with respect to ICP control. However, given the small numbers of females in this cohort, in keeping with other TBI studies, findings are not definitive at this time. Again, large multi-center data sets will be required to rectify such sample size issues.

3.6 Conclusions

This study revealed that increasing age is associated with worse cerebrovascular reactivity measures in moderate/severe TBI. PRx performed poorly to detect impaired cerebrovascular reactivity in older adults with controlled ICP/CPP. Pulse amplitude of ICP based indices, PAx and RAC, proved an age-related deterioration in cerebrovascular reactivity in older adults with moderate/severe TBI. Therefore, it suggests the need for future work investigating specific cerebrovascular reactivity index subgroup utility, as a “one-index fits all” approach may be inadequate in detecting cerebral physiologic insult burden. Biological sex failed to demonstrate

significant differences in measures of cerebrovascular reactivity. Further work is required in this area.

Chapter 4: Impact of Chronological Age and Biological Sex on Cerebrovascular Reactivity in Moderate/Severe Traumatic Brain Injury: A CAnadian High-Resolution TBI (CAHR-TBI) Study

The results presented in this chapter are currently under peer review. Please see the reference below:

> **Batson C**, Froese L, Sekhon M, Griesdale D, Gomez A, Thelin E, Raj R, Aries M, Gallagher C, Bernard F, Kramer A, Zeiler FA. Impact of Chronological Age and Biological Sex on Cerebrovascular Reactivity in Moderate/Severe Traumatic Brain Injury: A Canadian High-Resolution TBI (CAHR-TBI) Study. J Neurotrauma. Submitted June 22nd, 2022. (Under Review).

4.1 Introduction

It is important to highlight here the findings from the exploratory analysis in Chapter 3. This study revealed a statistically significant relationship between PAx, RAC and age with linear regression and age trichotomization analysis but not with PRx and age [180]. As well, in this cohort, biological sex did not have an impact on the cerebrovascular reactivity measures [180]. This cohort had well controlled ICP and CPP values over the course of their ICU stay. Subsequently, such findings suggested that AMP-based cerebrovascular reactivity indices performed superior to the standard PRx in detecting impaired reactivity in populations with advancing age.

Despite these interesting and significant findings, this exploratory analysis suffered from many limitations like small sample size, small female numbers, heterogenous population, gross averaging of long periods of data across the literature, sparse literature on the topic, power issues, etc., leaving the results preliminary and needing further investigation.

In an effort to remedy this, it was elected to perform a more in-depth analysis using a novel large multi-center data set. The CAHR-TBI Research Collaborative was created in 2019 for the purpose of investigating cerebral physiologic relationships in acute neural injury, using high-fidelity multi-

modal cerebral physiologic data sets collected in a multi-center fashion [168]. This study provides a follow-up validation analysis [180] of the impact of age and biological sex on ICP-based cerebrovascular reactivity in moderate/severe TBI using the multicenter CAHR-TBI dataset.

4.2 Methods

4.2.1 Study Type

This is a retrospective multicenter study of a prospectively maintained database of moderate to severe TBI patients. Data from the CAHR-TBI Research Collaborative [168], led by the Winnipeg Acute TBI Laboratories was used. This data came from the Universities of Manitoba, British Columbia and Calgary and contains demographic, injury, treatment, outcome information and high-frequency physiology from various MMM devices. Local research ethics board approval at the University of Manitoba is in place for all aspects of this database (H2017:181 and H2017:188). Similarly, obtained was ethics approval for retrospective access to the database and for data transfer with each center for this project (H2020:118, H20-03759 and REB20-0482).

4.2.2 Patient Population

Patient data was entered into the database from January 2019 to December 2021 for the University of Manitoba, 2014 to 2019 for the University of British Columbia and 2011 to 2021 for the University of Calgary. Inclusion criteria for this study were patients 16 years and older who suffered moderate to severe TBI with invasive ICP and ABP monitoring who were admitted to the ICUs of the Health Sciences Centre – University of Manitoba, Vancouver General Hospital – University of British Columbia and Foothills Medical Center – University of Calgary. Patients who were younger than 16 years, those who suffered mild TBI and those without invasive ICP monitoring were excluded from this study.

4.2.3 Patient Data Collected

For the purposes of this study, general admission demographics for this patient cohort was extracted from the database. The demographic variables included: age, sex, admission pupillary response, admission GCS total and motor (GCS-M) sub-scores, pre-hospital hypoxia, presence of traumatic subarachnoid hemorrhage index CT (CT-tSAH), presence of epidural hematoma index CT (CT-EDH), admission Marshall CT grade [181], and admission Rotterdam CT grades [182] for the University of Manitoba cohort. The University of British Columbia cohort included all of these except presence of CT-tSAH and presence of CT-EDH. The University of Calgary cohort included all of these except best admission GCS-M, presence of CT-tSAH and presence of CT-EDH.

4.2.4 Physiologic Data Acquisition

The usual protocol at these centers for critically ill TBI patients includes ABP and ICP monitoring which is also in keeping with the BTF guidelines [153]. ABP was monitored via radial arterial lines (zeroed at the level of the tragus) and ICP was monitored via intraparenchymal strain gauge monitors (Codman ICP Microsensor; Codman & Shurtleff Inc., Raynham, MA), with EVDs used in the minority of cases. All physiology data was recorded in digital high-frequency time series (i.e., 100 Hertz) using ADC signal converters (Data Translations, DT9804 or DT9826) where relevant. This digital data was linked and stored in time series using ICM+ software (Cambridge Enterprise Ltd, Cambridge, UK, http://icmplus.neurosurg.cam.ac.uk), similar to what was outlined in Chapter 3.

4.2.5 Physiologic Signal Processing

Artifact clearing was performed on the data using ICM+ software to manually remove signal interferences (similar to those outlined in Chapter 3), including drain opening-artifact for those small number of patients with EVDs. This was performed under the supervision of a qualified clinician with experience with all of the multimodal cerebral physiologic signals both in bedside care and in the laboratory environment. All signal files were cleaned without knowledge of patient age or sex as they were completely de-identified when stored in the signals database. CPP was

calculated and AMP was derived [25,77]. Next, the full waveform data for all physiology was decimated using non-overlapping moving average filter of 10-sec duration which facilitates focusing on the slow-wave frequency range associated with CA and interference with ventilation induced changes. This 10-sec by 10-sec data was then used to derive continuously updating cerebrovascular reactivity and compensatory reserve measures. As an example, PRx is computed as the moving Pearson correlation coefficient between 30 consecutive 10-sec mean paired values of ICP and MAP. The other indices are computed in a similar manner. The following cerebrovascular indices were derived: PRx [8,73], PAx [25,77], and RAC [78]. Lastly, RAP was also derived to facilitate surrogate evaluation of brain compliance [82]. All signals (recorded and derived) were output in minute averages into CSV datasets for further analysis.

4.2.6 Physiologic Data Post-Processing

Two main data sheets were created from the data i.e., the 1st 72 hours of recording and the entire recording period, in keeping with the analysis conducted in Chapter 3. The 1st 72 hours is the critical time where most acute physiology changes and aggressive management would occur post-TBI [73,159,160]. This period of time is crucial and was compared with the entire recording period to see what important findings arise. This was done to avoid the pitfalls of previous literature regarding grand averaging of large amounts of data relating to cerebrovascular reactivity, especially when withdrawal of the treatment due to refractory intracranial hypertension occurs with monitoring devices still in place. Also, insult burden metrics were derived for key physiology measures for all of the data sheets. These metrics were defined as the percent time spent above literature defined thresholds for ICP, CPP, PRx, PAx and RAC. These derived variables included:

1. % time with ICP above 20 and 22 mm Hg. These are BTF-based ICP treatment thresholds [21].
2. % time with CPP below 60 mm Hg and above 70 mm Hg. These are BTF-based CPP thresholds [70,153].
3. % time with PRx above 0, +0.25 and +0.35. These are literature-defined critical thresholds associated with outcomes in TBI [70,72].
4. % time with PAx above 0 and +0.25. These are literature-defined critical thresholds associated with outcomes in TBI [72].

5. % time with RAC above -0.10 and -0.05. These are literature-defined critical thresholds associated with outcomes in TBI [72].

4.2.5 Statistical Analysis

The data was analyzed using the R statistical software (R Core Team (2020). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/). Descriptive statistics; mean/SD and median/IQR were used to summarize patient demographics and physiology variables, where appropriate. Boxplots were used as a visual aid of the data. Shapiro-Wilks tests were performed on the continuous variables from these two data sets to test for normality, with all physiologic variables demonstrating non-parametric natures. Multiple comparisons were corrected for using false discovery rate (FDR) testing due to concerns that Bonferroni (used in Chapter 3) was too strict for an exploratory analysis. Bonferroni is considered to be conservative and ignores dependencies among the data therefore, FDR is better in this setting where a huge number of signals were assessed. Also, FDR is adaptive, scalable and a better suited method for this analysis.

The impact of biological sex on the continuously measured metrics (namely ICP, MAP, CPP, PRx, PAx, and RAC) was assessed by comparing values between males and females using the Mann-Whitney-U test. Age was assessed using linear regression, trichotomization and decades of age (dividing into six subgroups) categorical analyses. To begin, age was used as a continuous variable and compared to the physiology variables using Pearson correlations. Scatterplots; linear regression plotting (95% CI) were used for data visualization. Then, age was divided based on age trichotomization (i.e., Age < 40, Age 40 – 60 and Age > 60) and division by decades of age (i.e., Age < 30, 30 – 39, 40 – 49, 50 – 59, 60 – 69, > 69). A cut-off of 60 years was chosen as this is common for outcomes in various neuropathological and critical care states as patients older than 60 years suffer unfavorable outcomes [103,104,153]. The basis of the age trichotomization scheme was to evaluate the hypothesis of the age-related maturation of cerebrovascular function. Forty years was used as a cut-off as the literature shows that there is potentially more unfavorable outcomes across the age groups centered on 40 years with persons < 40 years likely to experience good

recovery unlike persons > 40 years [163–165]. For comparison of physiology metrics for the age trichotomization and decades of age scheme, Kruskal-Wallis testing and FDR testing were used.

Finally, physiologic signal co-variance between age and sex groups was evaluated using various exploratory clustering techniques – Agglomerative Hierarchical Clustering (AHC), K-means Clustering Analysis (KMCA), K-Medoids/Partitioning Around Medoids (PAM) and Principal Component Analysis (PCA). These four clustering techniques were conducted on male physiology, female physiology, age < 40 years physiology, age 40 – 60 years physiology and age > 60 years physiology for the 1st 72 hours and entire recording period. Such clustering analytics in cerebral physiologic signal analysis in TBI have been pioneered by the Winnipeg Acute TBI Laboratories [157,172,183], with detailed descriptions beyond the scope of this thesis. Refer to the referenced literature for details, and the brief primers on select clustering techniques provided in Appendices E and F of this thesis.

4.3 Results

4.3.1 Patient Demographics

Two hundred and eighty-three (283) patients (122 from the University of Calgary, 86 from the University of Manitoba and 75 from the University of British Columbia) were identified as qualified for the study; 224 males and 59 females with a median age of 38 (IQR: 24.0 – 53.3) years. All patients suffered moderate (GCS score 9 – 12) to severe TBI (GCS score < 9) requiring ICU admission, with a median GCS score of 6 (IQR: 3.0 – 7.0). Table 4.1 shows a summary of general patient demographics in means/medians. Also, a summary of medians and IQRs of recorded cerebral physiology during the acute phase (i.e., 1st 72 hours) and the entire recording period can be found in Table 4.2.

Table 4.1 Patients Demographic Information.

Demographic Information				
	Mean	**SD**	**Median**	**IQR**
Duration of Physiology Recording (hours)	184. 5	262.5	115.5	65.0 – 203.5
Age (years)	40.0	17.2	38.0	24.0 – 53.3
Best Admission GCS	5.7	2.5	6.0	3.0 – 7.0
Best Admission GCS – Motor	3.0	1.8	3.0	1.0 – 5.0
Pupils	Unilateral Unreactive	Bilateral Reactive	Bilateral Unreactive	
	40 (15%)	196 (72%)	37 (14%)	
	Males	**Females**		
Sex	224 (79%)	59 (21%)		
Admission Marshall CT Grade:	Males	Females		
I	-	1		
II	64	17		
III	51	17		
IV	29	3		
V	55	15		
VI	4	-		
ROTTERDAM CT Grade:	Males	Females		
I	1	-		
II	10	1		
III	28	7		
IV	33	6		
V	23	3		
VI	17	4		
	Yes	**No**		
Pre – Hospital Hypoxia	51 (38%)	82 (62%)		
Admission CT – tSAH	82 (94%)	5 (6%)		
Admission CT – EDH	11 (13%)	76 (87%)		

CT = computed tomography, EDH = epidural hematoma, GCS = Glasgow Coma Scale, IQR = interquartile range, SD = standard deviation, tSAH = traumatic subarachnoid hemorrhage.

Table 4.2 Cerebral Physiology for the 1st 72 hours and Entire Recording Period

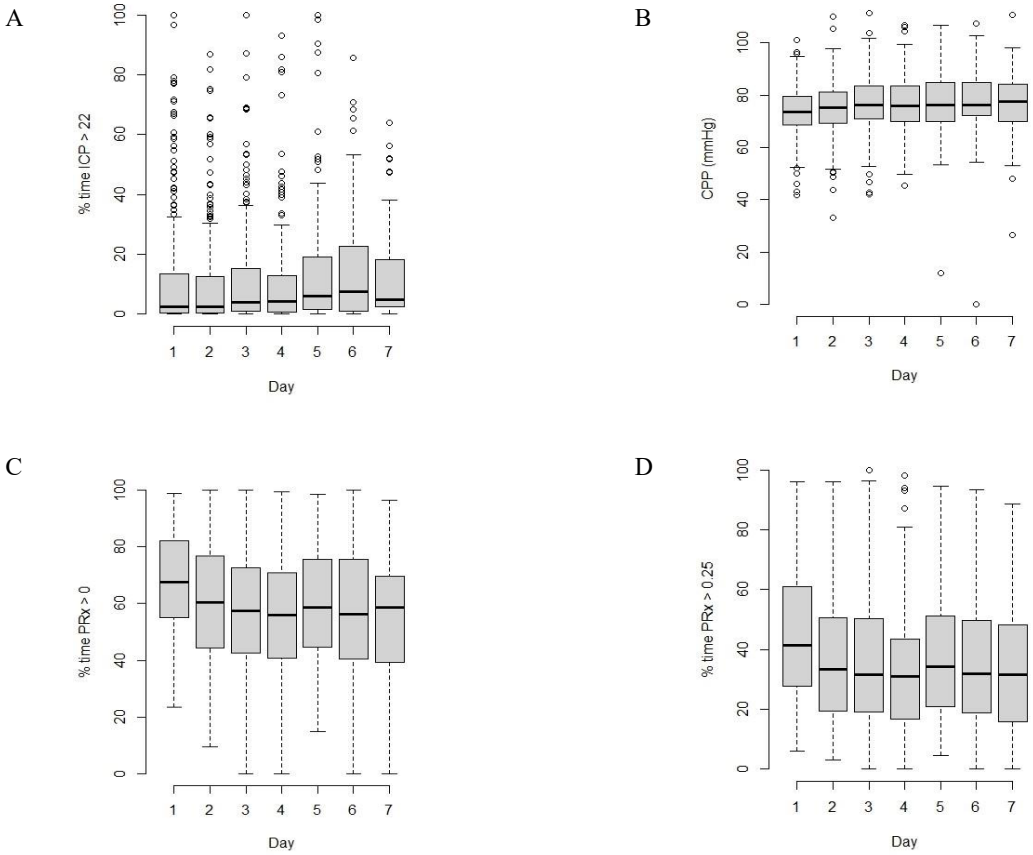
Physiologic Variables	1st 72 Hours of Data		Entire Recording Period	
	Median	IQR	Median	IQR
ICP (mm Hg)	12.8	9.3 – 16.8	13.1	9.2 – 16.4
% Time ICP > 20 mm Hg	6.1	1.2 – 23.2	7.2	1.6 – 23.1
% Time ICP > 22 mm Hg	3.4	0.8 – 14.7	4.0	0.9 – 14.0
MAP (mm Hg)	88.3	81.9 – 93.9	89.2	83.1 – 94.9
CPP (mm Hg)	74.9	69.9 – 80.8	75.8	70.9 – 82.0
% Time CPP > 70 mm Hg	71.2	52.0 – 91.2	74.1	56.4 – 90.9
% Time CPP < 60 mm Hg	3.5	0.8 – 10.5	3.8	1.0 – 9.4
PRx (a.u.)	0.122	0.014 – 0.250	0.117	0.006 – 0.243
% Time PRx > 0	63.2	50.4 – 76.9	61.9	49.8 – 75.1
% Time PRx > 0.25	37.6	24.5 – 52.5	37.8	25.0 – 51.1
% Time PRx > 0.35	27.9	17.3 – 40.3	27.9	17.6 – 40.4
PAx (a.u.)	-0.032	-0.137 – 0.104	-0.038	-0.129 – 0.083
% Time PAx > 0	46.1	34.2 – 63.6	45.6	34.2 – 60.3
% Time PAx > 0.25	19.4	12.9 – 35.9	20.7	13.8 – 33.5
RAC (a.u.)	-0.267	(-0.459) – (-0.110)	-0.290	(-0.458) – (-0.135)
% Time RAC > -0.10	30.5	15.6 – 49.0	30.2	16.0 – 45.4
% Time RAC > -0.05	26.7	13.2 – 43.6	26.4	13.7 – 40.4
RAP (a.u.)	0.628	0.453 – 0.745	0.625	0.464 – 0.739
% Time RAP > 0.4	79.3	64.1 – 88.8	78.6	63.5 – 88.0

a.u. = arbitrary units, CPP = cerebral perfusion pressure, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage.

4.3.2 Daily Physiologic Insult Burden

In an effort to gain a better understanding of the degree of impaired cerebrovascular reactivity seen in this cohort of patients, the % time of index impairment over the 1st week of their ICU stay was analyzed. Mostly, it can be seen that over the 1st week, ICP and CPP were well controlled with limited time spent above thresholds and within the guideline suggested ranges (ICP 7 – 20 mm Hg and CPP 60 – 70 mm Hg) [21,153]. Most patients spent the 1st week of their ICU stay with a daily PRx value above 0 and +0.25 for the majority of each day. Figure 4.1 shows boxplots for the 1st seven days, highlighting % time with ICP > 22 mm Hg (Figure 1A), mean CPP (Figure 1B), % time with PRx > 0 (Figure 1C) and % time with PRx > +0.25 (Figure 1D).

Figure 4.1 Boxplots of Daily Recordings of the 1st 7 days



Panel A - % time intracranial pressure (ICP) > 22 mm Hg, Panel B - mean cerebral perfusion pressure (CPP), Panel C - % time pressure reactivity index (PRx) > 0 and Panel D - % time PRx > +0.25.

4.3.3 Cerebrovascular Reactivity – Impact of Biological Sex

A comparison of males and females was done to evaluate the differences in physiological responses based on biological sex. Table 4.3 shows medians/IQRs, Mann-Whitney U and FDR p values, comparing the median physiological variables between males and females for the 1st 72 hours of recorded data. In Appendix D, Table D.1, a comparable table is shown with similar results for the entire recording period. There was no statistically significant difference in cerebrovascular reactivity between the sex groups on Mann-Whitney U testing, regardless of recording period evaluated. Also, there were no differences in markers of TBI severity (age, GCS, GCS-M, ROTTERDAM, Marshall) between males and females.

Table 4.3: Cerebral Physiology Based on Biological Sex: Medians/IQRs and Mann-Whitney-U Testing: 1st 72 Hours of Recording

Physiological Variable	Males (n = 224)		Females (n = 59)		Mann-Whitney U-Test p-value	FDR p value
	Median	IQR	Median	IQR		
ICP (mm Hg)	12.6	8.5 – 16.4	13.7	10.7 – 18.5	0.071	0.426
% Time ICP > 20 mm Hg	5.3	1.1 – 20.8	9.0	2.5 – 34.4	0.065	0.426
% Time ICP > 22 mm Hg	3.0	0.7 – 11.7	4.6	1.3 – 20.8	0.056	0.426
MAP (mm Hg)	88.1	81.9 – 93.8	89.4	82.0 – 95.3	0.297	0.691
CPP (mm Hg)	74.7	69.9 – 80.8	75.6	69.8 – 81.1	0.775	0.930
% Time CPP > 70 mm Hg	71.2	52.7 – 90.9	73.6	47.1 – 92.4	0.853	0.932
% Time CPP < 60 mm Hg	3.4	0.8 – 10.5	3.6	0.8 – 10.5	0.854	0.932
PRx (a.u.)	0.131	0.015 – 0.249	0.101	0.0 – 0.2	0.518	0.691
% Time PRx > 0	63.7	50.3 – 76.8	60.2	50.5 – 76.4	0.425	0.691
% Time PRx > 0.25	37.7	24.7 – 52.6	34.5	23.9 – 49.9	0.425	0.691
% Time PRx > 0.35	28.2	17.4 – 40.5	25.9	17.0 – 38.3	0.468	0.691
PAx (a.u.)	-0.040	-0.142 – 0.090	-0.008	-0.103 – 0.104	0.499	0.691
% Time PAx > 0	45.6	34.2 – 62.7	47.9	36.5 – 64.6	0.478	0.691
% Time PAx > 0.25	19.3	12.8 – 35.3	22.5	13.1 – 35.9	0.629	0.794
RAC (a.u.)	-0.261	(-0.443) – (-0.108)	-0.306	(-0.503) – (-0.116)	0.227	0.691

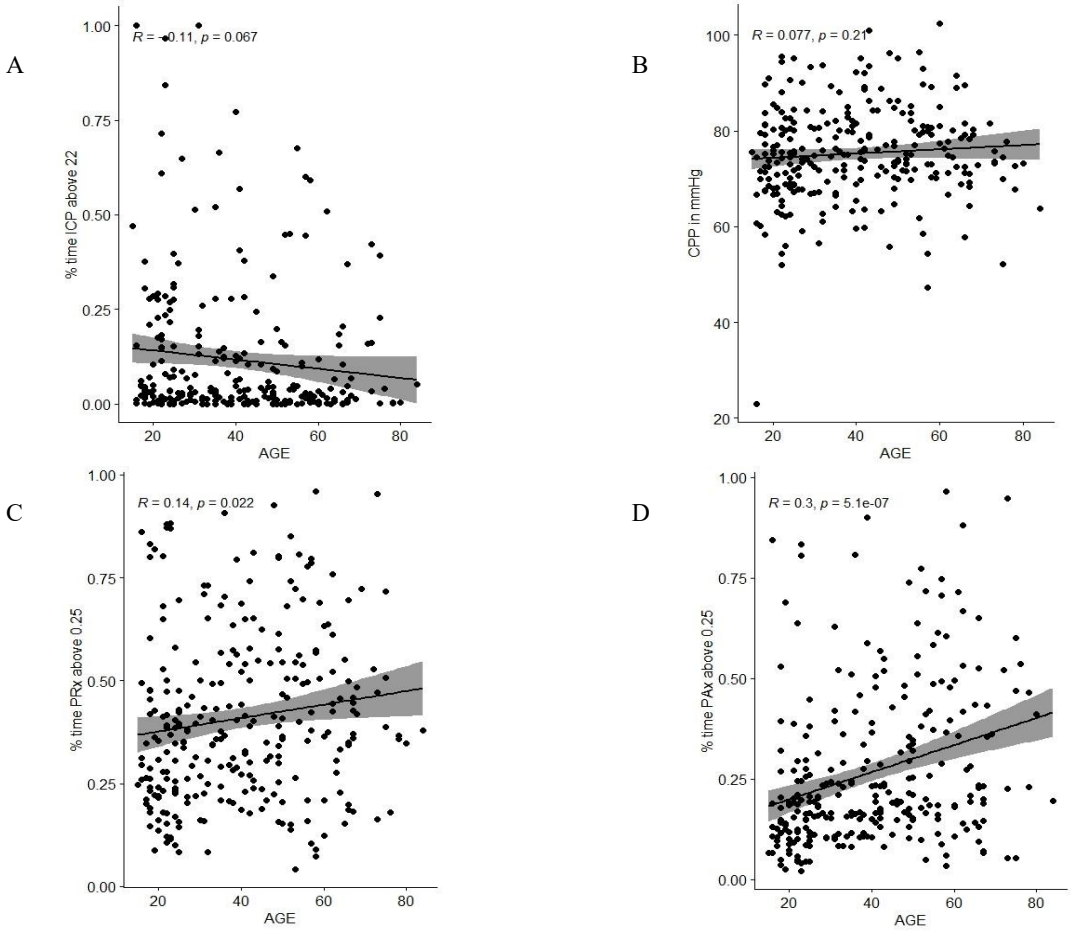
% Time RAC > -0.10	31.3	15.9 – 49.0	27.6	14.1 – 45.5	0.268	0.691
% Time RAC > -0.05	27.4	13.5 – 43.7	23.6	12.0 – 40.3	0.301	0.691
RAP (a.u.)	0.619	0.450 – 0.729	0.681	0.460 – 0.765	0.069	0.426
% Time RAP > 0.4	78.8	62.5 – 87.8	84.1	66.5 – 90.7	0.105	0.473
Age (years)	40.0	24.0 – 54.0	31.5	23.3 – 49.0	0.118	0.473
Best Admission GCS	6.0	3.0 – 7.0	6.0	3.0 – 7.0	0.906	0.945
Best Admission GCS – Motor	3.0	1.0 – 5.0	3.0	1.0 – 4.3	0.385	0.691
Rotterdam CT Grade	4.0	3.0 – 5.0	4.0	3.0 – 5.0	0.990	0.990
Admission Marshall CT Grade	3.0	2.0 – 5.0	3.0	2.0 – 5.0	0.491	0.691

a.u. = arbitrary units, CPP = cerebral perfusion pressure, FDR = false discovery rate, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage.

4.3.4 Cerebrovascular Reactivity – Impact of Age – Linear Regression

Linear regression was used to evaluate the relationship between cerebrovascular reactivity and age. ICP, CPP and PRx failed to demonstrate a significant linear relationship with age. However, the AMP-derived metrics (PAx and RAC) yielded a statistically significant relationship with age. An example is shown in figure 4.2 of scatterplots and linear regressions presented with 95% CI for the 1st 72 hours of recording, with similar findings for the entire recording period (found in Appendix D, Figure D.1).

Figure 4.2 Scatterplots and Linear Regression (1st 72 Hours of Recording)



Panel A - % Time ICP > 22 mm Hg vs. Age, Panel B - Mean CPP vs. Age, Panel C - % Time PRx > +0.25 vs. Age, and Panel D - % Time PAx > +0.25 vs. Age, P-values recorded are for the Pearson correlation coefficient, R = Pearson correlation coefficient. Panel C – does not remain significant after correction for multiple comparisons.

4.3.5 Cerebrovascular Reactivity – Impact of Age – Categorical Analysis

The relationship between age and cerebrovascular reactivity was further interrogated through categorical organization of age, using age trichotomization and analysis by decades of age. Table 4.4 provides the trichotomization of age subgroup analysis and Table 4.5 provides the decades of age subgroup analysis for the 1st 72 hours of recording, highlighting medians/IQRs across each age group, Kruskal-Wallis and FDR p-values. Data for the trichotomization and decades of age analyses for the entire recording period are shown in Appendix D: Tables D.2 and D.3 with similar findings for both recording periods. Age trichotomization and decades of age analyses revealed in both data sheets, a statistically significant worsening of cerebrovascular reactivity, as assessed by PAx and RAC, with increasing age category, as assessed through Kruskal-Wallis testing. This was the case with age trichotomization for mean PAx ($p = 0.0002$), % Time PAx > 0 ($p = 0.00005$), % Time PAx > 0.25 ($p = 0.000007$), mean RAC ($p = 0.0002$), % Time RAC > -0.10 ($p = 0.0001$), % Time RAC > -0.05 ($p = 0.0001$) and admission Marshall CT Grade ($p = 0.008$) in the 1st 72 hours recording sheet. Also, similar findings were noted with the decades of age analysis where mean PAx ($p = 0.0002$), % Time PAx > 0 ($p = 0.00004$), % Time PAx > 0.25 ($p = 0.000006$), mean RAC ($p = 0.0003$), % Time RAC > -0.10 ($p = 0.0002$) and % Time RAC > -0.05 ($p = 0.0002$) in the 1st 72 hours recording sheet. These all remained significant after FDR testing. It was noted that PRx failed to document such difference. Importantly, this relationship was displayed in the absence of significant differences in injury severity assessed by admission CT grading.

Table 4.4 Cerebral Physiology Association with Trichotomized Age (Age < 40, Age 40 – 60, Age > 60): Medians/IQRs, Kruskal-Wallis and FDR Testing for 1st 72 Hours of Recording

Physiological Variable	Age < 40 years (n = 146)		Age 40 – 60 years (n = 94)		Age > 60 years (n = 42)		Kruskal-Wallis Test p-value	FDR p values
	Median	IQR	Median	IQR	Median	IQR		
ICP (mm Hg)	13.3	9.9 – 18.0	12.4	7.7 – 16.1	11.7	8.3 – 14.5	0.056	0.156
% Time ICP > 20 mm Hg	7.2	1.8 – 32.1	4.5	1.1 – 17.4	3.5	0.8 – 19.2	0.180	0.276
% Time ICP > 22 mm Hg	3.5	0.9 – 17.3	2.9	0.7 – 10.5	2.5	0.4 – 11.1	0.266	0.320
MAP (mm Hg)	88.4	82.4 – 93.4	88.9	82.7 – 95.6	85.9	78.7 – 93.9	0.277	0.320
CPP (mm Hg)	74.4	68.2 – 80.5	76.6	71.6 – 83.9	74.5	71.1 – 79.2	0.131	0.232
% Time CPP > 70 mm Hg	69.7	46.4 – 91.8	76.8	56.6 – 92.5	68.3	53.2 – 84.3	0.252	0.320
% Time CPP < 60 mm Hg	4.1	0.8 – 11.6	2.4	0.5 – 7.6	3.1	1.8 – 7.9	0.292	0.320
PRx (a.u.)	0.103	0.013 – 0.213	0.146	0.020 – 0.293	0.141	0.045 – 0.244	0.163	0.268
% Time PRx > 0	59.6	49.0 – 73.9	63.7	52.3 – 81.6	65.4	54.0 – 74.6	0.106	0.203
% Time PRx > 0.25	35.0	23.2 – 47.4	40.8	26.7 – 57.5	38.8	33.3 – 50.7	0.063	0.156
% Time PRx > 0.35	26.0	16.2 – 35.6	32.1	18.4 – 47.3	31.0	22.8 – 39.8	0.068	0.156
PAx (a.u.)	-0.064	-0.162 – 0.023	-0.002	-0.085 – 0.178	0.011	-0.091 – 0.186	**0.0002**	**0.001**
% Time PAx > 0	42.1	29.8 – 53.1	51.6	39.2 – 68.9	53.1	39.1 – 71.0	**0.00005**	**0.001**

% Time PAx > 0.25	16.5	10.7 – 24.8	23.3	16.5 – 42.4	23.3	18.1 – 46.9	**0.000007**	**0.0002**
RAC (a.u.)	-0.344	(-0.507) – (-0.195)	-0.227	(-0.401) – (-0.078)	-0.170	(-0.376) – (-0.007)	**0.0002**	**0.001**
% Time RAC > -0.10	23.8	13.1 – 40.4	34.7	18.6 – 53.4	43.2	21.5 – 59.5	**0.0001**	**0.001**
% Time RAC > -0.05	20.5	10.4 – 35.9	30.4	15.9 – 47.5	37.7	19.1 – 54.2	**0.0001**	**0.001**
RAP (a.u.)	0.594	0.449 – 0.746	0.670	0.490 – 0.747	0.649	0.366 – 0.717	0.292	0.320
% Time RAP > 0.4	76.6	64.0 – 87.7	82.4	65.3 – 89.1	78.2	57.4 – 89.4	0.380	0.398
Best Admission GCS	6.0	3.0 – 7.0	6.0	4.0 – 8.0	5.0	3.0 – 7.0	0.495	0.495
Best Admission GCS – Motor	4.0	1.0 – 5.0	4.0	1.0 – 5.0	2.0	1.0 – 4.0	0.210	0.301
Rotterdam CT Grade	4.0	3.0 – 5.0	4.0	3.0 – 5.0	5.0	4.0 – 5.3	0.075	0.156
Admission Marshall CT Grade	3.0	2.0 – 4.0	3.0	2.0 – 5.0	4.0	3.0 – 5.0	**0.008**	**0.026**

a.u. = arbitrary units, CPP = cerebral perfusion pressure, FDR = false discovery rate, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values indicate those reaching statistical significance on Kruskal-Wallis and FDR Testing.

Table 4.5 Cerebral Physiology Association with Decades of Age Subgroups (Age < 30, Age 30 – 39, Age 40 – 49, Age 50 – 59, Age 60 – 69, Age > 69): Medians/IQRs, Kruskal-Wallis and FDR Testing for 1st 72 Hours of Recording

Physiological Variable	Age < 30 years (n = 102)		Age 30 – 39 years (n = 44)		Age 40 – 49 years (n = 47)		Age 50 – 59 years (n = 43)		Age 60 – 69 years (n = 34)		Age > 69 years (n = 12)		Kruskal-Wallis Test p-value	FDR p values
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR		
ICP (mm Hg)	13.4	10.1 – 18.1	12.9	9.6 – 17.7	13.0	7.9 – 15.4	12.0	7.2 – 16.3	11.5	8.0 – 13.4	13.4	10.4 – 17.9	0.144	0.295
% Time ICP > 20 mm Hg	7.3	2.3 – 30.4	5.9	0.8 – 32.0	6.7	1.8 – 18.3	3.5	1.0 – 15.8	2.8	0.8 – 12.7	8.1	0.7 – 27.4	0.260	0.398
% Time ICP > 22 mm Hg	3.6	1.2 – 18.9	3.2	0.6 – 14.4	3.6	1.2 – 11.4	1.9	0.5 – 9.3	1.6	0.5 – 6.6	4.6	0.4 – 17.7	0.305	0.413
MAP (mm Hg)	88.6	82.4 – 94.3	87.9	82.6 – 92.9	88.3	82.8 – 95.5	90.5	82.9 – 95.3	86.8	79.4 – 94.1	80.0	78.6 – 90.4	0.602	0.629
CPP (mm Hg)	73.6	68.1 – 80.2	75.4	69.6 – 80.9	76.9	71.6 – 84.9	75.2	71.7 – 81.6	76.9	71.3 – 80.2	73.3	69.4 – 74.8	0.207	0.360
% Time CPP > 70 mm Hg	66.4	46.1 – 87.0	74.3	54.6 – 93.1	77.4	53.9 – 90.9	76.3	57.2 – 92.9	70.0	57.6 – 86.8	65.3	44.3 – 81.0	0.361	0.440
% Time CPP < 60 mm Hg	4.5	0.8 – 11.4	3.3	0.9 – 13.2	2.7	0.6 – 10.5	2.0	0.3 – 6.8	3.0	1.2 – 6.9	3.4	2.3 – 12.1	0.509	0.558
PRx (a.u.)	0.092	0.007 – 0.193	0.139	0.052 – 0.273	0.113	0.025 – 0.282	0.237	-0.023 – 0.295	0.142	0.023 – 0.235	0.131	0.079 – 0.257	0.219	0.360
% Time PRx > 0	58.1	48.0 – 71.4	64.2	54.1 – 78.0	61.6	52.4 – 76.8	70.9	49.7 – 82.1	66.0	52.7 – 76.8	63.8	57.5 – 74.4	0.154	0.295
% Time PRx > 0.25	33.1	22.1 – 42.8	39.1	28.7 – 56.5	34.5	27.1 – 57.0	49.3	26.4 – 57.4	41.8	30.5 – 49.9	38.3	35.5 – 51.2	0.073	0.187
% Time PRx > 0.35	22.6	14.9 – 32.3	27.9	19.5 – 43.6	26.4	18.6 – 46.9	36.9	18.2 – 46.9	28.8	19.0 – 38.7	31.5	25.2 – 44.3	0.072	0.187
PAx (a.u.)	-0.087	-0.177 – 0.004	-0.013	-0.120 – 0.087	-0.034	-0.085 – 0.065	0.063	-0.079 – 0.226	-0.026	-0.088 – 0.143	0.158	-0.110 – 0.223	**0.0002**	**0.001**
% Time PAx > 0	38.1	27.6 – 50.4	47.3	34.8 – 62.9	45.8	39.7 – 57.2	59.0	38.5 – 75.9	47.1	39.1 – 64.1	66.6	39.0 – 73.5	**0.00004**	**0.0004**
% Time PAx > 0.25	15.5	10.3 – 20.8	22.0	11.6 – 34.1	21.2	16.5 – 32.7	33.7	16.5 – 49.2	23.3	14.7 – 43.2	43.8	21.8 – 52.5	**0.000006**	**0.0001**
RAC (a.u.)	-0.402	(-0.520) – (-0.201)	-0.283	(-0.401) – (-0.172)	-0.242	(-0.400) – (-0.122)	-0.174	(-0.401) – (-0.003)	-0.146	(-0.284) – (-0.026)	-0.185	-0.414 – 0.020	**0.0003**	**0.001**

% Time RAC > -0.10	18.8	10.7 – 39.7	29.3	18.7 – 42.3	32.4	16.9 – 46.8	41.7	25.7 – 56.9	43.6	23.5 – 58.0	42.3	20.8 – 61.2	**0.0002**	**0.001**
% Time RAC > -0.05	16.0	9.2 – 34.9	25.8	16.1 – 37.1	27.8	13.9 – 42.1	37.5	23.0 – 53.5	35.8	19.1 – 52.3	38.3	18.3 – 55.5	**0.0002**	**0.001**
RAP (a.u.)	0.580	0.438 – 0.766	0.615	0.458 – 0.683	0.654	0.460 – 0.743	0.679	0.578 – 0.748	0.556	0.308 – 0.688	0.690	0.550 – 0.762	0.364	0.440
% Time RAP > 0.4	76.2	62.0 – 90.2	77.8	64.6 – 87.0	82.3	62.8 – 88.4	84.4	73.9 – 89.3	76.3	45.3 – 87.2	87.3	74.3 – 91.2	0.281	0.404
Best Admission GCS	5.0	3.0 – 7.0	6.0	3.8 – 7.0	6.0	4.0 – 7.0	6.0	4.0 – 8.0	5.0	3.0 – 7.0	7.0	3.0 – 8.0	0.883	0.883
Best Admission GCS – Motor	4.0	1.0 – 4.3	4.0	1.3 – 5.0	2.0	1.0 – 5.0	4.0	2.0 – 5.0	2.0	1.0 – 4.0	3.0	1.0 – 4.0	0.421	0.484
Rotterdam CT Grade	4.0	3.0 – 5.0	4.0	3.0 – 5.0	3.0	2.8 – 5.0	4.0	3.3 – 5.0	4.5	4.0 – 5.8	5.0	4.3 – 5.0	0.130	0.295
Admission Marshall CT Grade	3.0	2.0 – 4.0	3.0	2.0 – 4.0	3.0	2.0 – 5.0	4.0	2.0 – 5.0	4.0	3.0 – 5.0	5.0	3.5 – 5.0	0.064	0.187

a.u. = arbitrary units, CPP = cerebral perfusion pressure, FDR = false discovery rate, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values indicate those reaching statistical significance on Kruskal-Wallis and FDR Testing.

4.3.6 Cerebrovascular Reactivity – Clustering Physiology by Age and Sex Categories

Males, females and trichotomized age subgroups were clustered based on their physiology for both data sheets using AHC, KMCA, PAM and PCA. Results from these analyses were inconclusive regarding identifying clear subgroup physiology patterns based on age or biological sex. Refer to Appendices E and F for a few samples of these clustering diagrams from the AHC and PCA analyses.

4.4 Discussion

This CAHR-TBI multicenter study has shown some novel findings and at the same time validated some earlier results from a small exploratory analysis done on the topic [180]. This TBI cohort comprises 224 males and 59 females, making it one of the largest multicenter high-resolution cerebral physiologic data sets in moderate/severe TBI.

Examination of the 1st 72 hours and entire recording data sheets revealed similar findings between cerebrovascular reactivity, age and biological sex. Analysis of the 1st 7 days using boxplots (Figure 4.1) of the daily summaries of the patients' ICU stay showed that acute management indices of ICP and CPP were well controlled according to the BTF normal ranges [153]. Concerning the insult burden of impaired cerebrovascular reactivity seen in our cohort, it can be seen from these boxplots that over the 1st 7 days of the ICU stay, patients spent most of each day in a state of impaired cerebrovascular reactivity despite suitable control of acute management parameters. Comparatively similar findings were demonstrated by Batson et al [180] and Zeiler et al [76,149].

From this study, no significant difference was seen between cerebrovascular reactivity and biological sex. With reference to Table 4.3, biological sex comparison between males and females for the 1st 72 hours of recording showed no statistically significant difference between the physiology. These findings are consistent with previous work from the Winnipeg Acute TBI Laboratories [180]. Still, these results contrast findings from two studies by Czosnyka and colleagues whereby PRx was found to be worse in females compared to males, $p = 0.022$ [143] and PRx was found to be worse in females compared to males < 50 years old, $p < 0.05$ [126]. However, sex-related findings throughout the literature has been limited and largely inconclusive [105,126,137,179] requiring future research involving serum hormone/CSF [167,168]. Understood are the vasodilatory benefits of the sex hormones in pre-menopausal women and the vasoconstrictive effects suffered by post-menopausal women and men due to PGI2 and TXA2 cerebral effects respectively [116,117]. From animal models it is seen that these hormones provide added benefits of reduced neural loss, improved neurophysiologic and functional outcomes in the case of progesterone [106,107]. And in the case of estrogen, it plays an anti-inflammatory role in protecting the vasculature by decreasing leukocyte adhesion, attenuating angiotensin II/ROS response and decreasing iNOS in response to

inflammatory processes [116,118]. Future multicenter prospective analyses must continue in this area involving hormonal, serum/CSF, inflammatory profiles and pre- vs. post-menopausal sub-analyses in order to benefit neurotrauma care.

Next, through evaluating the relationship between age and cerebrovascular reactivity, some important findings were validated and highlighted. Age is a very important prognostic marker in TBI [13,165,184]. Through linear regression and categorical analysis (i.e., age trichotomization and decades of age), it was demonstrated that with advancing age cerebrovascular reactivity worsened. However, contrary to early literature [13], PRx failed to document this association. Only AMP-based cerebrovascular reactivity metrics, PAx and RAC, were able to detect this relationship. Such findings validate previous work on the topic [15,180] and are in keeping with the general sentiment that cerebrovascular function deteriorates with advancing age in moderate/severe TBI populations [13,25,77,79,169,185]. Nevertheless, regarding the superior performance of PAx and RAC, a possible explanation is that ICP was low and well-controlled in our cohort [77]. Hence, in elderly patients with progressive cortical atrophy and well-controlled ICP, AMP-based cerebrovascular reactivity metrics appear better positioned to monitor/detect impaired reactivity. This is an important finding that has yet to be documented in the literature and highlights the potential importance of these alternative ICP-based cerebrovascular reactivity measures [25,77,78].

To unearth further patterns in the data, clustering techniques were applied to the data (refer to Appendices E and F). The results from these methods were somewhat inconclusive regarding identifying clear subgroup physiology patterns based on age and biological sex. AHC, KMCA and PAM revealed no discernible age and sex difference between groups. PCA showed that as age advanced, PAx and RAC accounted for more variance, while PRx accounted for little. This corroborates other findings here and in the prior exploratory analysis [180], that PAx and RAC appear to be superior in older patients with low ICP in detecting impaired cerebrovascular reactivity [76,79,82]. In order to shed further light on the true relationships between cerebral physiology and cellular/biological aging, future work should involve the use of the frailty index, epigenetic applications, etc., to quantify true biological age as opposed to using chronological age [1,102,146,186–188].

4.5 Limitations

While this work has validated some important findings, it does not come without limitations. First, the heterogeneous nature of TBI populations must be noted as patients differ in their demographics, treatment regimens, mechanism of injury (based on age group), injury patterns, comorbidities, etc. All these and other factors can possibly affect results and outcomes regarding age and sex effects on cerebrovascular reactivity in moderate/severe TBI. TBI is a syndrome comprised of distinct and overlapping phenotypes – diffuse axonal injury (DAI), contusional injury, SDH, EDH, etc. These phenotypes have unique pathophysiologic sequelae, injury patterns and distribution of anatomical structures affected. As such, the biggest confounder here are the underlying disease patterns and there may be sex or age differences if the focus was on a homogeneous injury pattern.

Second, while important findings are emerging regarding PAx and RAC, they are not widely described in the literature. These indices are rather new and require more robust work and expertise in highly analytic techniques to achieve future validation and use in neurotrauma care [15]. Our results here suggest utility of PAx and RAC in specific subgroups of TBI patients for cerebrovascular reactivity monitoring. Such findings need independent validation and need to be expanded to assess how PAx and RAC may be used for derivation of personalized physiologic targets in TBI (such as optimal CPP).

Third, chronological age may be insufficient in providing the best assessment of true cellular/biological age and its impact on cerebrovascular reactivity [1,102,146,186–188]. Biological age may be a better measure to use in this area of TBI studies via epigenetic techniques based on DNA methylation and histone modification profiles [1,102,146,186–188]. Additionally, assessment and assimilation of high frequency pediatric TBI physiological data will help with seeing the full picture of the cerebral vasculature in its immature form and it's responses in TBI and compare/contrast it with findings in the mature and degenerative (elderly) phases [175,177,189].

Moreover, cerebrovascular reactivity or CBF control is comprised of contributions from the myogenic mechanism, autonomic nervous system, neurovascular coupling, carbon dioxide/oxygen (CO_2/O_2) control amongst others. As such, this study's outcomes relating to the myogenic

mechanism may not be related to age/sex (as it pertains to PRx) but cerebrovascular reactivity may be altered in accordance with the above-mentioned CBF control mechanisms.

Lastly, the analysis of the relationship between cerebrovascular reactivity and biological sex was limited by simple binary male vs. female categorization. There was no access to the hormonal status of the female cohort or designation of pre- vs. post-menopausal status. The effect of female sex hormones on cerebrovascular function have been well documented in both health and disease [104,106,108,116,117,148]. Future studies on the impact of biological sex on cerebrovascular reactivity would benefit from quantification of sex hormones and pro-inflammatory cytokine profiles, serially sampled throughout the acute ICU stay and linked with high-fidelity cerebral physiologic data.

Chapter 5: Overall Thesis Conclusion

In summary, this thesis set out to uncover the impact of age and biological sex on cerebrovascular reactivity in moderate/severe TBI via two hypotheses. After delving into the literature and being largely unsuccessful with the findings relating to the topic, an exploratory analysis (Chapter 3) and a multicenter study (Chapter 4) were conducted to shed some light.

The following hypotheses of this thesis were addressed:

Hypothesis I: Cerebrovascular reactivity as assessed through ICP and ABP will be more impaired in TBI patients with advanced age, compared to the younger cohorts.

Chapters 3 and 4 addressed this hypothesis where it was indeed seen that cerebrovascular reactivity was more impaired in TBI patients with advanced age compared to younger cohorts. The age-related relationship was manifested and validated via significant statistical differences between advancing age and PAx and RAC but not PRx. These results were seen on assessment of the indices and age using scatterplots, linear regression, trichotomization of age and decades of age analyses.

Hypothesis II: Cerebrovascular reactivity will not be related to biological sex in TBI cohorts, regardless of method of assessment and age category.

Chapters 3 and 4 addressed this hypothesis where it was seen that cerebrovascular reactivity was indeed not related to biological sex regardless of method of assessment and age category. These results were seen on assessment of the indices with males and females using Mann-Whitney U testing.

Additional Findings:

These results are promising and exciting as it is a step forward to providing many benefits to neurotrauma care and sparking many future studies into cerebrovascular reactivity, age and sex relations. From the results it is important to highlight some key findings from Chapters 3 and 4 original works. First, through more fine analysis from these studies, compared to prior works with more coarse analysis from Czosnyka [13], it is indeed seen that autoregulation worsens with advancing age.

Second, cerebrovascular reactivity impairment was prominent even when ICP and CPP were controlled. Further to this, PRx performed poorly in detecting impaired cerebrovascular reactivity in low ICP states. Also, PRx performed poorly in detecting impaired cerebrovascular reactivity in advanced age compared to PAx and RAC. This could be due to cortical atrophy not allowing for the generation of critical ICPs to drive autoregulatory impairment or probably even more severe injury being required for this process [76,77,154,171].

Third, there was no clear sex-related differences even with sub-analysis based on peri-menopausal age groups. Much more in-depth hormonal studies, cytokine studies, etc., are needed to garner more information.

All of the above findings are surprising, as it was expected that PRx would perform well (as per previous literature [13,126]). This reinforces the need for further work in this area exploring alternative indices for autoregulation such as the AMP-based indices to detect impaired cerebrovascular reactivity as it is clearly superior in low ICP states and advanced age cohorts.

Also, important is the integration of epigenetics for true biological age determination. Biological age within TBI female patients need further analysis with both serum hormones, serum/CSF inflammatory profiles and maybe epigenetics (DNA methylation profiles). And too, integration of proteomics to quantify hormones and inflammatory profile differences. All these must occur in conjunction with high-frequency physiology.

Chapter 6: Future Directions

Novel and interesting findings have been outlined from the original thesis work in Chapters 3 and 4. However, limitations and unknowns still exist regarding studies into the association of age and biological sex with cerebrovascular reactivity in moderate/severe TBI. To address these challenges of the outlined thesis (Chapter 2, 3 and 4), certain approaches have to be considered into TBI research moving forward.

First, one solution for the issues of small number of females, heterogeneity of patient populations, small study sizes and the use of the same cohort of patients is to continue conducting large multicenter studies. This type of study is required to build power for male vs. female assessment, harmonize data between centers, account for treatments received, build statistical power and aid with adjusting for multiple comparisons. Large multicenter TBI data sets in use for TBI physiologic studies are the CENTER-TBI and CAHR-TBI datasets with over 250 (~ 50 female) participants and over 300 (~ 60 female) participants, respectively [167,168]. These are the largest multicenter datasets in existence, thus there is a critical need to expand this type of physiologic research to other centers to facilitate larger sample sizes. This work requires simplifying the degree of biomedical engineering expertise needed for this type of data collection as currently it remains a significant limiting factor to large scale data collection strategies to centers that lack highly specialized experts on site.

Second, more robust work into PAx and RAC need to be carried out in order to hopefully achieve the results needed so that they would eventually become validated for human use and contribute to neurotrauma care. This entails more pre-clinical studies in large mammals to truly understand the behavior of PAx and RAC with respect to measuring CA as only one study has looked at this [190]. The aim is to validate these measures pre-clinically against the LLA and upper limit of autoregulation (ULA). Also, more clinical investigation of PAx and RAC in relation to age and sex associations are needed as the studies discussed in Chapters 3 and 4 are the only ones in existence. These studies must focus on their role in bedside monitoring in TBI, for example, in low ICP states [77] and their role in personalized physiologic target derivation (e.g. optimal cerebral perfusion pressure [CPP_{opt}]) [162]. These can be achieved by securing adequate funding, which would

allow centers to then obtain the necessary equipment and hire the required experts to explore age, sex, PAx and RAC using multicenter high-frequency physiologic data sets.

Next, the initial future works on MMM and its links with age and sex, require the use of high-resolution measures. Relying on grand mean summary metrics for MMM physiology is insufficient, as signal variance is essentially eliminated, and the ability to discern sub-classes based on age and sex near impossible. As such, future works in this area require the use of time-series methodologies [156,191,192], including autoregressive integrative moving average (ARIMA) and vector autoregressive integrative moving average (VARIMA) techniques. These should be applied based on large populations of TBI patients with high-frequency physiology, using subgroups of age and sex. Further, sub-class evaluation can take place using semi-supervised or unsupervised machine learning techniques, and latent class analytics. It is key to then carry out age and sex subgroup studies in concert with insult burden measures (e.g., % time PRx > 0, > 0.25, > 0.35, etc.). This will help unearth patterns and more in-depth useful information.

Furthermore, more complex multi-variable (linear/logistic regression) models adjusting for age and sex in association with outcome are needed, as such literature is lacking. Such analyses may facilitate answering some of the preliminary questions regarding age/sex interactions, which currently remain unanswered in moderate/severe TBI. This work is the focus of various multicenter groups focused on high-frequency physiology data processing in both Europe [167,173,193,194] and Canada [168] and requires multi-disciplinary integrated teams of clinicians, engineers, physiologists and data scientists.

Fifth, the study of biological sex needs to go beyond just the binary designation of male and female. With all requirements in place, further subcategorization of females based on their menopausal status and hormonal profile is key to properly assess the link between sex, age and cerebrovascular reactivity. This will require integration of proteomics to quantify hormones and inflammatory profiles using serial serum hormones, CSF and microdialysis samples [10,12,100,167,168,195]. Sampling frequency was quite heterogeneous across the literature but a proposed plan could be to obtain samples on days 1, 3, 5, 7, 10 and at 3, 6, 12 and 24 months for analysis [10,12,100,167,168,195]. This would require specialized personnel, resources, equipment and centers.

Sixth, blood sampling will allow for genomic information. It is expected to be rapidly provided through genome wide association chips, allowing for simultaneous assessment for 1 million+ SNPs including those related to pro-inflammatory cytokines, neural repair and angiotensin pathways that are of interest in advanced age [1,102]. Advances in epigenetic techniques will lead to admission quantification of biological age based on methylation and histone modification profiling using blood samples [186–188]. It is well known the chronological age is a poor marker of biological age and function. Epigenetic techniques evaluating widespread genome methylation status, histone modifications, or telomere length of circulating white cells, can be used to quantify biological age. Such epigenetic information may allow us to more accurately determine biological age and its link to MMM based physiologic dysfunction in TBI. Such analysis requires true multi-disciplinary expertise and highly specialized centers to perform. Such work involves joining physiologists, engineers, geneticists, molecular biologists and clinicians and is the focus of upcoming projects from CENTER-TBI and CAHR-TBI [167,168].

Seventh, regarding the future of acute TBI monitoring and care, it is expected that the physiome will be integrated with additional aspects of "omics" data at the bedside, facilitating ongoing transition into personalized therapeutic approaches [1,10,18,167,168,195–197]. Such omics data is expected to take the form of integrated proteomic, genomic and epigenomic information. Proteome data can be gleamed from serial serum CSF and microdialysis sampling. Serum/CSF/microdialysate can be exploited to quantify circulating levels of cytokines [100,101,198,199], such as IL-6, nitric oxide synthase activity (through nitrate/nitrite levels), prostaglandin levels, free radical analysis, and assessment of sex hormone concentrations. With the advances seen in multi-plex immune-assays, numerous biomarkers can be readily obtained, including those pertaining to: neural injury [195], vascular/endothelial function and integrity [200], pro-inflammatory cytokine responses [10,100,201] and metabolic by-products [11,38,202,203].

Omics information provides the opportunity to both improve prognostication modelling in moderate/severe TBI care (physiome, proteome, genome, epigenome), but also improve our ability to monitor treatment response (physiome and proteome), predict/sub-classify treatment responders (physiome, proteome, genome, epigenome), and uncover therapeutic pathways (physiome,

proteome and genome) [204,205]. Such a wealth of information will require multi-disciplinary teams of clinicians, epidemiologists, data scientists, statisticians and biomedical engineers. It will also necessitate the utilization of complex machine learning and artificial intelligence techniques to aid in the interpretation of such large and continuously updating data sets. Preliminary advances in this field are being made by various multi-disciplinary international collaborative efforts in Canada, [168] the US, [206] and Europe [167,173,191,194].

References

1. Zeiler FA, Thelin EP, Donnelly J, et al. Genetic Drivers of Cerebral Blood Flow Dysfunction in TBI: A Speculative Synthesis. Nat Rev Neurol 2019;15(1):25–39; doi: 10.1038/s41582-018-0105-9.

2. Gardner AJ and Zafonte R. Neuroepidemiology of Traumatic Brain Injury. Handb Clin Neurol 2016;138:207–223; doi: 10.1016/B978-0-12-802973-2.00012-4.

3. Paulson OB, Strandgaard S and Edvinsson L. Cerebral Autoregulation. Cerebrovasc Brain Metab Rev 1990;2(2):161–192.

4. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous Monitoring of Cerebrovascular Pressure Reactivity Allows Determination of Optimal Cerebral Perfusion Pressure in Patients with Traumatic Brain Injury: Critical Care Medicine 2002;30(4):733–738; doi: 10.1097/00003246-200204000-00002.

5. Dewan MC, Rattani A, Gupta S, et al. Estimating the Global Incidence of Traumatic Brain Injury. Journal of Neurosurgery 2019;130(4):1080–1097; doi: 10.3171/2017.10.JNS17352.

6. Zeiler FA, Donnelly J, Calviello L, et al. Pressure Autoregulation Measurement Techniques in Adult Traumatic Brain Injury, Part II: A Scoping Review of Continuous Methods. Journal of Neurotrauma 2017;34(23):3224–3237; doi: 10.1089/neu.2017.5086.

7. Zeiler FA, Ercole A, Cabeleira M, et al. Univariate Comparison of Performance of Different Cerebrovascular Reactivity Indices for Outcome Association in Adult TBI: A CENTER-TBI Study. Anke A. ed. Acta Neurochirurgica 2019;161(6):1217–1227; doi: https://dx.doi.org/10.1007/s00701-019-03844-1.

8. Czosnyka M, Smielewski P, Kirkpatrick P, et al. Continuous Assessment of the Cerebral Vasomotor Reactivity in Head Injury. Neurosurgery 1997;41(1):11–17; discussion 17-19; doi: 10.1097/00006123-199707000-00005.

9. Rosenfeld JV, Maas AI, Bragge P, et al. Early Management of Severe Traumatic Brain Injury. The Lancet 2012;380(9847):1088–1098; doi: 10.1016/S0140-6736(12)60864-2.

10. Thelin EP, Tajsic T, Zeiler FA, et al. Monitoring the Neuroinflammatory Response Following Acute Brain Injury. Front Neurol 2017;8:351; doi: 10.3389/fneur.2017.00351.

11. Stovell MG, Yan J-L, Sleigh A, et al. Assessing Metabolism and Injury in Acute Human Traumatic Brain Injury with Magnetic Resonance Spectroscopy: Current and Future Applications. Front Neurol 2017;8:426; doi: 10.3389/fneur.2017.00426.

12. Timofeev I, Carpenter KLH, Nortje J, et al. Cerebral Extracellular Chemistry and Outcome Following Traumatic Brain Injury: A Microdialysis Study of 223 Patients. Brain 2011;134(Pt 2):484–494; doi: 10.1093/brain/awq353.

13. Czosnyka M, Balestreri M, Steiner L, et al. Age, Intracranial Pressure, Autoregulation, and Outcome after Brain Trauma. Journal of Neurosurgery 2005;102(3):450–454; doi: 10.3171/jns.2005.102.3.0450.

14. Batson C, Gomez A, Sainbhi AS, et al. Association of Age and Sex With Multi-Modal Cerebral Physiology in Adult Moderate/Severe Traumatic Brain Injury: A Narrative Overview and Future Avenues for Personalized Approaches. Front Pharmacol 2021;12:676154; doi: 10.3389/fphar.2021.676154.

15. Batson C, Stein KY, Gomez A, et al. Intracranial Pressure–Derived Cerebrovascular Reactivity Indices, Chronological Age, and Biological Sex in Traumatic Brain Injury: A Scoping Review. Neurotrauma Reports 2022;3(1):44–56; doi: 10.1089/neur.2021.0054.

16. Hasen M, Almojuela A and Zeiler FA. Autonomic Dysfunction and Associations with Functional and Neurophysiological Outcome in Moderate/Severe Traumatic Brain Injury: A Scoping Review. Journal of Neurotrauma 2019;36(10):1491–1504; doi: 10.1089/neu.2018.6073.

17. Lazaridis C, DeSantis SM, Smielewski P, et al. Patient-Specific Thresholds of Intracranial Pressure in Severe Traumatic Brain Injury. J Neurosurg 2014;120(4):893–900; doi: 10.3171/2014.1.JNS131292.

18. Zeiler FA, McFadyen C, Newcombe VFJ, et al. Genetic Influences on Patient-Oriented Outcomes in Traumatic Brain Injury: A Living Systematic Review of Non-Apolipoprotein E Single-Nucleotide Polymorphisms. J Neurotrauma 2019; doi: 10.1089/neu.2017.5583.

19. Beqiri E, Smielewski P, Robba C, et al. Feasibility of Individualised Severe Traumatic Brain Injury Management Using an Automated Assessment of Optimal Cerebral Perfusion Pressure: The COGiTATE Phase II Study Protocol. BMJ Open 2019;9(9):e030727; doi: 10.1136/bmjopen-2019-030727.

20. Zeiler FA and Czosnyka M. Monitoring in Neurotrauma. n.d.; p. 24.

21. Hawryluk GWJ, Aguilera S, Buki A, et al. A Management Algorithm for Patients with Intracranial Pressure Monitoring: The Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med 2019;45(12):1783–1794; doi: 10.1007/s00134-019-05805-9.

22. Chesnut R, Aguilera S, Buki A, et al. A Management Algorithm for Adult Patients with Both Brain Oxygen and Intracranial Pressure Monitoring: The Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). Intensive Care Med 2020;46(5):919–929; doi: 10.1007/s00134-019-05900-x.

23. Anonymous. Monitoring in Neurotrauma. n.d.

24. Zeiler FA, Ercole A, Cabeleira M, et al. Compensatory-Reserve-Weighted Intracranial Pressure versus Intracranial Pressure for Outcome Association in Adult Traumatic Brain

Injury: A CENTER-TBI Validation Study. Acta Neurochirurgica 2019;161(7):1275–1284; doi: 10.1007/s00701-019-03915-3.

25. Hasen M, Gomez A, Froese L, et al. Alternative Continuous Intracranial Pressure-Derived Cerebrovascular Reactivity Metrics in Traumatic Brain Injury: A Scoping Overview. Acta Neurochir 2020;162(7):1647–1662; doi: 10.1007/s00701-020-04378-7.

26. Gomez A, Dian J and Zeiler FA. Continuous and Entirely Non-Invasive Method for Cerebrovascular Reactivity Assessment: Technique and Implications. J Clin Monit Comput 2020; doi: 10.1007/s10877-020-00472-4.

27. Thiara S, Griesdale DE, Henderson WR, et al. Effect of Cerebral Perfusion Pressure on Acute Respiratory Distress Syndrome. Can J Neurol Sci 2018;45(3):313–319; doi: 10.1017/cjn.2017.292.

28. Aaslid R, Markwalder T-M and Nornes H. Noninvasive Transcranial Doppler Ultrasound Recording of Flow Velocity in Basal Cerebral Arteries. Journal of Neurosurgery 1982;57(6):769–774; doi: 10.3171/jns.1982.57.6.0769.

29. Aaslid R. The Doppler Principle Applied to Measurement of Blood Flow Velocity in Cerebral Arteries. In: Transcranial Doppler Sonography. (Aaslid R. ed) Springer Vienna: Vienna; 1986; pp. 22–38; doi: 10.1007/978-3-7091-8864-4_3.

30. Goraj B, Rifkinson-Mann S, Leslie DR, et al. Correlation of Intracranial Pressure and Transcranial Doppler Resistive Index after Head Trauma. 1994;7.

31. Kashif FM, Verghese GC, Novak V, et al. Model-Based Noninvasive Estimation of Intracranial Pressure from Cerebral Blood Flow Velocity and Arterial Pressure. Science Translational Medicine 2012;4(129):129ra44-129ra44; doi: 10.1126/scitranslmed.3003249.

32. Zweifel C, Czosnyka M, Carrera E, et al. Reliability of the Blood Flow Velocity Pulsatility Index for Assessment of Intracranial and Cerebral Perfusion Pressures in Head-Injured Patients. Neurosurgery 2012;71(4):853–861; doi: 10.1227/NEU.0b013e3182675b42.

33. Cardim D, Robba C, Bohdanowicz M, et al. Non-Invasive Monitoring of Intracranial Pressure Using Transcranial Doppler Ultrasonography: Is It Possible? Neurocrit Care 2016;25(3):473–491; doi: 10.1007/s12028-016-0258-6.

34. Czosnyka M and Kirkpatrick PJ. Cerebral Perfusion Pressure in Head-Injured Patients: A Noninvasive Assessment Using Transcranial Doppler Ultrasonography. J Neurosurg 1998;88:7.

35. Rasulo FA, Calza S, Robba C, et al. Transcranial Doppler as a Screening Test to Exclude Intracranial Hypertension in Brain-Injured Patients: The IMPRESSIT-2 Prospective Multicenter International Study. Crit Care 2022;26(1):110; doi: 10.1186/s13054-022-03978-2.

36. Tazarourte K, Atchabahian A, Tourtier J-P, et al. Pre-Hospital Transcranial Doppler in Severe Traumatic Brain Injury: A Pilot Study: Pre-Hospital Transcranial Doppler. Acta Anaesthesiologica Scandinavica 2011;55(4):422–428; doi: 10.1111/j.1399-6576.2010.02372.x.

37. Okonkwo DO, Shutter LA, Moore C, et al. Brain Oxygen Optimization in Severe Traumatic Brain Injury Phase-II: A Phase II Randomized Trial. Crit Care Med 2017;45(11):1907–1914; doi: 10.1097/CCM.0000000000002619.

38. Zeiler FA, Thelin EP, Helmy A, et al. A Systematic Review of Cerebral Microdialysis and Outcomes in TBI: Relationships to Patient Functional Outcome, Neurophysiologic Measures, and Tissue Outcome. Acta Neurochir 2017;159(12):2245–2273; doi: 10.1007/s00701-017-3338-2.

39. Mathieu F, Khellaf A, Thelin EP, et al. Continuous Thermal Diffusion-Based Cerebral Blood Flow Monitoring in Adult Traumatic Brain Injury: A Scoping Systematic Review. Journal of Neurotrauma 2019;36(11):1707–1723; doi: 10.1089/neu.2018.6309.

40. Le Roux P, Menon DK, Citerio G, et al. Consensus Summary Statement of the International Multidisciplinary Consensus Conference on Multimodality Monitoring in Neurocritical Care: A Statement for Healthcare Professionals from the Neurocritical Care Society and the European Society of Intensive Care Medicine. Neurocrit Care 2014;21 Suppl 2:S1-26; doi: 10.1007/s12028-014-0041-5.

41. Dickman CA, Carter LP, Baldwin HZ, et al. Continuous Regional Cerebral Blood Flow Monitoring in Acute Craniocerebral Trauma. Neurosurgery 1991;28(3):467–472; doi: 10.1097/00006123-199103000-00026.

42. Schröder ML and Muizelaar JP. Monitoring of Regional Cerebral Blood Flow (CBF) in Acute Head Injury by Thermal Diffusion. In: Monitoring of Cerebral Blood Flow and Metabolism in Intensive Care. (Unterberg AW, Schneider G-H, and Lanksch WR. eds) Springer Vienna: Vienna; 1993; pp. 47–49; doi: 10.1007/978-3-7091-9302-0_8.

43. Hlatky R, Furuya Y, Robertson CS, et al. Brain Tissue P02: Correlation with Cerebral Blood Flow. n.d.;2.

44. Hutchinson PJ, Jalloh I, Helmy A, et al. Consensus Statement from the 2014 International Microdialysis Forum. Intensive Care Med 2015;41(9):1517–1528; doi: 10.1007/s00134-015-3930-y.

45. Mathieu F, Khellaf A, Ku JC, et al. Continuous Near-Infrared Spectroscopy Monitoring in Adult Traumatic Brain Injury: A Systematic Review. Journal of Neurosurgical Anesthesiology 2020;32(4):288–299; doi: 10.1097/ANA.0000000000000620.

46. Oddo M, Schmidt JM, Carrera E, et al. Impact of Tight Glycemic Control on Cerebral Glucose Metabolism after Severe Brain Injury: A Microdialysis Study. Crit Care Med 2008;36(12):3233–3238; doi: 10.1097/CCM.0b013e31818f4026.

47. Stein NR, McArthur DL, Etchepare M, et al. Early Cerebral Metabolic Crisis After TBI Influences Outcome Despite Adequate Hemodynamic Resuscitation. Neurocrit Care 2012;17(1):49–57; doi: 10.1007/s12028-012-9708-y.

48. Vespa PM, McArthur D, O'Phelan K, et al. Persistently Low Extracellular Glucose Correlates with Poor Outcome 6 Months after Human Traumatic Brain Injury despite a Lack of Increased Lactate: A Microdialysis Study. J Cereb Blood Flow Metab 2003;23(7):865–877; doi: 10.1097/01.WCB.0000076701.45782.EF.

49. Zimphango C, Alimagham FC, Carpenter KLH, et al. Monitoring Neurochemistry in Traumatic Brain Injury Patients Using Microdialysis Integrated with Biosensors: A Review. Metabolites 2022;12(5):393; doi: 10.3390/metabo12050393.

50. Wijayatilake DS, Talati C and Panchatsharam S. The Monitoring and Management of Severe Traumatic Brain Injury in the United Kingdom: Is There a Consensus? Journal of Neurosurgical Anesthesiology 2015;27(3):241–245; doi: 10.1097/ANA.0000000000000143.

51. van Santbrink H, Schouten JW, Steyerberg EW, et al. Serial Transcranial Doppler Measurements in Traumatic Brain Injury with Special Focus on the Early Posttraumatic Period. n.d.;9.

52. Zurynski YA, Dorsch NWC and Fearnside MR. Incidence and Effects of Increased Cerebral Blood Flow Velocity after Severe Head Injury: A Transcranial Doppler Ultrasound Study II. Effect of Vasospasm and Hyperemia on Outcome. Journal of the Neurological Sciences 1995;134(1–2):41–46; doi: 10.1016/0022-510X(95)00178-X.

53. Chan K-H, Miller JD, Dearden NM, et al. The Effect of Changes in Cerebral Perfusion Pressure upon Middle Cerebral Artery Blood Flow Velocity and Jugular Bulb Venous Oxygen Saturation after Severe Brain Injury. Journal of Neurosurgery 1992;77(1):55–61; doi: 10.3171/jns.1992.77.1.0055.

54. Moreno JA, Mesalles E, Gener J, et al. Evaluating the Outcome of Severe Head Injury with Transcranial Doppler Ultrasonography. Neurosurg Focus 2000;8(1):e8; doi: 10.3171/foc.2000.8.1.1702.

55. Fatima N, Shuaib A, Chughtai T, et al. The Role of Transcranial Doppler in Traumatic Brain Injury: A Systemic Review and Meta-Analysis. Asian J Neurosurg 2019;14(3):626; doi: 10.4103/ajns.AJNS_42_19.

56. Sokoloff C, Williamson D, Serri K, et al. Clinical Usefulness of Transcranial Doppler as a Screening Tool for Early Cerebral Hypoxic Episodes in Patients with Moderate and Severe Traumatic Brain Injury. Neurocrit Care 2020;32(2):486–491; doi: 10.1007/s12028-019-00763-y.

57. Ziegler D, Cravens G, Angles G, et al. Use of Transcranial Doppler in Patients with Severe Traumatic Brain Injury. Crit Care 2010;14(Suppl 1):P292; doi: 10.1186/cc8524.

58. Zweifel C, Castellani G, Czosnyka M, et al. Noninvasive Monitoring of Cerebrovascular Reactivity with Near Infrared Spectroscopy in Head-Injured Patients. Journal of Neurotrauma 2010;27(11):1951–1958; doi: 10.1089/neu.2010.1388.

59. Weatherall A, Skowno J, Lansdown A, et al. Feasibility of Cerebral Near-Infrared Spectroscopy Monitoring in the Pre-Hospital Environment. Acta Anaesthesiol Scand 2012;56(2):172–177; doi: 10.1111/j.1399-6576.2011.02591.x.

60. Storm C, Leithner C, Krannich A, et al. Regional Cerebral Oxygen Saturation after Cardiac Arrest in 60 Patients—A Prospective Outcome Study. 2014;5.

61. Alotaiby T, El-Samie FEA, Alshebeili SA, et al. A Review of Channel Selection Algorithms for EEG Signal Processing. EURASIP J Adv Signal Process 2015;2015(1):66; doi: 10.1186/s13634-015-0251-9.

62. Anonymous. Guideline Three: Minimum Technical Standards for EEG Recording in Suspected Cerebral Death. Journal of Clinical Neurophysiology 1986;3:12–17; doi: 10.1097/00004691-198610001-00004.

63. Lassen NA. Regulation of Cerebral Circulation. Acta Anaesthesiologica Scandinavica 1971;15:78–80; doi: 10.1111/j.1399-6576.1971.tb00661.x.

64. Rangel-Castilla L, Gasco J, Nauta HJW, et al. Cerebral Pressure Autoregulation in Traumatic Brain Injury. Neurosurg Focus 2008;25(4):E7; doi: 10.3171/FOC.2008.25.10.E7.

65. Armstead WM. Cerebral Blood Flow Autoregulation and Dysautoregulation. Anesthesiol Clin 2016;34(3):465–477; doi: 10.1016/j.anclin.2016.04.002.

66. Santos E, Zheng Z, Unterberg AW, et al. Long Pressure Reactivity Index (L-PRx) as a Measure of Autoregulation Correlates with Outcome in Traumatic Brain Injury Patients. Acta Neurochirurgica 2012;154(9):1575–1581; doi: http://dx.doi.org/10.1007/s00701-012-1423-0.

67. Brady KM, Lee JK, Kibler KK, et al. Continuous Measurement of Autoregulation by Spontaneous Fluctuations in Cerebral Perfusion Pressure: Comparison of 3 Methods. Stroke 2008;39(9):2531–2537; doi: 10.1161/STROKEAHA.108.514877.

68. Zeiler FA, Donnelly J, Calviello L, et al. Validation of Pressure Reactivity and Pulse Amplitude Indices against the Lower Limit of Autoregulation, Part I: Experimental Intracranial Hypertension. J Neurotrauma 2018;35(23):2803–2811; doi: 10.1089/neu.2017.5603.

69. Zeiler FA, Lee JK, Smielewski P, et al. Validation of Intracranial Pressure-Derived Cerebrovascular Reactivity Indices against the Lower Limit of Autoregulation, Part II: Experimental Model of Arterial Hypotension. J Neurotrauma 2018;35(23):2812–2819; doi: 10.1089/neu.2017.5604.

70. Sorrentino E, Diedler J, Kasprowicz M, et al. Critical Thresholds for Cerebrovascular Reactivity After Traumatic Brain Injury. Neurocrit Care 2012;16(2):258–266; doi: 10.1007/s12028-011-9630-8.

71. Donnelly J, Czosnyka M, Adams H, et al. Twenty-Five Years of Intracranial Pressure Monitoring After Severe Traumatic Brain Injury: A Retrospective, Single-Center Analysis. Neurosurgery 2019;85(1):E75–E82; doi: 10.1093/neuros/nyy468.

72. Zeiler FA, Donnelly J, Smielewski P, et al. Critical Thresholds of Intracranial Pressure-Derived Continuous Cerebrovascular Reactivity Indices for Outcome Prediction in Noncraniectomized Patients with Traumatic Brain Injury. Journal of Neurotrauma 2018;35(10):1107–1115; doi: 10.1089/neu.2017.5472.

73. Zeiler FA, Ercole A, Beqiri E, et al. Association between Cerebrovascular Reactivity Monitoring and Mortality Is Preserved When Adjusting for Baseline Admission Characteristics in Adult Traumatic Brain Injury: A CENTER-TBI Study. J Neurotrauma 2020;37(10):1233–1241; doi: 10.1089/neu.2019.6808.

74. Mathieu F, Newcombe V, Whitehouse D, et al. Relationship between Measures of Cerebrovascular Reactivity and Intracranial Lesion Progression in Acute TBI Patients. Journal of Neurotrauma 2019;36(13):A59–A60; doi: http://dx.doi.org/10.1089/neu.2019.29100.abstracts.

75. Zeiler FA, Beqiri E, Cabeleira M, et al. Brain Tissue Oxygen and Cerebrovascular Reactivity in Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury Exploratory Analysis of Insult Burden. J Neurotrauma 2020;37(17):1854–1863; doi: 10.1089/neu.2020.7024.

76. Zeiler FA, Ercole A, Cabeleira M, et al. Descriptive Analysis of Low versus Elevated Intracranial Pressure on Cerebral Physiology in Adult Traumatic Brain Injury: A CENTER-TBI Exploratory Study. Acta Neurochir (Wien) 2020;162(11):2695–2706; doi: 10.1007/s00701-020-04485-5.

77. Aries MJH, Czosnyka M, Budohoski KP, et al. Continuous Monitoring of Cerebrovascular Reactivity Using Pulse Waveform of Intracranial Pressure. Neurocrit Care 2012;17(1):67–76; doi: 10.1007/s12028-012-9687-z.

78. Zeiler FA, Donnelly J, Menon DK, et al. A Description of a New Continuous Physiological Index in Traumatic Brain Injury Using the Correlation between Pulse Amplitude of Intracranial Pressure and Cerebral Perfusion Pressure. Journal of Neurotrauma 2018;35(7):963–974; doi: 10.1089/neu.2017.5241.

79. Zeiler FA, Mathieu F, Monteiro M, et al. Diffuse Intracranial Injury Patterns Are Associated with Impaired Cerebrovascular Reactivity in Adult Traumatic Brain Injury: A CENTER-TBI Validation Study. J Neurotrauma 2020;37(14):1597–1608; doi: 10.1089/neu.2019.6959.

80. Zeiler FA, Kim D-J, Cabeleira M, et al. Impaired Cerebral Compensatory Reserve Is Associated with Admission Imaging Characteristics of Diffuse Insult in Traumatic Brain Injury. Acta Neurochir (Wien) 2018;160(12):2277–2287; doi: 10.1007/s00701-018-3681-y.

81. Kim D-J, Czosnyka Z, Keong N, et al. Index of Cerebrospinal Compensatory Reserve in Hydrocephalus. Neurosurgery 2009;64(3):494–501; doi: http://dx.doi.org/10.1227/01.NEU.0000338434.59141.89.

82. Calviello L, Donnelly J, Cardim D, et al. Compensatory-Reserve-Weighted Intracranial Pressure and Its Association with Outcome After Traumatic Brain Injury. Neurocrit Care 2018;28(2):212–220; doi: 10.1007/s12028-017-0475-7.

83. McKetton L, Sobczyk O, Duffin J, et al. The Aging Brain and Cerebrovascular Reactivity. NeuroImage 2018;181:132–141; doi: 10.1016/j.neuroimage.2018.07.007.

84. Miller KB, Howery AJ, Rivera-Rivera LA, et al. Age-Related Reductions in Cerebrovascular Reactivity Using 4D Flow MRI. Front Aging Neurosci 2019;11:281; doi: 10.3389/fnagi.2019.00281.

85. Taneja K, Liu P, Xu C, et al. Quantitative Cerebrovascular Reactivity in Normal Aging: Comparison Between Phase-Contrast and Arterial Spin Labeling MRI. Front Neurol 2020;11:758; doi: 10.3389/fneur.2020.00758.

86. Mariappan R, Mehta J, Chui J, et al. Cerebrovascular Reactivity to Carbon Dioxide Under Anesthesia: A Qualitative Systematic Review. Journal of Neurosurgical Anesthesiology 2015;27(2):123–135; doi: 10.1097/ANA.0000000000000092.

87. Aguilar-Navarro SG, Mimenza-Alvarado AJ, Corona-Sevilla I, et al. Cerebral Vascular Reactivity in Frail Older Adults with Vascular Cognitive Impairment. Brain Sciences 2019;9(9):214; doi: 10.3390/brainsci9090214.

88. Klein T, Bailey TG, Wollseiffen P, et al. The Effect of Age on Cerebral Blood Flow Responses during Repeated and Sustained Stand to Sit Transitions. Physiol Rep 2020;8(9); doi: 10.14814/phy2.14421.

89. Tomoto T, Riley J, Turner M, et al. Cerebral Vasomotor Reactivity during Hypo- and Hypercapnia across the Adult Lifespan. J Cereb Blood Flow Metab 2020;40(3):600–610; doi: 10.1177/0271678X19828327.

90. Camici GG, Savarese G, Akhmedov A, et al. Molecular Mechanism of Endothelial and Vascular Aging: Implications for Cardiovascular Disease. 2015; doi: 10.5167/UZH-155179.

91. Grinberg LT, Korczyn AD and Heinsen H. Cerebral Amyloid Angiopathy Impact on Endothelium. Experimental Gerontology 2012;47(11):838–842; doi: 10.1016/j.exger.2012.08.005.

92. Weller RO, Hawkes CA, Kalaria RN, et al. White Matter Changes in Dementia: Role of Impaired Drainage of Interstitial Fluid: White Matter Changes and Impaired Drainage of ISF. Brain Pathology 2015;25(1):63–78; doi: 10.1111/bpa.12218.

93. Qi X and Ma J. The Role of Amyloid Beta Clearance in Cerebral Amyloid Angiopathy: More Potential Therapeutic Targets. Transl Neurodegener 2017;6(1):22; doi: 10.1186/s40035-017-0091-7.

94. Hamel E, Nicolakakis N, Aboulkassim T, et al. Oxidative Stress and Cerebrovascular Dysfunction in Mouse Models of Alzheimer's Disease: Oxidative Stress in Alzheimer's Disease. Experimental Physiology 2008;93(1):116–120; doi: 10.1113/expphysiol.2007.038729.

95. Carvalho C and Moreira PI. Oxidative Stress: A Major Player in Cerebrovascular Alterations Associated to Neurodegenerative Events. Front Physiol 2018;9:806; doi: 10.3389/fphys.2018.00806.

96. Wang X, Liu Y, Jia Y, et al. Proteome Profiling of Cerebral Vessels in Rhesus Macaques: Dysregulation of Antioxidant Activity and Extracellular Matrix Proteins Contributes to Cerebrovascular Aging in Rhesus Macaques. Front Aging Neurosci 2019;11:293; doi: 10.3389/fnagi.2019.00293.

97. Gu Y, Gutierrez J, Meier IB, et al. Circulating Inflammatory Biomarkers Are Related to Cerebrovascular Disease in Older Adults. Neurol Neuroimmunol Neuroinflamm 2019;6(1):e521; doi: 10.1212/NXI.0000000000000521.

98. Low A, Mak E, Rowe JB, et al. Inflammation and Cerebral Small Vessel Disease: A Systematic Review. Ageing Research Reviews 2019;53:100916; doi: 10.1016/j.arr.2019.100916.

99. Mészáros Á, Molnár K, Nógrádi B, et al. Neurovascular Inflammaging in Health and Disease. Cells 2020;9(7):1614; doi: 10.3390/cells9071614.

100. Zeiler FA, Thelin EP, Czosnyka M, et al. Cerebrospinal Fluid and Microdialysis Cytokines in Severe Traumatic Brain Injury: A Scoping Systematic Review. Front Neurol 2017;8:331; doi: 10.3389/fneur.2017.00331.

101. Thelin EP, Hall CE, Gupta K, et al. Elucidating Pro-Inflammatory Cytokine Responses after Traumatic Brain Injury in a Human Stem Cell Model. Journal of Neurotrauma 2018;35(2):341–352; doi: 10.1089/neu.2017.5155.

102. Cardoso AL, Fernandes A, Aguilar-Pimentel JA, et al. Towards Frailty Biomarkers: Candidates from Genes and Pathways Regulated in Aging and Age-Related Diseases. Ageing Research Reviews 2018;47:214–277; doi: 10.1016/j.arr.2018.07.004.

103. Maas AIR, Menon DK, Adelson PD, et al. Traumatic Brain Injury: Integrated Approaches to Improve Prevention, Clinical Care, and Research. Lancet Neurol 2017;16(12):987–1048; doi: 10.1016/S1474-4422(17)30371-X.

104. Steyerberg EW, Wiegers E, Sewalt C, et al. Case-Mix, Care Pathways, and Outcomes in Patients with Traumatic Brain Injury in CENTER-TBI: A European Prospective, Multicentre, Longitudinal, Cohort Study. Lancet Neurol 2019;18(10):923–934; doi: 10.1016/S1474-4422(19)30232-7.

105. Mikolić A, van Klaveren D, Oude Groeniger J, et al. Differences between Men and Women in Treatment and Outcome after Traumatic Brain Injury. Journal of Neurotrauma 2020;neu.2020.7228; doi: 10.1089/neu.2020.7228.

106. Clevenger AC, Kim H, Salcedo E, et al. Endogenous Sex Steroids Dampen Neuroinflammation and Improve Outcome of Traumatic Brain Injury in Mice. J Mol Neurosci 2018;64(3):410–420; doi: 10.1007/s12031-018-1038-x.

107. Khaksari M, Soltani Z and Shahrokhi N. Effects of Female Sex Steroids Administration on Pathophysiologic Mechanisms in Traumatic Brain Injury. Transl Stroke Res 2018;9(4):393–416; doi: 10.1007/s12975-017-0588-5.

108. Wright DW, Kellermann AL, Hertzberg VS, et al. ProTECT: A Randomized Clinical Trial of Progesterone for Acute Traumatic Brain Injury. Annals of Emergency Medicine 2007;49(4):391-402.e2; doi: 10.1016/j.annemergmed.2006.07.932.

109. Skolnick BE, Maas AI, Narayan RK, et al. A Clinical Trial of Progesterone for Severe Traumatic Brain Injury. N Engl J Med 2014;371(26):2467–2476; doi: 10.1056/NEJMoa1411090.

110. Pan Z-Y, Zhao Y-H, Huang W-H, et al. Effect of Progesterone Administration on the Prognosis of Patients with Severe Traumatic Brain Injury: A Meta-Analysis of Randomized Clinical Trials. Drug Des Devel Ther 2019;13:265–273; doi: 10.2147/DDDT.S192633.

111. Lu X-Y, Sun H, Li Q-Y, et al. Progesterone for Traumatic Brain Injury: A Meta-Analysis Review of Randomized Controlled Trials. World Neurosurgery 2016;90:199–210; doi: 10.1016/j.wneu.2016.02.110.

112. Ma J, Huang S, Qin S, et al. Progesterone for Acute Traumatic Brain Injury. Cochrane Injuries Group. ed. Cochrane Database of Systematic Reviews 2016;2017(2); doi: 10.1002/14651858.CD008409.pub4.

113. Pan Z-Y, Zhao Y-H, Huang W-H, et al. Effect of Progesterone Administration on the Prognosis of Patients with Severe Traumatic Brain Injury: A Meta-Analysis of Randomized Clinical Trials. DDDT 2019;Volume 13:265–273; doi: 10.2147/DDDT.S192633.

114. Schumacher M, Denier C, Oudinet J-P, et al. Progesterone Neuroprotection: The Background of Clinical Trial Failure. The Journal of Steroid Biochemistry and Molecular Biology 2016;160:53–66; doi: 10.1016/j.jsbmb.2015.11.010.

115. Korley F, Pauls Q, Yeatts SD, et al. Progesterone Treatment Does Not Decrease Serum Levels of Biomarkers of Glial and Neuronal Cell Injury in Moderate and Severe Traumatic Brain Injury Subjects: A Secondary Analysis of the Progesterone for Traumatic Brain

Injury, Experimental Clinical Treatment (ProTECT) III Trial. Journal of Neurotrauma 2021;38(14):1953–1960; doi: 10.1089/neu.2020.7072.

116. Krause DN, Duckles SP and Pelligrino DA. Influence of Sex Steroid Hormones on Cerebrovascular Function. Journal of Applied Physiology 2006;101(4):1252–1261; doi: 10.1152/japplphysiol.01095.2005.

117. Deer RR and Stallone JN. Effects of Age and Sex on Cerebrovascular Function in the Rat Middle Cerebral Artery. Biol Sex Differ 2014;5(1):12; doi: 10.1186/s13293-014-0012-8.

118. De Silva TM, Broughton BRS, Drummond GR, et al. Gender Influences Cerebral Vascular Responses to Angiotensin II Through Nox2-Derived Reactive Oxygen Species. Stroke 2009;40(4):1091–1097; doi: 10.1161/STROKEAHA.108.531707.

119. Arrick DM, Li C and Mayhan WG. Sex-Related Differences in Reactivity of Cerebral Arterioles during Moderate Exercise Training. Microcirculation 2016;23(7):549–557; doi: 10.1111/micc.12306.

120. Brotfain E, E. Gruenbaum S, Boyko M, et al. Neuroprotection by Estrogen and Progesterone in Traumatic Brain Injury and Spinal Cord Injury. CN 2016;14(6):641–653; doi: 10.2174/1570159X14666160309123554.

121. Martin-Jiménez C, Gaitán-Vaca DM, Areiza N, et al. Astrocytes Mediate Protective Actions of Estrogenic Compounds after Traumatic Brain Injury. Neuroendocrinology 2019;108(2):142–160; doi: 10.1159/000495078.

122. Yilmaz C, Karali K, Fodelianaki G, et al. Neurosteroids as Regulators of Neuroinflammation. Frontiers in Neuroendocrinology 2019;55:100788; doi: 10.1016/j.yfrne.2019.100788.

123. Späni CB, Braun DJ and Van Eldik LJ. Sex-Related Responses after Traumatic Brain Injury: Considerations for Preclinical Modeling. Frontiers in Neuroendocrinology 2018;50:52–66; doi: 10.1016/j.yfrne.2018.03.006.

124. Reed JT, Pareek T, Sriramula S, et al. Aging Influences Cerebrovascular Myogenic Reactivity and BK Channel Function in a Sex-Specific Manner. Cardiovascular Research 2020;116(7):1372–1385; doi: 10.1093/cvr/cvz314.

125. Higgins J, Thomas J, Chandler J, et al. Cochrane Handbook for Systematic Reviews of Interventions. 2nd ed. John Wiley & Sons: Chichester, UK; 2019.

126. Czosnyka M, Hutchinson P, Timofeev I, et al. Gender-Related Differences in Intracranial Hypertension and Outcome after Traumatic Brain Injury. Acta Neurochirurgica Supplements 2008;102:25–28; doi: http://dx.doi.org/10.1007/978-3-211-85578-2_5.

127. Adams H, Donnelly J, Czosnyka M, et al. Temporal Profile of Intracranial Pressure and Cerebrovascular Reactivity in Severe Traumatic Brain Injury and Association with Fatal

Outcome: An Observational Study. Schreiber M. ed. PLoS Med 2017;14(7):e1002353; doi: 10.1371/journal.pmed.1002353.

128. Nourallah B, Zeiler FA, Calviello L, et al. Critical Thresholds for Intracranial Pressure Vary over Time in Non-Craniectomised Traumatic Brain Injury Patients. Acta Neurochir 2018;160(7):1315–1324; doi: 10.1007/s00701-018-3555-3.

129. Martini RP, Deem S, Yanez ND, et al. Management Guided by Brain Tissue Oxygen Monitoring and Outcome Following Severe Traumatic Brain Injury: Clinical Article. JNS 2009;111(4):644–649; doi: 10.3171/2009.2.JNS08998.

130. Stiefel MF, Spiotta A, Gracias VH, et al. Reduced Mortality Rate in Patients with Severe Traumatic Brain Injury Treated with Brain Tissue Oxygen Monitoring. Journal of Neurosurgery 2005;103(5):805–811; doi: 10.3171/jns.2005.103.5.0805.

131. Adatia K, Geocadin RG, Healy R, et al. Effect of Body Temperature on Cerebral Autoregulation in Acutely Comatose Neurocritically Ill Patients: Critical Care Medicine 2018;46(8):e733–e741; doi: 10.1097/CCM.0000000000003181.

132. Adatia K, Geocadin RG, Healy R, et al. Lateral Brain Displacement and Cerebral Autoregulation in Acutely Comatose Patients. Critical Care Medicine 2020;Publish Ahead of Print; doi: 10.1097/CCM.0000000000004365.

133. Dias C, Silva MJ, Pereira E, et al. Optimal Cerebral Perfusion Pressure Management at Bedside: A Single-Center Pilot Study. Neurocrit Care 2015;23(1):92–102; doi: 10.1007/s12028-014-0103-8.

134. Bouzat P, Francony G, Declety P, et al. Transcranial Doppler to Screen on Admission Patients With Mild to Moderate Traumatic Brain Injury. Neurosurgery 2011;68(6):1603–1610; doi: 10.1227/NEU.0b013e31820cd43e.

135. Cardim D, Czosnyka M, Chandrapatham K, et al. Arterial and Venous Cerebral Blood Flow Velocities and Their Correlation in Healthy Volunteers and Traumatic Brain Injury Patients. Journal of Neurosurgical Anesthesiology 2020;Publish Ahead of Print; doi: 10.1097/ANA.0000000000000704.

136. Hu K, Peng CK, Czosnyka M, et al. Nonlinear Assessment of Cerebral Autoregulation from Spontaneous Blood Pressure and Cerebral Blood Flow Fluctuations. Cardiovasc Eng 2008;8(1):60–71; doi: 10.1007/s10558-007-9045-5.

137. Zeiler FA, Donnelly J, Nourallah B, et al. Intracranial and Extracranial Injury Burden as Drivers of Impaired Cerebrovascular Reactivity in Traumatic Brain Injury. Journal of Neurotrauma 2018;35(14):1569–1577; doi: 10.1089/neu.2017.5595.

138. Kurtz P, Claassen J, Schmidt JM, et al. Reduced Brain/Serum Glucose Ratios Predict Cerebral Metabolic Distress and Mortality After Severe Brain Injury. Neurocrit Care 2013;19(3):311–319; doi: 10.1007/s12028-013-9919-x.

139. Mellergård P, Sjögren F and Hillman J. The Cerebral Extracellular Release of Glycerol, Glutamate, and FGF2 Is Increased in Older Patients Following Severe Traumatic Brain Injury. Journal of Neurotrauma 2012;29(1):112–118; doi: 10.1089/neu.2010.1732.

140. Chamoun R, Suki D, Gopinath SP, et al. Role of Extracellular Glutamate Measured by Cerebral Microdialysis in Severe Traumatic Brain Injury: Clinical Article. JNS 2010;113(3):564–570; doi: 10.3171/2009.12.JNS09689.

141. Clausen T, Khaldi A, Zauner A, et al. Cerebral Acid—Base Homeostasis after Severe Traumatic Brain Injury. Journal of Neurosurgery 2005;103(4):597–607; doi: 10.3171/jns.2005.103.4.0597.

142. Liu X, Donnelly J, Czosnyka M, et al. Cerebrovascular Pressure Reactivity Monitoring Using Wavelet Analysis in Traumatic Brain Injury Patients: A Retrospective Study. Schreiber M. ed. PLoS Med 2017;14(7):e1002348; doi: 10.1371/journal.pmed.1002348.

143. Czosnyka M, Hutchinson PJ, Balestreri M, et al. Monitoring and Interpretation of Intracranial Pressure after Head Injury. Acta neurochirurgica Supplement 2006;96:114–118.

144. Hiler M, Czosnyka M, Hutchinson P, et al. Predictive Value of Initial Computerized Tomography Scan, Intracranial Pressure, and State of Autoregulation in Patients with Traumatic Brain Injury. JNS 2006;104(5):731–737; doi: 10.3171/jns.2006.104.5.731.

145. Radolovich DK, Aries MJH, Castellani G, et al. Pulsatile Intracranial Pressure and Cerebral Autoregulation After Traumatic Brain Injury. Neurocrit Care 2011;15(3):379–386; doi: 10.1007/s12028-011-9553-4.

146. Pal S and Tyler JK. Epigenetics and Aging. Sci Adv 2016;2(7):e1600584; doi: 10.1126/sciadv.1600584.

147. Tollesfsbol TO. Epigenetics in Human Disease. Academic Press: London; Waltham, MA; 2012.

148. Farin A, Deutsch R, Biegon A, et al. Sex-Related Differences in Patients with Severe Head Injury: Greater Susceptibility to Brain Swelling in Female Patients 50 Years of Age and Younger. Journal of Neurosurgery 2003;98(1):32–36; doi: 10.3171/jns.2003.98.1.0032.

149. Zeiler FA, Ercole A, Beqiri E, et al. Cerebrovascular Reactivity Is Not Associated with Therapeutic Intensity in Adult Traumatic Brain Injury: A CENTER-TBI Analysis. Acta Neurochir (Wien) 2019;161(9):1955–1964; doi: 10.1007/s00701-019-03980-8.

150. Froese L, Dian J, Batson C, et al. The Impact of Vasopressor and Sedative Agents on Cerebrovascular Reactivity and Compensatory Reserve in Traumatic Brain Injury: An Exploratory Analysis. Neurotrauma Rep 2020;1(1):157–168; doi: 10.1089/neur.2020.0028.

151. Froese L, Dian J, Batson C, et al. The Impact of Hypertonic Saline on Cerebrovascular Reactivity and Compensatory Reserve in Traumatic Brain Injury: An Exploratory Analysis. Acta Neurochir (Wien) 2020;162(11):2683–2693; doi: 10.1007/s00701-020-04579-0.

152. Froese L, Batson C, Gomez A, et al. The Limited Impact of Current Therapeutic Interventions on Cerebrovascular Reactivity in Traumatic Brain Injury: A Narrative Overview. Neurocrit Care 2021;34:325–335; doi: 10.1007/s12028-020-01003-4.

153. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury. 2016;244.

154. Åkerlund CA, Donnelly J, Zeiler FA, et al. Impact of Duration and Magnitude of Raised Intracranial Pressure on Outcome after Severe Traumatic Brain Injury: A CENTER-TBI High-Resolution Group Study. PLoS One 2020;15(12):e0243427; doi: 10.1371/journal.pone.0243427.

155. Steiner LA, Balestreri M, Johnston AJ, et al. Effects of Moderate Hyperventilation on Cerebrovascular Pressure-Reactivity after Head Injury. Acta neurochirurgica Supplement 2005;95:17–20.

156. Zeiler FA, Cabeleira M, Hutchinson PJ, et al. Evaluation of the Relationship between Slow-Waves of Intracranial Pressure, Mean Arterial Pressure and Brain Tissue Oxygen in TBI: A CENTER-TBI Exploratory Analysis. J Clin Monit Comput 2021;35(4):711–722; doi: 10.1007/s10877-020-00527-6.

157. Zeiler FA, Donnelly J, Cardim D, et al. ICP Versus Laser Doppler Cerebrovascular Reactivity Indices to Assess Brain Autoregulatory Capacity. Neurocrit Care 2018;28(2):194–202; doi: 10.1007/s12028-017-0472-x.

158. Zeiler FA, Ercole A, Cabeleira M, et al. Patient-Specific ICP Epidemiologic Thresholds in Adult Traumatic Brain Injury: A CENTER-TBI Validation Study. Journal of Neurosurgical Anesthesiology 2021;33(1):28–38; doi: 10.1097/ANA.0000000000000616.

159. Zeiler FA, Ercole A, Placek MM, et al. Association Between Physiologic Signal Complexity and Outcomes in Moderate and Severe Traumatic Brain Injury: A CENTER-TBI Exploratory Analysis of Multiscale Entropy. Journal of Neurotrauma 2020;38:272–282; doi: 10.1089/neu.2020.7249.

160. Zeiler FA, Mathieu F, Monteiro M, et al. Systemic Markers of Injury and Injury Response Are Not Associated with Impaired Cerebrovascular Reactivity in Adult Traumatic Brain Injury: A Collaborative European Neurotrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study. J Neurotrauma 2021;38(7):870–878; doi: 10.1089/neu.2020.7304.

161. Jain V, Choudhary J and Pandit R. Blood Pressure Target in Acute Brain Injury. Indian J Crit Care Med 2019;23(Suppl 2):S136–S139; doi: 10.5005/jp-journals-10071-23191.

162. Zeiler FA, Ercole A, Cabeleira M, et al. Comparison of Performance of Different Optimal Cerebral Perfusion Pressure Parameters for Outcome Prediction in Adult Traumatic Brain Injury: A Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) Study. J Neurotrauma 2019;36(10):1505–1517; doi: 10.1089/neu.2018.6182.

163. Bricolo A, Turazzi S, Alexandre A, et al. Decerebrate Rigidity in Acute Head Injury. Journal of Neurosurgery 1977;47(5):680–698; doi: 10.3171/jns.1977.47.5.0680.

164. Hukkelhoven CWPM, Steyerberg EW, Rampen AJJ, et al. Patient Age and Outcome Following Severe Traumatic Brain Injury: An Analysis of 5600 Patients. Journal of Neurosurgery 2003;99(4):666–673; doi: 10.3171/jns.2003.99.4.0666.

165. Dhandapani S, Manju D, Sharma B, et al. Prognostic Significance of Age in Traumatic Brain Injury. J Neurosci Rural Pract 2012;3(2):131–135; doi: 10.4103/0976-3147.98208.

166. Dijkland SA, Helmrich IRAR, Nieboer D, et al. Outcome Prediction after Moderate and Severe Traumatic Brain Injury: External Validation of Two Established Prognostic Models in 1742 European Patients. J Neurotrauma 2021;38(10):1377–1388; doi: 10.1089/neu.2020.7300.

167. Maas AIR, Menon DK, Steyerberg EW, et al. Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): A Prospective Longitudinal Observational Study. Neurosurgery 2015;76(1):67–80; doi: 10.1227/NEU.0000000000000575.

168. Bernard F, Gallagher C, Griesdale D, et al. The CAnadian High-Resolution Traumatic Brain Injury (CAHR-TBI) Research Collaborative. Can J Neurol Sci 2020;47(4):551–556; doi: 10.1017/cjn.2020.54.

169. Lingsma H, Andriessen TMJC, Haitsema I, et al. Prognosis in Moderate and Severe Traumatic Brain Injury: External Validation of the IMPACT Models and the Role of Extracranial Injuries. Journal of Trauma and Acute Care Surgery 2013;74(2):639–646; doi: 10.1097/TA.0b013e31827d602e.

170. Calviello LA, Zeiler FA, Donnelly J, et al. Cerebrovascular Consequences of Elevated Intracranial Pressure After Traumatic Brain Injury. Acta neurochirurgica Supplement 2021;131:43–48; doi: https://dx.doi.org/10.1007/978-3-030-59436-7_10.

171. Donnelly J, Smielewski P, Adams H, et al. Observations on the Cerebral Effects of Refractory Intracranial Hypertension After Severe Traumatic Brain Injury. Neurocrit Care 2020;32(2):437–447; doi: 10.1007/s12028-019-00748-x.

172. Zeiler FA, Donnelly J, Menon DK, et al. Continuous Autoregulatory Indices Derived from Multi-Modal Monitoring: Each One Is Not Like the Other. J Neurotrauma 2017;34(22):3070–3080; doi: 10.1089/neu.2017.5129.

173. Bennis FC, Teeuwen B, Zeiler FA, et al. Improving Prediction of Favourable Outcome After 6 Months in Patients with Severe Traumatic Brain Injury Using Physiological Cerebral Parameters in a Multivariable Logistic Regression Model. Neurocrit Care 2020;33(2):542–551; doi: 10.1007/s12028-020-00930-6.

174. Young AMH, Donnelly J, Liu X, et al. Pre-Hospital Predictors of Impaired ICP Trends in Continuous Monitoring of Paediatric Traumatic Brain Injury Patients. Acta Neurochir Suppl 2018;126:7–10; doi: 10.1007/978-3-319-65798-1_2.

175. Young AMH, Guilfoyle MR, Donnelly J, et al. Multimodality Neuromonitoring in Severe Pediatric Traumatic Brain Injury. Pediatr Res 2018;83(1–1):41–49; doi: 10.1038/pr.2017.215.

176. Young AMH, Donnelly J, Liu X, et al. Computed Tomography Indicators of Deranged Intracranial Physiology in Paediatric Traumatic Brain Injury. Acta Neurochir Suppl 2018;126:29–34; doi: 10.1007/978-3-319-65798-1_7.

177. Kayhanian S, Young AMH, Ewen RL, et al. Thresholds for Identifying Pathological Intracranial Pressure in Paediatric Traumatic Brain Injury. Sci Rep 2019;9(1):3537; doi: 10.1038/s41598-019-39848-1.

178. Gomez A, Batson C, Froese L, et al. Genetic Variation and Impact on Outcome in Traumatic Brain Injury: An Overview of Recent Discoveries. Curr Neurol Neurosci Rep 2021;21(5):19; doi: 10.1007/s11910-021-01106-1.

179. Cabella B, Donnelly J, Cardim D, et al. An Association Between ICP-Derived Data and Outcome in TBI Patients: The Role of Sample Size. Neurocrit Care 2017;27(1):103–107; doi: 10.1007/s12028-016-0319-x.

180. Batson C, Froese L, Gomez A, et al. Impact of Age and Biological Sex on Cerebrovascular Reactivity in Adult Moderate/Severe Traumatic Brain Injury: An Exploratory Analysis. Neurotrauma Reports 2021;2(1):488–501; doi: 10.1089/neur.2021.0039.

181. Marshall LF, Marshall SB, Klauber MR, et al. The Diagnosis of Head Injury Requires a Classification Based on Computed Axial Tomography. J Neurotrauma 1992;9 Suppl 1:S287-292.

182. Maas AIR, Hukkelhoven CWPM, Marshall LF, et al. Prediction of Outcome in Traumatic Brain Injury with Computed Tomographic Characteristics: A Comparison between the Computed Tomographic Classification and Combinations of Computed Tomographic Predictors. Neurosurgery 2005;57(6):1173–1182; discussion 1173-1182; doi: 10.1227/01.neu.0000186013.63046.6b.

183. Zeiler FA, Cardim D, Donnelly J, et al. Transcranial Doppler Systolic Flow Index and ICP-Derived Cerebrovascular Reactivity Indices in Traumatic Brain Injury. Journal of Neurotrauma 2018;35(2):314–322; doi: 10.1089/neu.2017.5364.

184. Gómez PA, Lobato RD, Boto GR, et al. Age and Outcome after Severe Head Injury. Acta Neurochir (Wien) 2000;142(4):373–380; discussion 380-381; doi: 10.1007/s007010050445.

185. Schwarze JJ, Klingelhofer J, Raabe A, et al. Adaptive Noninvasive Assessment of Intracranial Pressure and Cerebral Autoregulation. Stroke 2003;34(1):84–89; doi: http://dx.doi.org/10.1161/01.STR.0000047849.01376.AE.

186. Ishikawa N, Nakamura K-I, Izumiyama-Shimomura N, et al. Changes of Telomere Status with Aging: An Update: Telomeres and Aging. Geriatrics & Gerontology International 2016;16:30–42; doi: 10.1111/ggi.12772.

187. Bisset ES and Howlett SE. The Biology of Frailty in Humans and Animals: Understanding Frailty and Promoting Translation. Aging Med 2019;2(1):27–34; doi: 10.1002/agm2.12058.

188. Zarzour A, Kim HW and Weintraub NL. Epigenetic Regulation of Vascular Diseases. ATVB 2019;39(6):984–990; doi: 10.1161/ATVBAHA.119.312193.

189. Brady KM, Shaffner DH, Lee JK, et al. Continuous Monitoring of Cerebrovascular Pressure Reactivity after Traumatic Brain Injury in Children. Pediatrics 2009;124(6):e1205–e1212; doi: http://dx.doi.org/10.1542/peds.2009-0550.

190. Sainbhi AS, Froese L, Gomez A, et al. Continuous Time-Domain Cerebrovascular Reactivity Metrics and Discriminate Capacity for the Upper and Lower Limits of Autoregulation: A Scoping Review of the Animal Literature. Neurotrauma Rep 2021;2(1):639–659; doi: 10.1089/neur.2021.0043.

191. Thelin EP, Raj R, Bellander B-M, et al. Comparison of High versus Low Frequency Cerebral Physiology for Cerebrovascular Reactivity Assessment in Traumatic Brain Injury: A Multi-Center Pilot Study. J Clin Monit Comput 2020;34(5):971–994; doi: 10.1007/s10877-019-00392-y.

192. Zeiler FA, Aries M, Cabeleira M, et al. Statistical Cerebrovascular Reactivity Signal Properties after Secondary Decompressive Craniectomy in Traumatic Brain Injury: A CENTER-TBI Pilot Analysis. Anke A. ed. Journal of Neurotrauma 2020;37(11):1306–1314; doi: https://dx.doi.org/10.1089/neu.2019.6726.

193. Howells T, Lewen A, Skold MK, et al. An Evaluation of Three Measures of Intracranial Compliance in Traumatic Brain Injury Patients. Intensive Care Medicine 2012;38(6):1061–8; doi: https://dx.doi.org/10.1007/s00134-012-2571-7.

194. Güiza F, Meyfroidt G, Piper I, et al. Cerebral Perfusion Pressure Insults and Associations with Outcome in Adult Traumatic Brain Injury. J Neurotrauma 2017;34(16):2425–2431; doi: 10.1089/neu.2016.4807.

195. Thelin EP, Zeiler FA, Ercole A, et al. Serial Sampling of Serum Protein Biomarkers for Monitoring Human Traumatic Brain Injury Dynamics: A Systematic Review. Front Neurol 2017;8:300; doi: 10.3389/fneur.2017.00300.

196. Zeiler FA, Ercole A, Czosnyka M, et al. Continuous Cerebrovascular Reactivity Monitoring in Moderate/Severe Traumatic Brain Injury: A Narrative Review of Advances in Neurocritical Care. British Journal of Anaesthesia 2020;124(4):440–453; doi: 10.1016/j.bja.2019.11.031.

197. McFadyen CA, Zeiler FA, Newcombe V, et al. Apolipoprotein E4 Polymorphism and Outcomes from Traumatic Brain Injury: A Living Systematic Review and Meta-Analysis. J Neurotrauma 2019; doi: 10.1089/neu.2018.6052.

198. Helmy A, Guilfoyle MR, Carpenter KLH, et al. Sex and the Cytokines: Are There Fundamental Differences in Response to Brain Injury? Neurosurgery 2011;69(4):E1029–E1030; doi: 10.1227/NEU.0b013e3182299839.

199. Helmy A, Carpenter KL, Menon DK, et al. The Cytokine Response to Human Traumatic Brain Injury: Temporal Profiles and Evidence for Cerebral Parenchymal Production. J Cereb Blood Flow Metab 2011;31(2):658–670; doi: 10.1038/jcbfm.2010.142.

200. Guilfoyle MR, Carpenter KLH, Helmy A, et al. Matrix Metalloproteinase Expression in Contusional Traumatic Brain Injury: A Paired Microdialysis Study. J Neurotrauma 2015;32(20):1553–1559; doi: 10.1089/neu.2014.3764.

201. Needham EJ, Helmy A, Zanier ER, et al. The Immunological Response to Traumatic Brain Injury. J Neuroimmunol 2019;332:112–125; doi: 10.1016/j.jneuroim.2019.04.005.

202. Killen MJ, Giorgi-Coll S, Helmy A, et al. Metabolism and Inflammation: Implications for Traumatic Brain Injury Therapeutics. Expert Rev Neurother 2019;19(3):227–242; doi: 10.1080/14737175.2019.1582332.

203. Orešič M, Posti JP, Kamstrup-Nielsen MH, et al. Human Serum Metabolites Associate With Severity and Patient Outcomes in Traumatic Brain Injury. EBioMedicine 2016;12:118–126; doi: 10.1016/j.ebiom.2016.07.015.

204. Helmy A, Guilfoyle MR, Carpenter KLH, et al. Recombinant Human Interleukin-1 Receptor Antagonist Promotes M1 Microglia Biased Cytokines and Chemokines Following Human Traumatic Brain Injury. J Cereb Blood Flow Metab 2016;36(8):1434–1448; doi: 10.1177/0271678X15620204.

205. Thelin EP, Carpenter KLH, Hutchinson PJ, et al. Microdialysis Monitoring in Clinical Traumatic Brain Injury and Its Role in Neuroprotective Drug Development. AAPS J 2017;19(2):367–376; doi: 10.1208/s12248-016-0027-7.

206. Yue JK, Vassar MJ, Lingsma HF, et al. Transforming Research and Clinical Knowledge in Traumatic Brain Injury Pilot: Multicenter Implementation of the Common Data Elements for Traumatic Brain Injury. J Neurotrauma 2013;30(22):1831–1844; doi: 10.1089/neu.2013.2970.

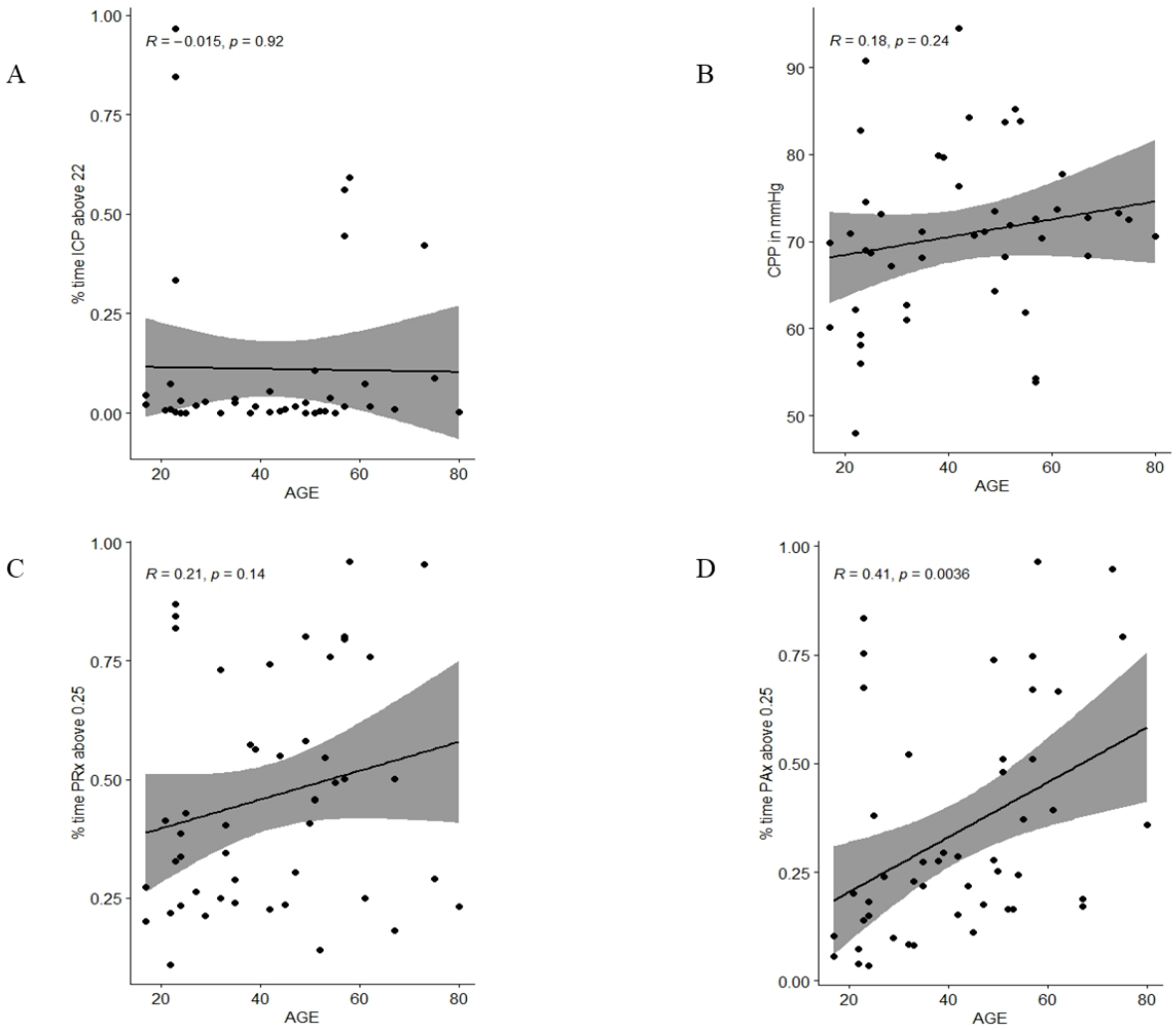
Appendix A: Cerebral Physiology Based on Biological Sex: Medians/IQRs and Mann-Whitney-U Testing of the Entire Recording Period

Physiological Variable	Males (n = 42)		Females (n = 7)		Mann-Whitney-U Test p-value
	Median	IQR	Median	IQR	
ICP (mm Hg)	9.5	7.1 – 13.3	18.5	12.0 – 22.9	**0.010**
% Time ICP > 20 mm Hg	2.3	0.3 – 7.2	38.0	6.8 – 82.6	**0.015**
% Time ICP > 22 mm Hg	1.6	0.2 – 4.2	29.8	3.1 – 77.4	**0.015**
MAP (mmHg)	80.9	77.4 – 88.0	81.9	80.8 – 86.2	0.812
CPP (mm Hg)	71.2	68.2 – 77.0	60.7	56.8 – 68.9	0.053
% Time CPP > 70 mm Hg	61.2	42.9 – 73.9	33.4	22.9 – 52.1	**0.026**
% Time CPP < 60 mm Hg	9.9	2.9 – 17.6	21.4	11.6 – 34.2	0.086
PRx (a.u.)	0.150	0.030 – 0.278	0.073	0.021 – 0.637	0.886
% Time PRx > 0	68.5	51.3 – 82.8	57.4	49.2 – 85.2	0.909
% Time PRx > 0.25	41.4	24.9 – 57.3	34.5	26.1 – 81.1	0.842
% Time PRx > 0.35	31.9	17.0 – 45.1	24.6	18.7 – 78.1	0.753
PAx (a.u.)	0.018	-0.098 – 0.210	0.017	-0.026 – 0.442	0.510
% Time PAx > 0	51.4	36.1 – 70.8	53.8	45.0 – 81.3	0.587
% Time PAx > 0.25	24.4	15.2 – 48.0	27.3	20.6 – 71.1	0.474
RAC (a.u.)	-0.191	(-0.313) – (-0.029)	-0.192	-0.355 – 0.283	0.819
% Time RAC > -0.10	40.6	27.0 – 60.4	38.5	25.6 – 79.1	0.864
% Time RAC > -0.05	36.9	23.3 – 55.8	33.9	22.4 – 76.9	0.797
RAP (a.u.)	0.592	0.406 – 0.736	0.695	0.560 – 0.802	0.170
% Time RAP > 0.4	75.9	56.6 – 85.0	85.1	73.1 – 91.8	0.170
Age (years)	44.5	27.5 – 54.8	24.0	23.0 – 34.0	0.092
Best Admission GCS	7.0	5.3 – 9.0	7.0	3.0 – 7.5	0.267
Best Admission GCS - Motor	5.0	3.0 – 5.0	5.0	1.0 – 5.0	0.572
Rotterdam CT Grade	4.5	4.0 – 5.0	5.0	4.0 – 5.5	0.638

a.u. = arbitrary units, AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, CT = computed tomography, GCS = Glasgow Coma Scale, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP =

compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values are those reaching statistical significance of 0.05 on Mann-Whitney-U Testing.

Appendix B: Scatterplots with 95% confidence interval between age and % time ICP > 22 mm Hg, mean CPP, % time PRx > 0.25 and % time PAx > 0.25 of the Entire Recording Period



p = p-value, R = Pearson Correlation Coefficient. Panel A - % Time with ICP >22 mm Hg vs. Age, Panel B – Mean CPP vs. Age, Panel C - % Time with PRx > +0.25 vs. Age, Panel D - % Time with PAx > +0.25 vs. Age. P-values recorded are for the Pearson correlation coefficient.

Appendix C: Cerebral Physiology Association with Trichotomized Age (Age < 40, Age 40 – 60, Age > 60): Medians/IQRs and Kruskal-Wallis Testing of the Entire Recording Period

Physiological Variable	Age < 40 years (n = 24)		Age 40 – 60 years (n = 18)		Age > 60 years (n = 7)		Kruskal-Wallis Test p-value
	Median	IQR	Median	IQR	Median	IQR	
ICP (mm Hg)	11.8	8.8 – 13.6	9.8	7.1 – 14.5	7.9	6.7 – 12.4	0.668
% Time ICP > 20 mm Hg	5.1	0- 7.4	1.9	0.9 – 9.8	2.3	1.9 – 10.9	0.826
% Time ICP > 22 mm Hg	2.0	0 – 3.5	1.7	0.4 – 5.4	1.6	1.0 – 8.0	0.808
MAP (mm Hg)	81.2	76.4 – 86.7	83.5	80.0 – 90.5	80.9	76.7 – 85.5	0.521
CPP (mm Hg)	68.7	61.0 – 73.2	71.9	68.2 – 83.8	72.7	71.6 – 73.5	0.176
% Time CPP > 70 mm Hg	42.9	39.4 – 67.7	65.2	50.7 – 74.7	71.7	54.4 – 72.8	0.095
% Time CPP < 60 mm Hg	12.4	7.2 – 21.5	5.5	2.6 – 18.4	11.6	6.8 – 15.3	0.335
PRx (a.u.)	0.098	0.032 – 0.215	0.240	0.145 – 0.424	0.030	0.004 – 0.328	0.258
% Time PRx > 0	59.7	49.4 – 78.7	73.7	65.3 – 83.3	51.8	49.7 – 78.5	0.217
% Time PRx > 0.25	33.6	24.4 – 49.7	52.3	42.0 – 75.4	29.1	24.0 – 63.0	0.183
% Time PRx > 0.35	24.4	17.3 – 36.3	39.4	32.4 – 65.6	22.7	14.7 – 55.0	0.202
PAx (a.u.)	-0.013	-0.135 – 0.059	0.049	-0.045 – 0.230	0.111	0.032 – 0.456	0.090
% Time PAx > 0	45.2	33.3 – 58.3	53.5	44.8 – 77.0	62.0	52.5 – 90.0	0.059
% Time PAx > 0.25	20.1	9.1 – 28.5	28.2	18.6 – 51.0	39.2	27.4 – 72.9	**0.036**
RAC (a.u.)	-0.263	(-0.416) – (-0.103)	-0.175	(-0.304) – (-0.016)	-0.023	-0.189 – 0.388	0.099
% Time RAC > -0.10	36.5	16.6 – 50.1	42.9	28.0 – 64.4	60.4	38.9 – 88.9	0.183
% Time RAC > -0.05	33.2	15.0 – 43.3	37.8	24.0 – 60.4	55.9	33.1 – 87.0	0.177
RAP (a.u.)	0.497	0.400 – 0.703	0.673	0.548 – 0.752	0.638	0.319 – 0.736	0.343
% Time RAP > 0.4	67.5	55.8 – 85.2	80.4	70.0 – 88.8	79.9	41.7 – 87.4	0.426
Best Admission GCS	7.0	5.0 – 8.5	8.0	4.5 – 8.0	8.0	6.0 – 11.0	0.550
Best Admission GCS – Motor	5.0	3.0 – 5.0	5.0	2.5 – 5.0	5.0	2.5 – 5.5	0.921
Rotterdam CT Grade	5.0	4.0 – 6.0	4.0	3.3 – 5.0	5.0	4.0 – 5.0	0.652

a.u. = arbitrary units, AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, CT = computed tomography, GCS = Glasgow Coma Scale, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values are those reaching statistical significance of 0.05 on Kruskal-Wallis Testing. There were no statistically significant p-values after Bonferroni correction for multiple comparisons (alpha 0.001).

Appendix D:

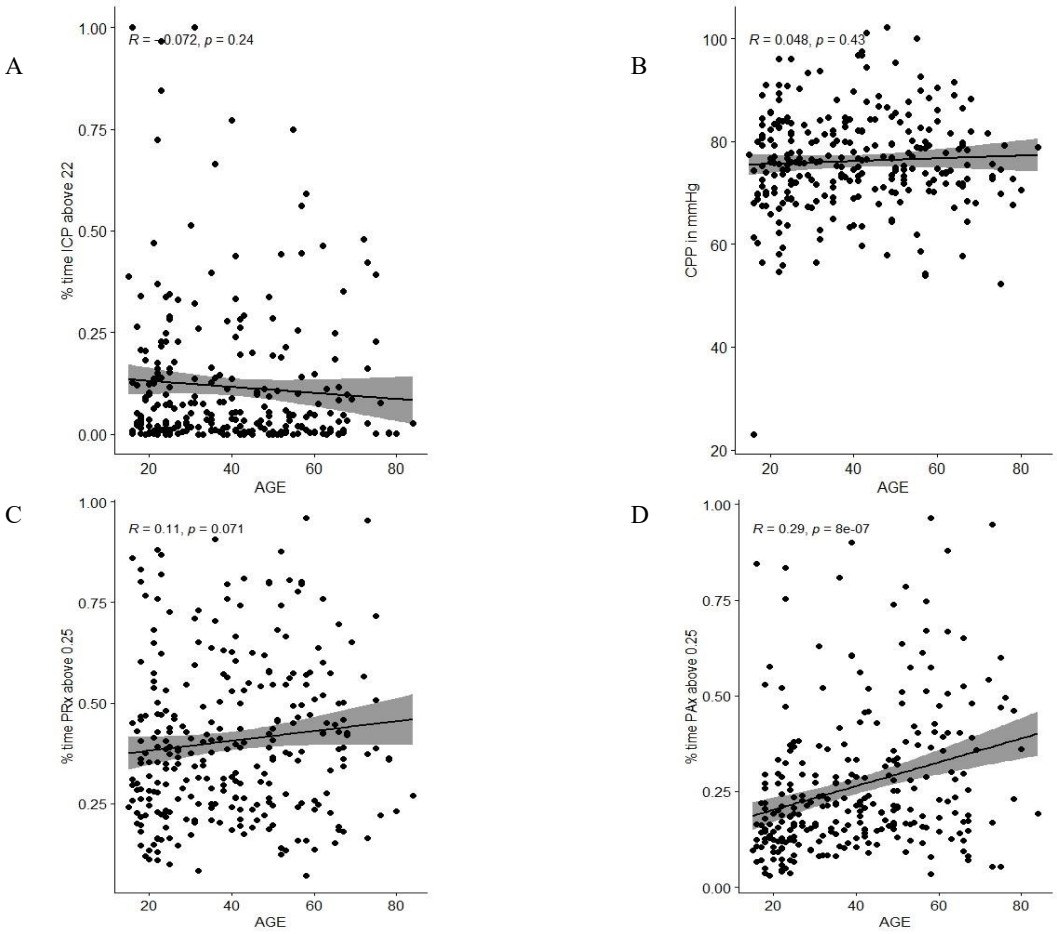
Table D.1: Cerebral Physiology Based on Biological Sex: Medians/IQRs, Mann-Whitney-U and FDR Testing: Entire Recording Period

Physiological Variable	Males (n = 224)		Females (n = 59)		Mann-Whitney-U Test p-value	FDR p values
	Median	IQR	Median	IQR		
ICP (mm Hg)	12.9	8.4 - 15.9	13.4	10.9 - 17.2	0.123	0.329
% Time ICP > 20 mm Hg	6.6	1.2 – 19.7	9.4	3.1 – 31.5	0.107	0.329
% Time ICP > 22 mm Hg	3.5	0.8 – 12.5	5.1	1.9 – 19.5	0.124	0.329
MAP (mm Hg)	88.7	83.1 - 94.7	89.9	82.6 - 96.4	0.417	0.747
CPP (mm Hg)	75.6	71.3 - 82.1	76.9	70.0 - 81.7	0.944	0.990
% Time CPP > 70 mm Hg	74.0	56.6 – 90.7	76.3	49.1 – 92.0	0.970	0.990
% Time CPP < 60 mm Hg	3.7	1.1 – 9.1	3.4	0.8 – 9.6	0.861	0.990
PRx (a.u.)	0.121	0.007 - 0.247	0.106	0.005 - 0.221	0.530	0.795
% Time PRx > 0	63.0	50.0 – 75.3	61.5	48.6 – 70.5	0.372	0.747
% Time PRx > 0.25	38.1	24.9 – 52.5	36.2	25.4 – 48.7	0.430	0.747
% Time PRx > 0.35	28.0	17.7 – 40.7	27.1	17.4 – 37.3	0.436	0.747
PAx (a.u.)	-0.046	(-0.137) - (-0.023)	-0.106	-0.106 - 0.095	0.674	0.951
% Time PAx > 0	45.2	33.9 – 59.7	46.0	36.1 – 60.4	0.790	0.990
% Time PAx > 0.25	20.3	13.4 – 33.3	21.9	14.1 – 35.9	0.925	0.990
RAC (a.u.)	-0.271	(-0.443) – (-0.124)	-0.335	(-0.512) – (-0.189)	0.080	0.329
% Time RAC > -0.10	31.5	17.2 – 46.9	24.7	13.7 – 40.1	0.092	0.329
% Time RAC > -0.05	27.4	14.8 – 41.0	21.8	11.9 – 34.8	0.103	0.329
RAP (a.u.)	0.615	0.452 - 0.723	0.708	0.548 - 0.765	**0.018**	0.329
% Time RAP > 0.4	77.3	62.4 – 86.8	85.8	72.1 – 89.4	**0.038**	0.329
Age (years)	40.0	24.0 – 54.0	31.5	23.3 – 49.0	0.118	0.329
Best Admission GCS	6.0	3.0 – 7.0	6.0	3.0 – 7.0	0.906	0.990

Best Admission GCS - Motor	3.0	1.0 – 5.0	3.0	1.0 - 4.3	0.385	0.747
Rotterdam CT Grade	4.0	3.0 – 5.0	4.0	3.0 – 5.0	0.990	0.990
Admission Marshall CT Grade	3.0	2.0 – 5.0	3.0	2.0 – 5.0	0.491	0.785

a.u. = arbitrary units, CPP = cerebral perfusion pressure, FDR = false discovery rate, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values are those reaching statistical significance on Mann-Whitney-U Testing.

Figure D.1: Scatterplots and Linear Regression (Entire Recording Period): % Time ICP > 22 mm Hg vs. Age, Mean CPP vs. Age, % Time PRx > +0.25 vs. Age, and % Time PAx > +0.25 vs. Age



p = p-value, R = Pearson correlation coefficient. Panel A - % Time with ICP >22 mm Hg vs. Age, Panel B – Mean CPP vs. Age, Panel C - % Time with PRx >+0.25 vs. Age, Panel D - % Time with PAx >+0.25 vs. Age. P-values recorded are for the Pearson correlation coefficient.

Table D.2: Cerebral Physiology Association with Trichotomized Age (Age < 40, Age 40 – 60, Age > 60): Medians/IQRs, Kruskal-Wallis and FDR Testing for the Entire Recording Period

Physiological Variable	Age < 40 years (n = 146)		Age 40 – 60 years (n = 94)		Age > 60 years (n = 42)		Kruskal-Wallis Test p-value	FDR p values
	Median	IQR	Median	IQR	Median	IQR		
ICP (mm Hg)	13.4	10.4 - 16.5	12.3	7.6 - 15.9	11.6	8.4 - 15.8	0.128	0.267
% Time ICP > 20 mm Hg	9.1	2.1 – 24.5	5.3	1.1 – 18.3	5.1	0.9 – 17.2	0.199	0.361
% Time ICP > 22 mm Hg	5.1	1.3 – 14.8	3.4	0.6 – 10.6	3.0	0.5 – 11.3	0.337	0.369
MAP (mm Hg)	89.1	83.7 - 94.6	90.7	83.3 - 96.3	87.5	80.0 - 93.6	0.258	0.369
CPP (mm Hg)	75.8	69.1 - 81.5	77.1	71.8 - 84.3	74.5	71.8 - 79.6	0.295	0.369
% Time CPP > 70 mm Hg	72.7	55.6 – 90.8	76.3	55.9 – 93.1	71.9	57.2 – 85.7	0.312	0.369
% Time CPP < 60 mm Hg	4.1	1.0 – 10.3	2.9	0.7 – 7.1	3.8	2.0 – 8.3	0.220	0.361
PRx (a.u.)	0.106	0.0 - 0.2	0.136	0.0 - 0.3	0.121	0.006 - 0.243	0.518	0.518
% Time PRx > 0	60.2	49.2 – 71.0	63.5	51.1 – 78.2	64.2	50.2 – 70.8	0.296	0.369
% Time PRx > 0.25	35.7	24.9 – 46.8	39.0	25.2 – 56.6	39.0	25.9 – 50.7	0.303	0.369
% Time PRx > 0.35	27.5	17.5 – 36.9	31.2	18.8 – 45.7	31.2	19.0 – 40.3	0.326	0.369
PAx (a.u.)	-0.052	-0.166 - 0.025	-0.002	-0.096 - 0.130	0.033	-0.095 - 0.181	**0.0003**	**0.003**
% Time PAx > 0	42.0	30.3 – 53.8	51.6	39.2 – 64.9	51.3	38.6 – 68.8	**0.00009**	**0.001**

% Time PAx > 0.25	16.9	12.0 – 27.2	22.3	16.4 – 39.1	28.2	17.0 – 46.9	**0.00004**	**0.001**
RAC (a.u.)	-0.366	(-0.511) – (-0.187)	-0.262	(-0.403) - (-0.112)	-0.234	-0.359 - 0.006	**0.001**	**0.007**
% Time RAC > -0.10	23.3	13.1 – 40.2	32.0	20.8 – 48.0	33.7	26.5 – 60.4	**0.002**	**0.007**
% Time RAC > -0.05	20.9	11.2 – 35.2	28.5	17.9 – 43.0	30.0	23.3 – 55.9	**0.002**	**0.007**
RAP (a.u.)	0.601	0.446 - 0.724	0.676	0.560 - 0.750	0.642	0.438 - 0.757	0.073	0.190
% Time RAP > 0.4	76.0	62.7 – 86.0	82.4	70.8 – 89.0	79.2	58.7 – 90.1	0.102	0.235
Best Admission GCS	6.0	3.0 – 7.0	6.0	4.0 – 8.0	5.0	3.0 – 7.0	0.495	0.518
Best Admission GCS – Motor	4.0	1.0 – 5.0	4.0	1.0 – 5.0	2.0	1.0 – 4.0	0.210	0.361
Rotterdam CT Grade	4.0	3.0 – 5.0	4.0	3.0 – 5.0	5.0	4.0 - 5.3	0.075	0.191
Admission Marshall CT Grade	3.0	2.0 – 4.0	3.0	2.0 – 5.0	4.0	3.0 – 5.0	**0.008**	**0.026**

a.u. = arbitrary units, CPP = cerebral perfusion pressure, FDR = false discovery rate, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values indicate those reaching statistical significance on Kruskal-Wallis and FDR Testing.

Table D.3: Cerebral Physiology Association with Decades of Age Subgroups (Age < 30, Age 30 – 39, Age 40 – 49, Age 50 – 59, Age 60 – 69, Age > 69): Medians/IQRs, Kruskal-Wallis and FDR Testing for the Entire Recording Period

Physiological Variable	Age < 30 years (n = 102)		Age 30 – 39 years (n = 44)		Age 40 – 49 years (n = 47)		Age 50 – 59 years (n = 43)		Age 60 – 69 years (n = 34)		Age > 69 years (n = 12)		Kruskal-Wallis Test p-value	FDR p value
	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR	Median	IQR		
ICP (mm Hg)	13.4	10.4 – 16.7	13.6	10.5 – 16.0	12.3	7.5 – 15.7	12.1	7.7 – 17.0	11.2	8.0 – 14.1	12.5	10.4 – 18.4	0.363	0.596
% Time ICP > 20 mm Hg	8.7	2.3 – 25.9	10.4	2.1 – 22.7	5.9	1.6 – 17.8	5.2	1.0 – 18.8	3.5	1.0 – 13.5	8.0	0.7 – 35.0	0.468	0.610
% Time ICP > 22 mm Hg	4.5	1.4 – 16.1	5.3	1.1 – 13.8	3.5	0.9 – 10.2	3.4	0.5 – 12.3	3.0	0.5 – 9.2	5.1	0.3 – 26.9	0.611	0.673
MAP (mm Hg)	89.5	84.2 – 95.3	88.6	83.3 – 92.9	88.9	81.8 – 97.8	91.2	83.4 – 95.8	87.5	80.4 – 94.6	86.4	78.9 – 92.5	0.676	0.706
CPP (mm Hg)	75.7	69.9 – 81.7	76.1	71.2 – 81.1	77.0	71.4 – 84.7	77.0	71.8 – 82.5	75.1	71.8 – 81.9	73.0	70.5 – 76.5	0.478	0.610
% Time CPP > 70 mm Hg	72.0	49.1 – 90.7	73.5	58.8 – 71.7	76.0	58.2 – 91.2	76.3	56.7 – 94.2	74.1	58.5 – 89.1	67.3	53.8 – 77.2	0.615	0.673
% Time CPP < 60 mm Hg	4.0	0.9 – 10.9	4.1	1.1 – 8.3	2.5	0.7 – 9.7	3.5	0.2 – 6.2	3.8	1.6 – 8.8	5.0	2.3 – 8.1	0.595	0.673
PRx (a.u.)	0.101	-0.002 – 0.206	0.117	0.043 – 0.272	0.089	0.007 – 0.265	0.191	0.008 – 0.286	0.127	6.67E-05 – 0.235	0.109	0.023 – 0.279	0.471	0.610
% Time PRx > 0	59.4	46.2 – 70.3	62.2	52.0 – 80.2	58.8	51.0 – 75.8	68.3	51.3 – 80.8	65.5	50.2 – 70.8	62.1	51.2 – 71.2	0.269	0.562
% Time PRx > 0.25	35.0	23.3 – 45.8	38.2	27.9 – 56.7	32.5	25.0 – 54.7	45.5	27.4 – 57.0	42.5	25.9 – 50.2	36.9	26.1 – 52.2	0.297	0.568
% Time PRx > 0.35	26.4	17.5 – 35.0	28.1	19.4 – 42.8	25.7	18.3 – 43.7	34.1	20.1 – 46.0	31.6	19.0 – 38.7	27.1	19.2 – 45.3	0.345	0.596
PAx (a.u.)	-0.087	(-0.203) – (-0.004)	-0.005	-0.130 – 0.080	-0.048	-0.113 – 0.054	0.055	-0.051 – 0.172	-0.021	-0.092 – 0.129	0.146	-0.099 – 0.203	**0.00005**	**0.0004**
% Time PAx > 0	38.0	27.1 – 50.5	48.2	35.2 – 59.8	42.5	38.1 – 54.9	58.0	44.0 – 70.8	46.8	38.6 – 64.6	65.4	39.7 – 72.6	**0.00001**	**0.0002**
% Time PAx > 0.25	15.9	10.6 – 23.9	22.4	14.9 – 30.4	21.0	15.4 – 31.3	32.0	16.9 – 42.7	25.4	17.0 – 40.4	41.1	18.6 – 50.7	**0.00001**	**0.0002**
RAC (a.u.)	-0.394	(-0.533) – (-0.219)	-0.281	(-0.390) – (-0.168)	-0.274	(-0.441) – (-0.177)	-0.229	(-0.401) – (-0.045)	-0.220	(-0.343) – (-0.003)	-0.238	-0.459 – 0.020	**0.002**	**0.006**

% Time RAC > -0.10	20.2	11.1 – 37.5	32.6	21.1 – 42.3	32.0	16.1 – 43.0	39.6	23.6 – 54.3	33.6	27.0 – 59.5	36.9	18.8 – 61.3	**0.002**	**0.006**
% Time RAC > -0.05	17.0	9.5 – 33.9	28.7	18.7 – 37.1	28.1	13.9 – 38.4	35.7	20.4 – 49.8	29.9	24.6 – 55.7	33.6	16.6 – 56.7	**0.001**	**0.006**
RAP (a.u.)	0.587	0.442 – 0.742	0.603	0.459 – 0.703	0.663	0.535 – 0.750	0.676	0.578 – 0.746	0.563	0.317 – 0.720	0.695	0.606 – 0.776	0.148	0.339
% Time RAP > 0.4	75.0	63.1 – 86.3	76.9	62.2 – 85.9	82.6	67.9 – 88.8	81.8	73.9 – 89.2	73.9	46.7 – 89.1	85.0	78.6 – 90.7	0.134	0.339
Best Admission GCS	5.0	3.0 – 7.0	6.0	3.8 – 7.0	6.0	4.0 – 7.0	6.0	4.0 – 8.0	5.0	3.0 – 7.0	7.0	3.0 – 8.0	0.883	0.883
Best Admission GCS - Motor	3.5	1.0 – 4.3	4.0	1.3 – 5.0	2.0	1.0 – 5.0	4.0	2.0 – 5.0	2.0	1.0 – 4.0	3.0	1.0 – 4.0	0.421	0.610
Rotterdam CT Grade	4.0	3.0 – 5.0	4.0	3.0 – 5.0	3.0	2.8 – 5.0	4.0	3.3 – 5.0	4.5	4.0 – 5.8	5.0	4.3 – 5.0	0.130	0.339
Admission Marshall CT Grade	3.0	2.0 – 4.0	3.0	2.0 – 4.0	3.0	2.0 – 5.0	4.0	2.0 – 5.0	4.0	3.0 – 5.0	5.0	3.5 – 5.0	0.064	0.210

a.u. = arbitrary units, CPP = cerebral perfusion pressure, FDR = false discovery rate, ICP = intracranial pressure, IQR = interquartile range, MAP = mean arterial pressure, mm Hg = millimeters of mercury, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, < = less than, > = greater than, % = percentage. Bolded p-values indicate those reaching statistical significance on Kruskal-Wallis and FDR Testing.

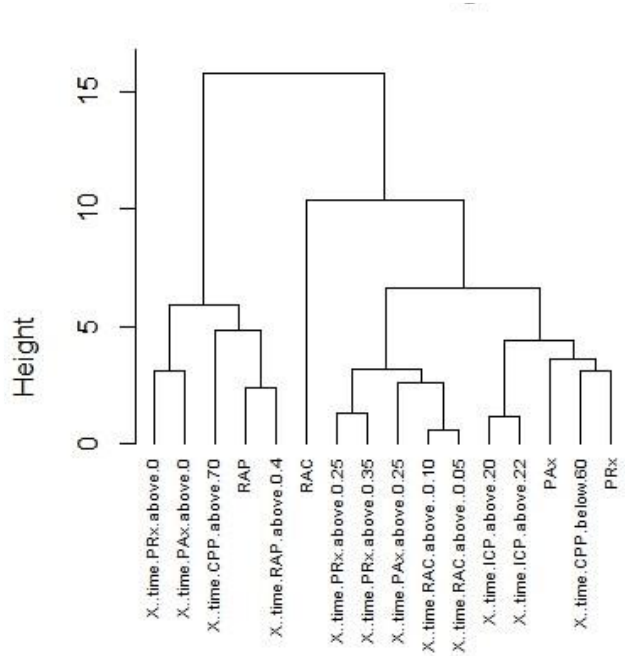
Appendix E:

Interpreting Dendrograms: The height of the connections corresponds to the similarity within the responses of the variables; the lower the connection, the more similar the physiology and vice versa. Using the height of the connections between the physiologies within the dendrogram, clusters of physiologies can be extracted.

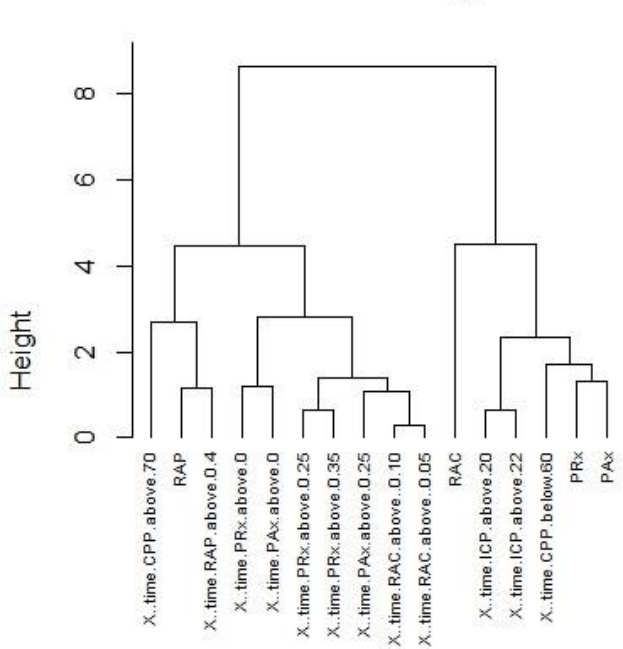
For example, in Figure E.1 A. Males, % Time RAC above -0.10 and % Time RAC above -0.05 are most closely related as they have the lowest connection on the dendrogram. If we choose 4 clusters, the 1st cluster contains % Time PRx above 0, % Time PAx above 0, % Time CPP above 70, RAP and % Time RAP above 0.4. The 2nd cluster contains RAC. The 3rd cluster contains % Time PRx above 0.25 and 0.35, % Time PAx above 0.25, % Time RAC above -0.10 and -0.05. The 4th cluster contains % Time ICP above 20 and 22, PAx, % Time CPP below 60 and PRx. The tallest connections are between RAC and physiology in the 3rd and 4th clusters making them the most dissimilar.

Figure E.1: Agglomerative Hierarchical Clustering of Male and Female Physiology During the 1st 72 Hours of Recording

A. Males



B. Females

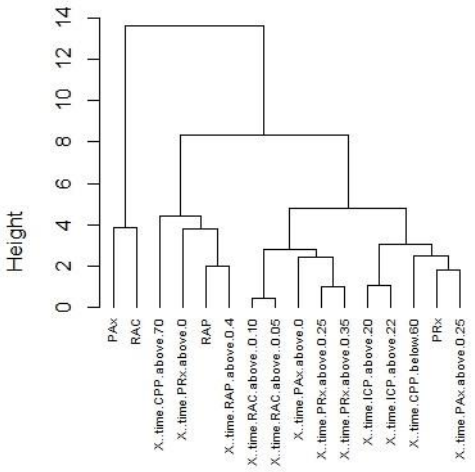


No clear difference in physiology clustering was noted between Males and Females

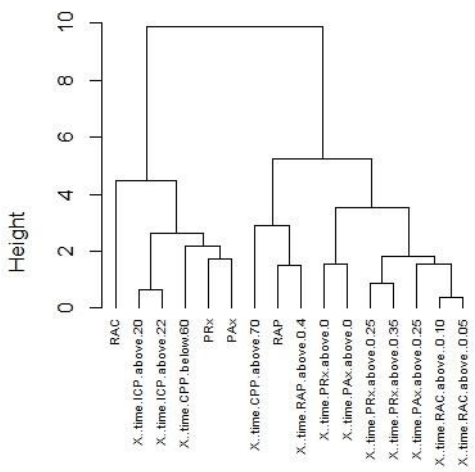
CPP = cerebral perfusion pressure, ICP = intracranial pressure, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, Figure A – Agglomerative Hierarchical Clustering of male physiology, Figure B – Agglomerative Hierarchical Clustering of female physiology.

Figure E.2: Agglomerative Hierarchical Clustering of Physiology for Trichotomized Age Groups During the 1st 72 Hours of Recording

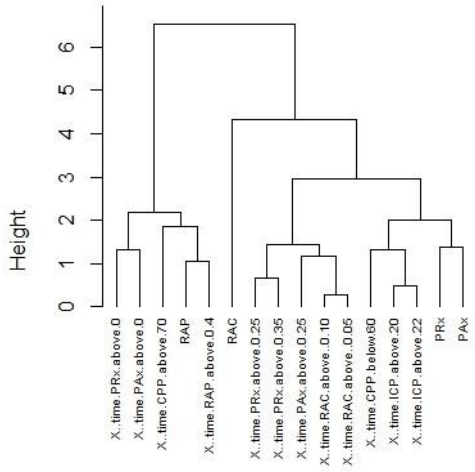
A. Age < 40



B. Age 40 – 60



C. Age > 60

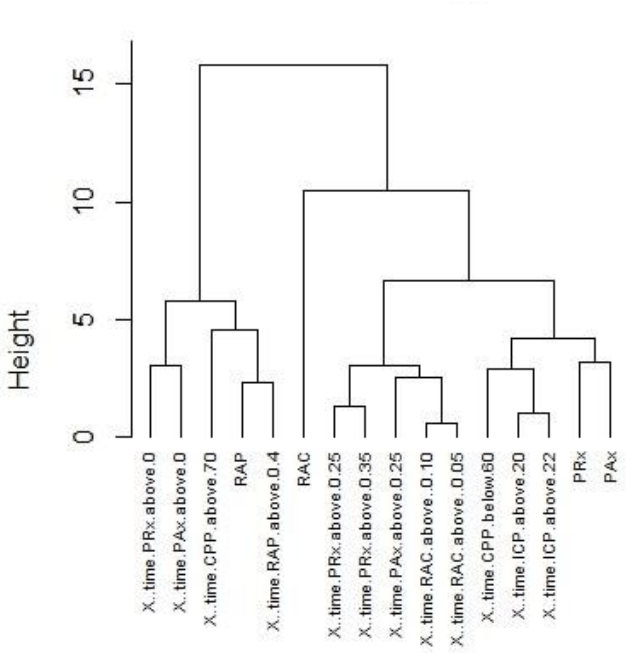


No clear difference in physiology clustering was noted with increasing age

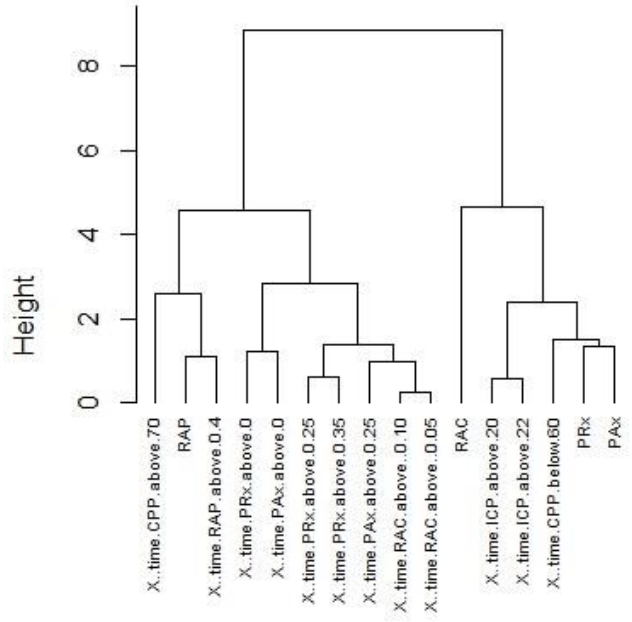
CPP = cerebral perfusion pressure, ICP = intracranial pressure, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, Figure A – Agglomerative Hierarchical Clustering of age < 40 physiology, Figure B – Agglomerative Hierarchical Clustering of age 40 – 60 physiology, Figure C – Agglomerative Hierarchical Clustering of age > 60 physiology.

Figure E.3: Agglomerative Hierarchical Clustering of Male and Female Physiology During the Entire Recording Period

A. Males



B. Females

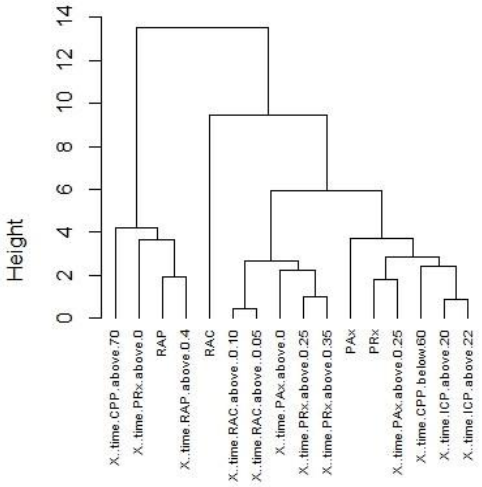


No clear difference in physiology clustering was noted between Males and Females

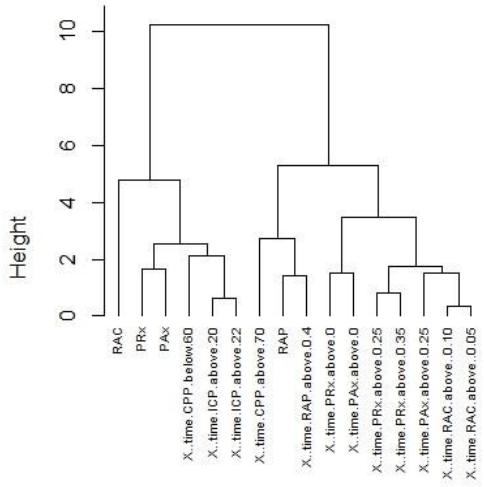
CPP = cerebral perfusion pressure, ICP = intracranial pressure, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, Figure A – Agglomerative Hierarchical Clustering of male physiology, Figure B – Agglomerative Hierarchical Clustering of female physiology.

Figure E.4: Agglomerative Hierarchical Clustering of Physiology for Trichotomized Age Groups During the Entire Recording Period

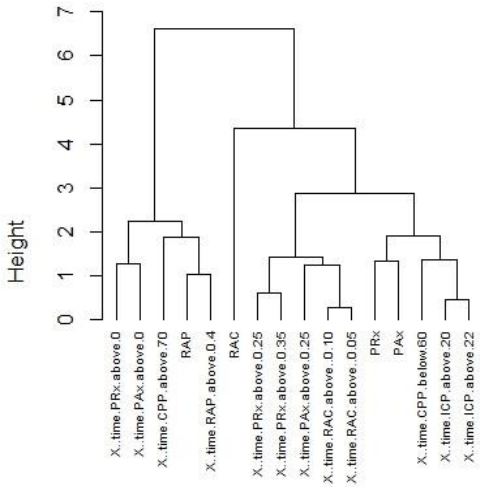
A. Age < 40



B. Age 40 – 60



C. Age > 60



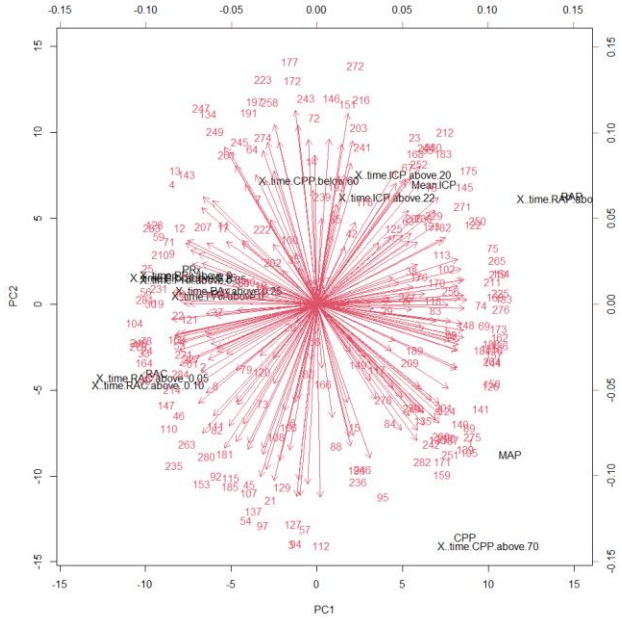
No clear difference in physiology clustering was noted with increasing age

CPP = cerebral perfusion pressure, ICP = intracranial pressure, PAx = pulse amplitude index, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index, Figure A – Agglomerative Hierarchical Clustering of age < 40 physiology, Figure B – Agglomerative Hierarchical Clustering of age 40 – 60 physiology, Figure C – Agglomerative Hierarchical Clustering of age > 60 physiology

Appendix F:

Interpreting Principal Component Analysis Factor Biplots and Scree plots: this is a dimensionality-reduction method which aims to reduce the number of variables of a data set while preserving as much information as possible. In Figure F.1.2, the 1st scree plot shows a line with black round dots, the 1st dot corresponds to 37.5% of the data (most of the data) and is represented by principal component 1 (PC1) on the factor biplot above (Figure F.1.1), the 2nd dot on the scree plot corresponds to about 20% of the data and is represented by PC2 on the factor biplot, etc. Regarding the factor biplot, indices closer to the center e.g., % Time PAx above 0.25 accounts for more variance as opposed to indices further away e.g., Mean ICP which accounts for little.

Figure F.1.1: Principal Component Analysis of Male Physiology for the 1st 72 Hours of Recording



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.1.2: Scree Plot of Male Physiology for the 1st 72 Hours of Recording

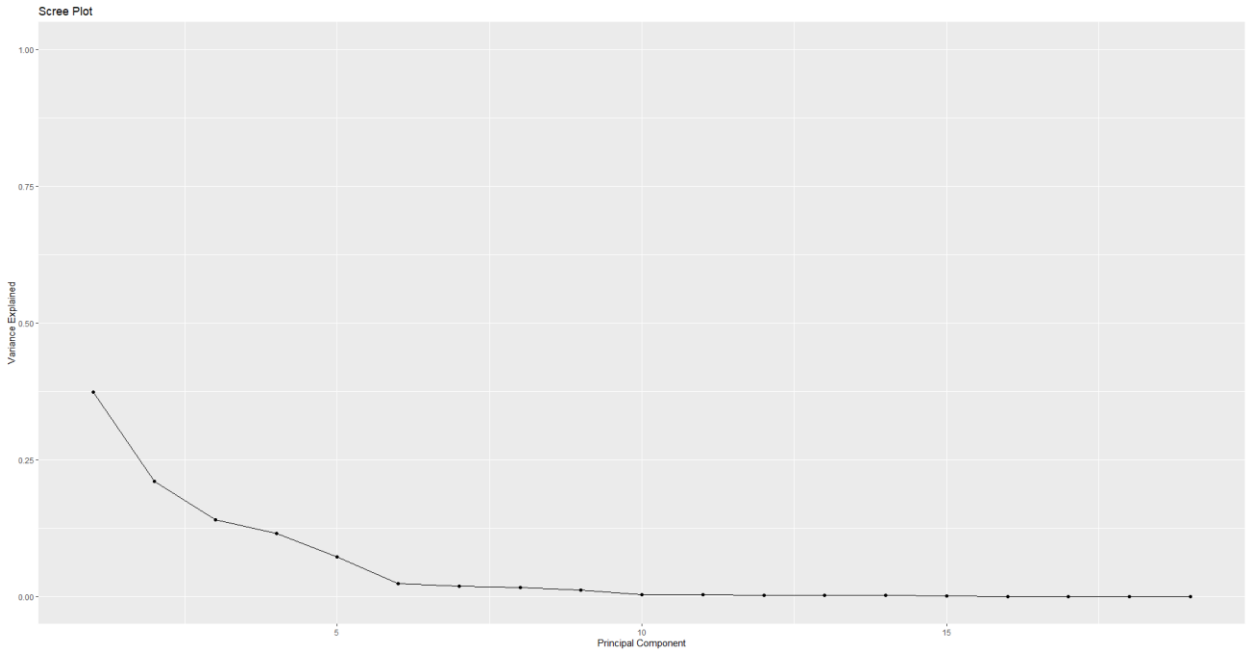
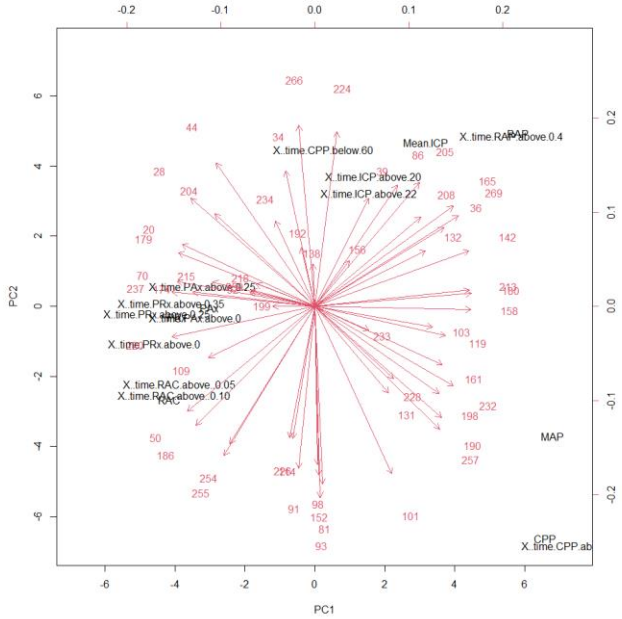


Figure F.2.1: Principal Component Analysis of Female Physiology for the 1st 72 Hours of Recording



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.2.2: Scree Plot of Female Physiology for the 1st 72 Hours of Recording

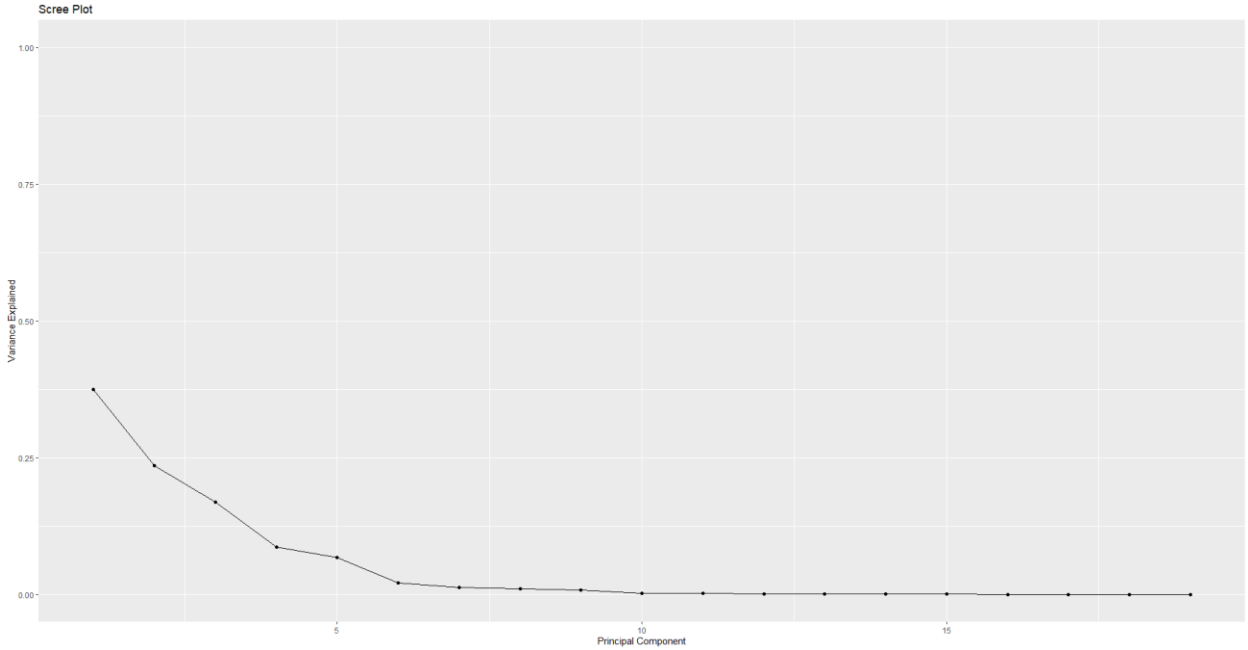
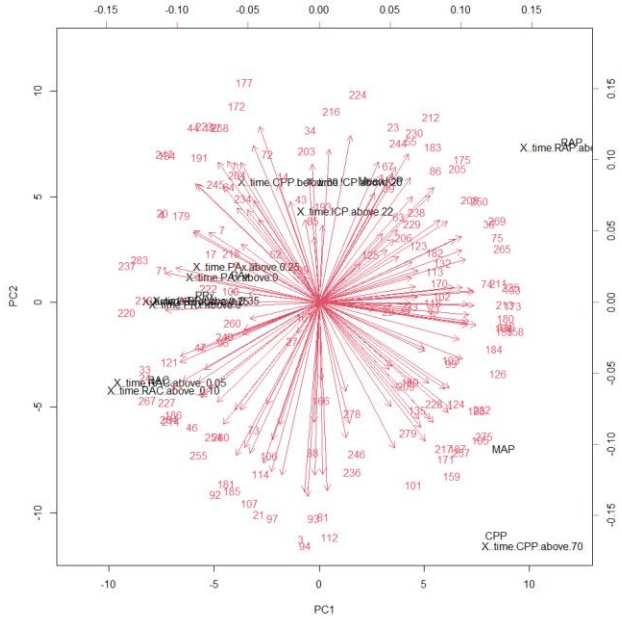


Figure F.3.1:Principal Component Analysis of Age < 40 Physiology for the 1st 72 Hours of Recording



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.3.2: Scree Plot of Age < 40 Physiology for the 1st 72 Hours of Recording

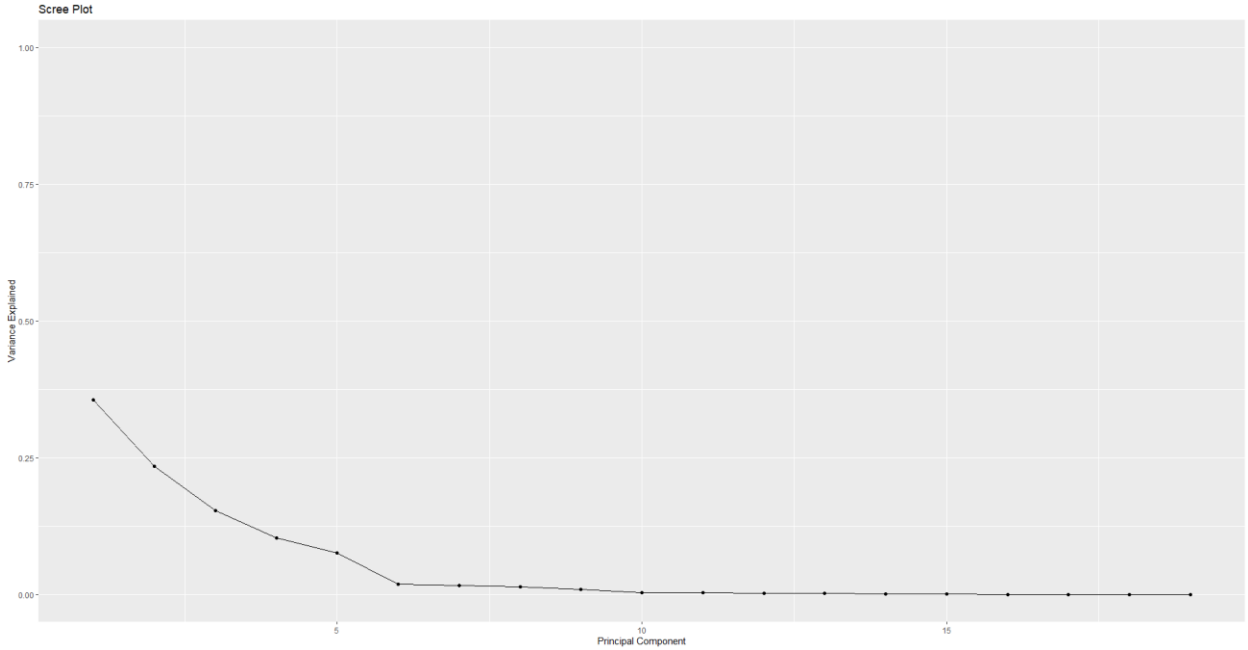
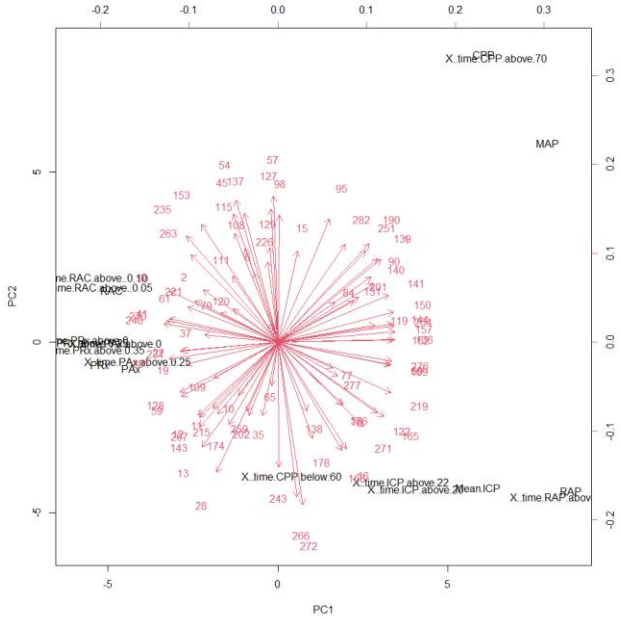


Figure F.4.1: Principal Component Analysis of Age 40 - 60 Physiology for the 1st 72 Hours of Recording



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.4.2: Scree Plot of Age 40 - 60 Physiology for the 1st 72 Hours of Recording

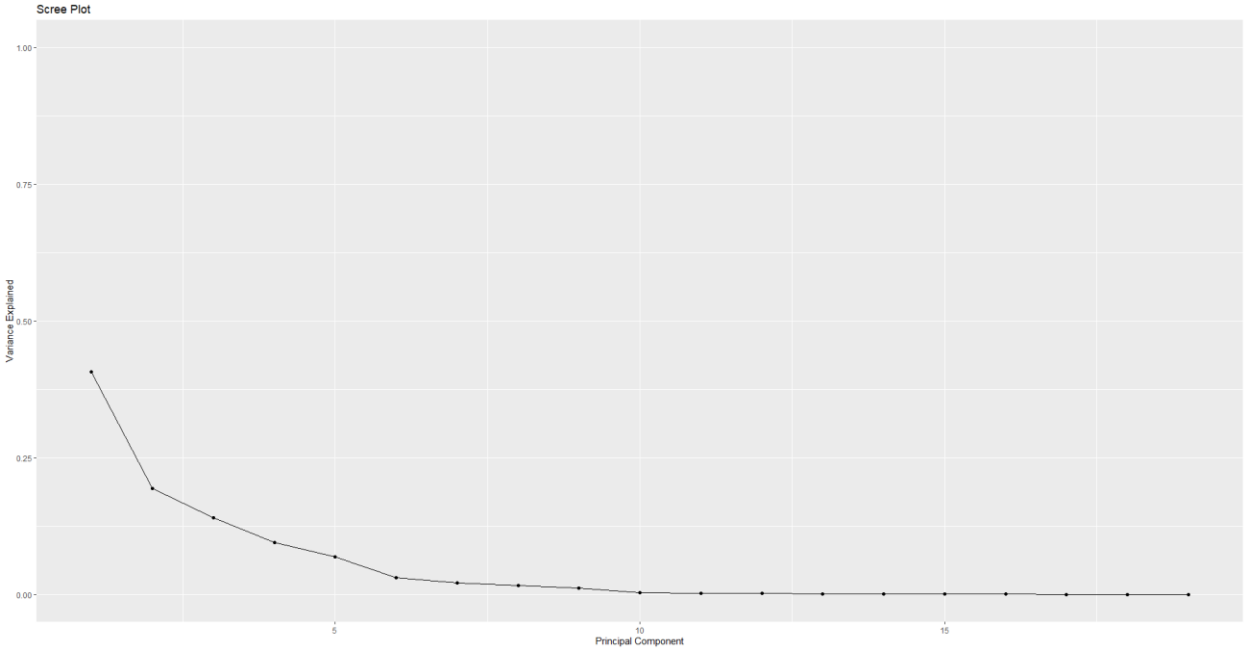
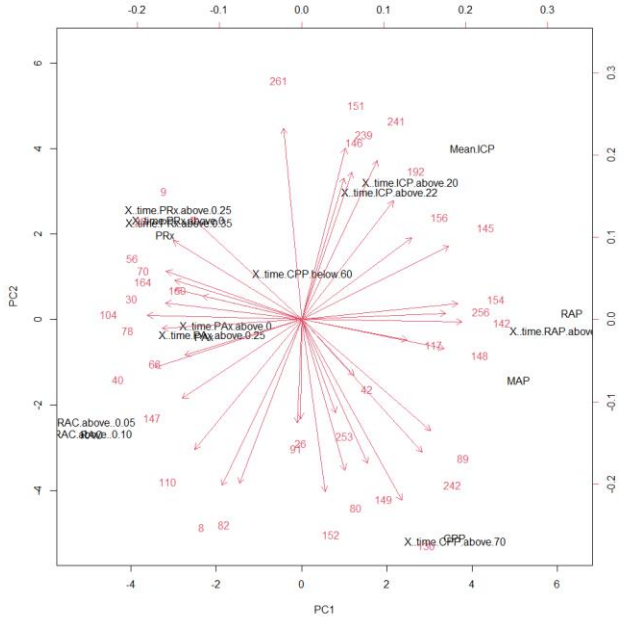


Figure F.5.1: Principal Component Analysis of Age > 60 Physiology for the 1st 72 Hours of Recording



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.5.2: Scree Plot of Age > 60 Physiology for the 1st 72 Hours of Recording

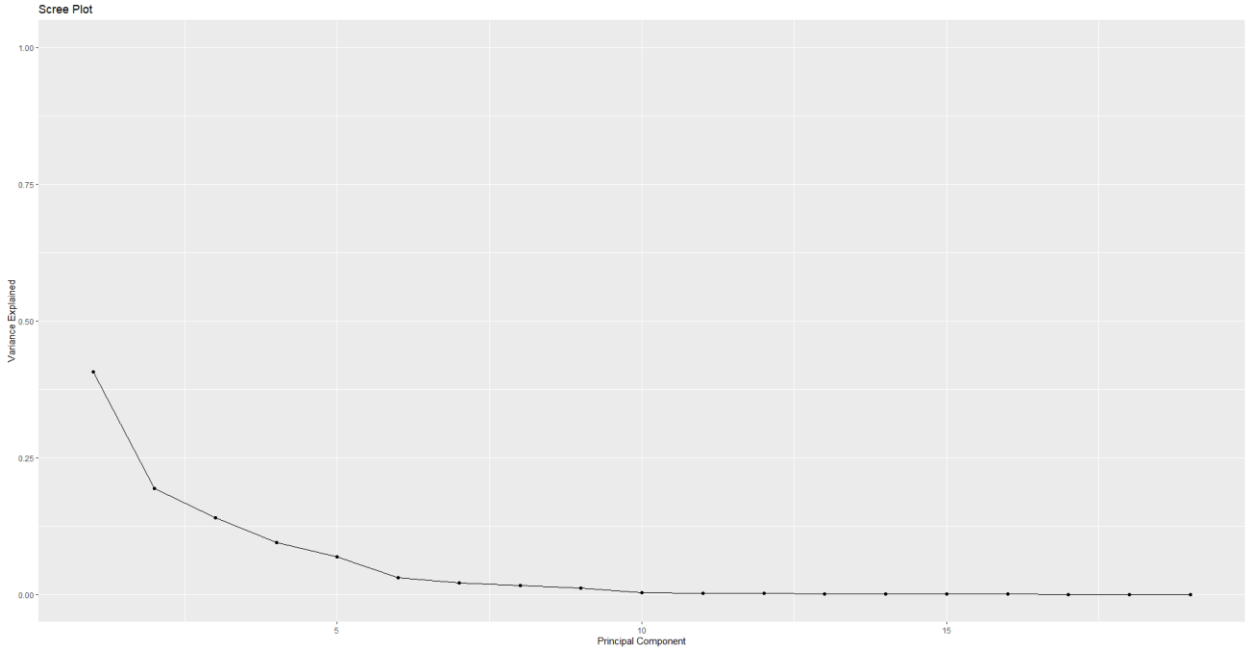
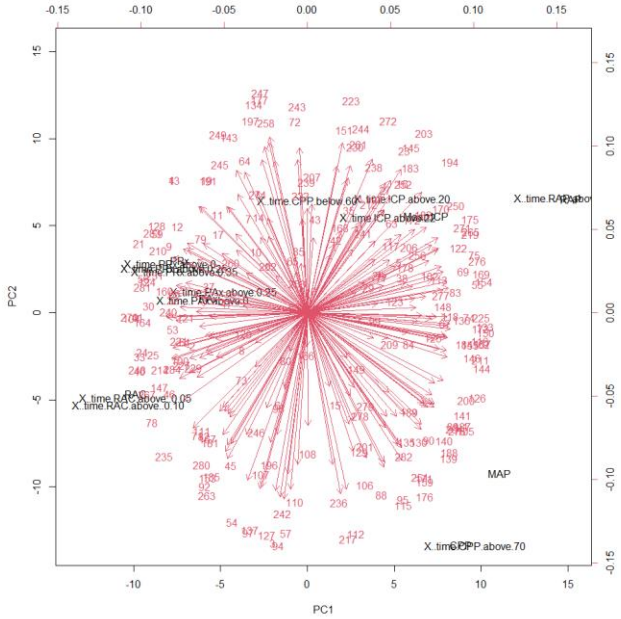


Figure F.6.1: Principal Component Analysis of Male Physiology for the Entire Recording Period



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.6.2: Scree Plot of Male Physiology for the Entire Recording Period

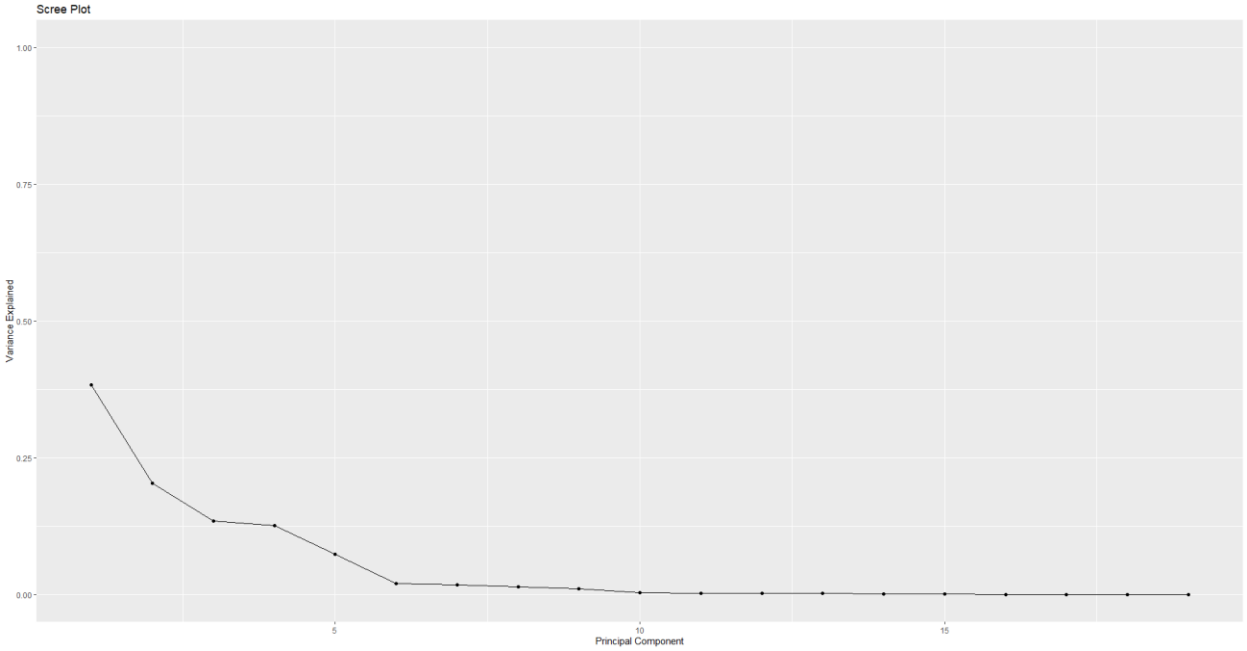
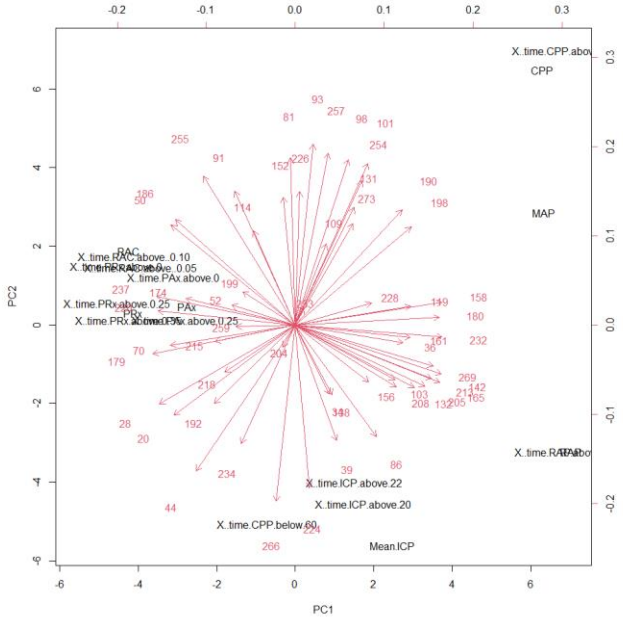


Figure F.7.1: Principal Component Analysis of Female Physiology for the Entire Recording Period



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.7.2: Scree Plot of Female Physiology for the Entire Recording Period

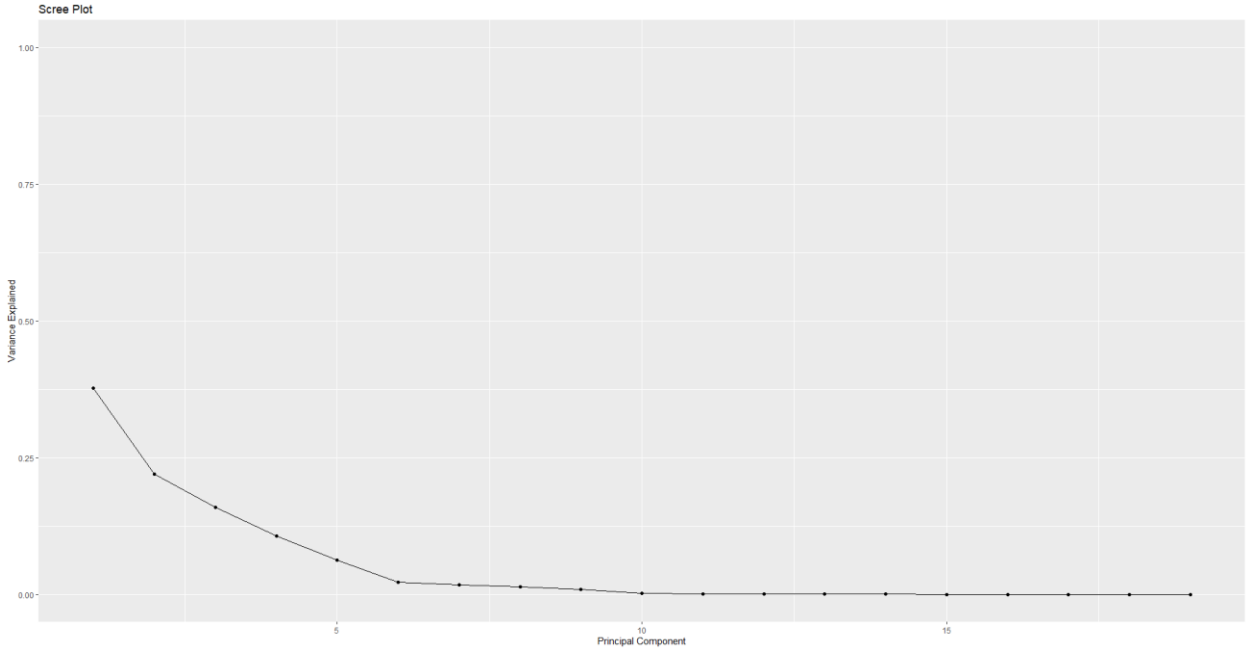
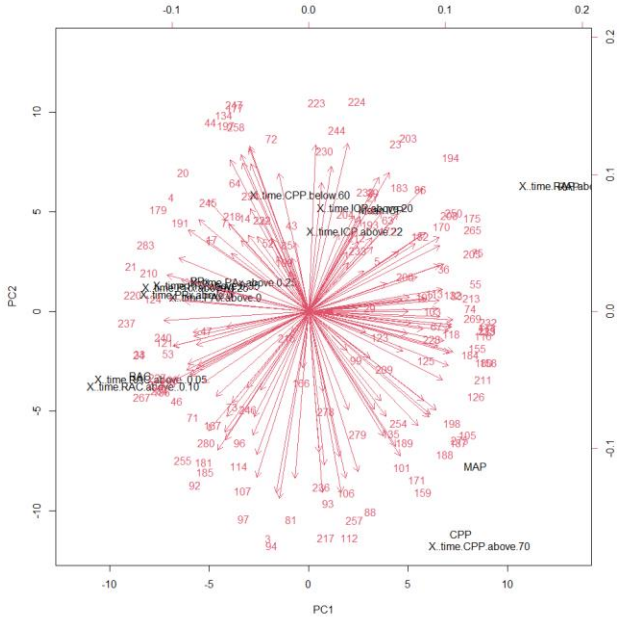


Figure F.8.1: Principal Component Analysis of Age < 40 Physiology for the Entire Recording Period



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.8.2: Scree Plot of Age < 40 Physiology for the Entire Recording Period

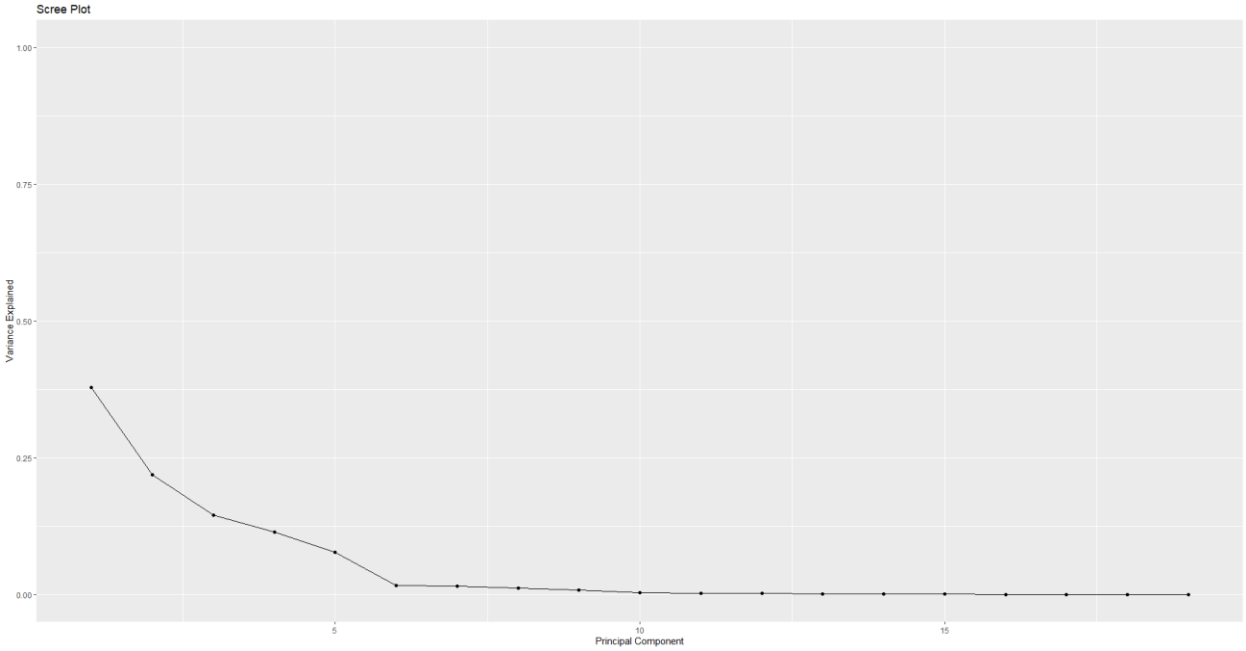
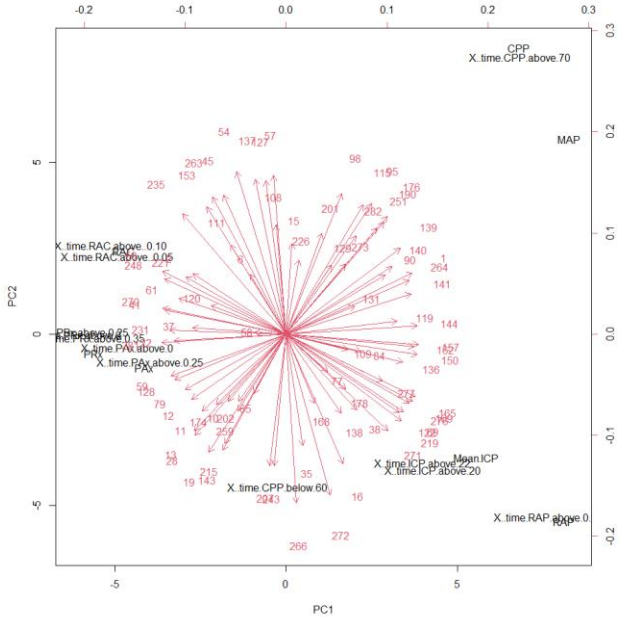


Figure F.9.1: Principal Component Analysis of Age 40 - 60 Physiology for the Entire Recording Period



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.9.2: Scree Plot of Age 40 - 60 Physiology for the Entire Recording Period

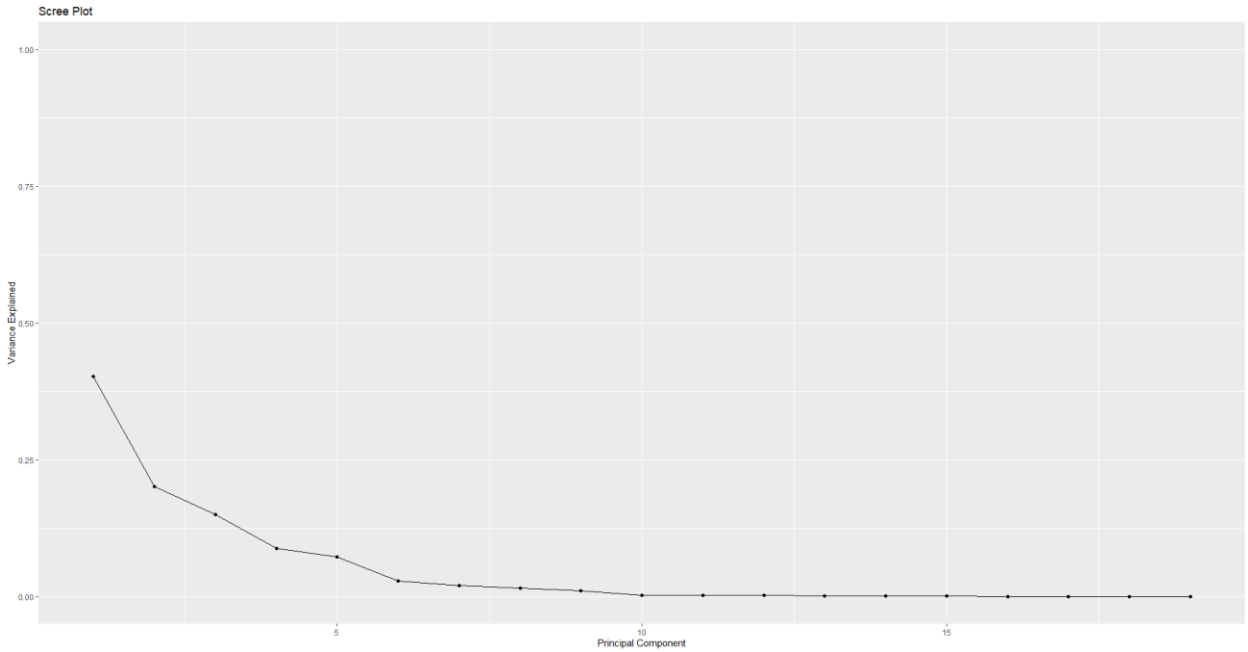
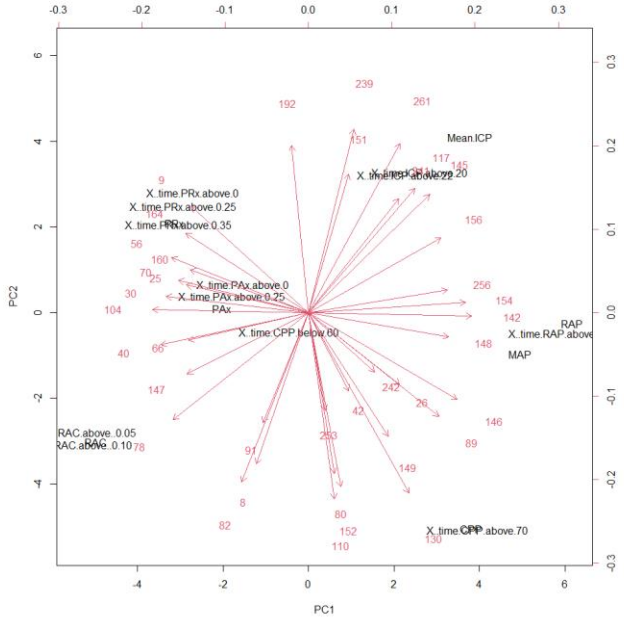


Figure F.10.1: Principal Component Analysis of Age > 60 Physiology for the Entire Recording Period



CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, PAx = pulse amplitude index, PC1 = principal component 1, PC2 = principal component 2, PRx = pressure reactivity index, RAC = correlation between slow-waves of AMP and CPP, RAP = compensatory reserve index.

Figure F.10.2: Scree Plot of Age > 60 Physiology for the Entire Recording Period

