

Continuous Cerebral Compensatory Reserve Monitoring in Acute Neural Injury: Statistical Properties and Behaviours

by
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A Thesis submitted to the Faculty of Graduate Studies of
The University of Manitoba
in Partial Fulfilment of the Requirements of the Degree of

MASTER OF SCIENCE

Biomedical Engineering
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Primary Original Works (n=2)

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LIST OF ABBREVIATIONS

A/D – analog-to-digital
ABP – arterial blood pressure
ACF – autocorrelation function
ADF – augmented Dicky Fuller
AHC – agglomerative hierarchical clustering
AIC – Akaike information criterion
AMP – pulse amplitude of ICP
AMP_{ABP} – the pulsatile amplitude of ABP
AMP_{CaBV} – the ratio between the pulsatile amplitude of CaBV
AR order – autoregressive order of ARIMA
ARIMA – autoregressive integrative moving average
AUC – area under the curve
au – arbitrary units
BIC – Bayesian information criteria
BIS – bispectral index
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
CC – cerebral compliance
CCR – cerebral compensatory reserve
CENTER-TBI – Collaborative European NeuroTrauma Effectiveness Research in TBI
C_a – cerebral arterial compliance
C_i – cerebrospinal space compliance
CA – cerebral autoregulation
CaBV – cerebral arterial blood volume
C_{CaBV} – a cerebrospinal compliance measure, represents changes in CaBV
C_{CSF} – a cerebrospinal compliance measure, were derived from Marmarou’s model of CSF dynamics
CI – confidence interval
CM – closing margin
CPP – cerebral perfusion pressure
CO₂ – carbon dioxide
COx – cerebral oxygenation index
COx_L – cerebral oxygenation index of left hemisphere
COx_R – cerebral oxygenation index of right hemisphere
COx-a – cerebral oxygenation index from ABP
COx_a_L – cerebral oxygenation index from ABP of left hemisphere
COx_a_R – cerebral oximetry index from ABP of right hemisphere
C_{P1/P2} – a cerebrospinal compliance measure, derived as the amplitudes of peaks P1 and P2 of the ICP pulse waveform
CSF – cerebrospinal fluid

CrCP – critical closing pressure
 CT – computed tomography
 CVR – cerebrovascular reactivity
 DAI – diffuse axonal injury
 E – elastance
 EEG – Electroencephalogram
 EVDs – external ventricular drains
 FV – doppler flow velocity
 GainFv – a transfer function gains of R waves between ABP and FV
 GCS – Glasgow Coma Scale
 GOS – Glasgow Outcome Score
 GOSE – Glasgow outcome scale extended
 HFC – high frequency centroid
 HHC – higher harmonics centroid
 HIBI – hypoxic ischemic brain injury
 I – integrated order for ARIMA
 ICH – intracerebral hemorrhage
 ICM+ – intensive care monitoring “plus”
 ICP – intracranial pressure
 ICU – intensive care unit
 ICV – intracranial volume
 iNPH – idiopathic normal pressure hydrocephalus
 IRF – impulse response function
 IQR – interquartile range
 k – number of clusters in KMCA
 KMCA – k-means cluster analysis
 KPSS – Kwiatkowski–Phillips–Schmidt–Shin
 L/P ratio – lactate/pyruvate ratio
 LL – log likelihood
 MA order – moving average order of ARIMA
 MAP – mean arterial pressure
 ML – machine learning
 MMM – multimodal monitoring
 mmHg – millimeter of Mercury
 MTF – the transfer function of ABP to ICP at the fundamental cardiac frequency
 Mx - index of autoregulation
 NIRS – near-infrared spectroscopy
 NPH – normal pressure hydrocephalus
 NREM – non-rapid eye movement
 NS – non-significant
 O₂ – oxygen
 p, d, q – ARIMA/VARIMA model
 P-V curve – Pressure-volume curve
 P1 – first peak of ICP pulse, also known as percussion wave

P2 – second peak of ICP pulse, also known as tidal wave
PAX – pulse amplitude index
PCA – principal component analysis
PCI – a CC/CCR index
PbtO₂ – extracellular brain tissue oxygen
PACF – partial autocorrelation function
PI – pulsatility index
PRx – pressure reactivity index
PTH – post-traumatic hydrocephalus
PVI – pressure-volume index
R waves – respiratory oscillations
R_{CSF} – resistance to CSF outflow
RAC – correlation between AMP and CPP
RAP – CC/CCR index
REB – research ethics board
REM – rapid eye movement
RPS – ratio of pulse slopes
rSO₂ – regional cerebral oxygen saturation
sec – seconds
SAH – subarachnoid hemorrhage
SIBICC – Seattle International Severe Traumatic Brain Injury Consensus Conference
Slow – amplitude of Slow vasogenic waves of ICP
SR – systematic review
TBI – traumatic brain injury
TCD – transcranial Doppler
VARIMA – vector autoregressive integrative moving average
WCSS – within-cluster sum of squared errors
WT – wall tension

ABSTRACT

Traumatic brain injury (TBI) is one of the leading causes of death and disability within Canada and globally. The mechanisms involved in secondary brain injury after TBI (i.e., the cascade of systemic and local cellular events that lead to tissue damage within the brain) are amenable to therapeutic intervention. Intracranial pressure (ICP) is the cornerstone for these current management paradigms in moderate-to-severe TBI, which is also used as a surrogate for cerebral compliance (CC)/compensatory reserve (CCR) (CC/CCR; the brain's ability to accommodate changes in intracranial volume without causing significant increases in ICP). This approach relies on manual visual inspection for intervention, which is prone to error and inter-/intra-observer reliability issues. An effective alternative is the CC/CCR index RAP, which has recently been used in hydrocephalus studies and proven useful in predicting shunt failure.

RAP is a continuous measurement, derived using the moving correlation between ICP and the pulse amplitude of ICP (AMP), with progressively positive values denoting impaired CC/CCR. Despite its application in hydrocephalus literature, RAP has not been extensively explored in moderate-to-severe TBI. Currently, we have limited, or no, understanding of: A. the temporal statistical structure of the RAP index, including its artifact profile/management strategy, and B. overall insult burden of impaired RAP in association with other cerebral physiology in moderate-to-severe TBI. Therefore, this thesis aims to address these gaps.

This work shows that the time-series statistical features of RAP demonstrated inherent autoregressive features and data trends, regardless of temporal resolution. The difference in temporal characteristics indicates RAP contains distinct information compared to its constituent ICP or AMP alone. Furthermore, such time-domain statistical features of RAP signals can be used to identify artifactual segments in RAP data streams. Additionally, this work explored the relationship of RAP with other cerebral physiology in moderate-to-severe TBI across different predefined RAP ranges ($[-1, 0)$, $[0, 0.4]$, $(0.4, 1]$, which was defined based on the overall physiological state observed in prior literature). Consistent patterns of the physiological parameters were observed across these RAP ranges. Notably, impaired RAP state (i.e. large positive values) was associated with increased ICP, AMP, impaired cerebral autoregulation and decreased regional cerebral oxygen saturation (rSO_2) and extracellular brain tissue oxygen ($PbtO_2$).

This thesis provides an improved understanding of RAP's temporal structure and its relationship with other parameters, which are critical prior to future adoption of the RAP index into bedside monitoring, leveraging RAP data for patient trajectory modeling, and clinical interventional studies based on RAP values.

1 Introduction

1.1 General Introduction

Traumatic brain injury (TBI) represents a major public health challenge worldwide, with over 50 million new cases annually and an estimated global economic burden exceeding CAD 540 billion annually.¹ In Canada and globally, TBI remains a leading cause of death and disability.¹ Much of the cost and devastation to life occurs in people under the age of 40 in moderate-to-severe TBI cohorts, where mortality rates remain at 30-40%.²

The impact of moderate-to-severe TBI involves primary and secondary injuries. Primary injuries occur at the moment of impact, causing immediate structural brain damage. In contrast, secondary injuries develop over time through systemic and cellular processes that exacerbate the damage to brain tissue. Unlike primary injuries, secondary injury mechanisms may respond to therapeutic interventions, offering opportunities to enhance patient outcomes. To prevent secondary injury across patient populations, current management strategies for moderate-to-severe TBI focus on guideline-based interventions that target physiological parameters using data from invasive pressure sensor technologies.³⁻⁶ A key focus is maintaining intracranial pressure (ICP) below 22 mmHg, triggering therapeutic measures when exceeded.^{3,4}

Among the secondary injury mechanisms in TBI, impaired cerebral compliance (CC)/compensatory reserve (CCR) is a key factor in poor patient outcome. Prior literature has demonstrated that CC/CCR metric is significantly associated with patient outcomes, with impaired and exhausted compliance also significantly linked to low cerebral perfusion pressure (CPP) and extracellular brain tissue oxygen (PbtO₂).^{7,8} CC/CCR reflects the ability of the cerebrospinal system to accommodate or buffer the changes in intracranial volume (ICV) without a significant shift in ICP.⁹ ICP, which is often derived from invasive strain-gauge pressure sensors, is also used as a surrogate for assessing CC/CCR. However, the methodologies associated with this approach are susceptible to inaccuracies, as they often depend on subjective visual assessment of pulse waveform morphology at the bedside, an approach that introduces variability due to inter- and intra-observer inconsistencies. Therefore, the accurate and objective evaluation of continuous CC/CCR metrics is of paramount importance.

One such physiological marker, the cerebral compliance or compensatory reserve index (RAP), has emerged as a promising indicator of CC/CCR. RAP is derived as the moving Pearson correlation coefficient between ICP and its fundamental pulse amplitude (AMP).¹⁰⁻¹³ The RAP index ranges from -1 to +1, with lower positive values indicative of preserved CC/CCR, whereas elevated positive or negative values reflect

progressively impaired or exhausted CC/CCR, respectively.¹⁰ Recent findings in the hydrocephalus literature have demonstrated the utility of the RAP index in predicting shunt failure, where increasingly positive RAP values have been associated with deteriorating CC/CCR.¹⁰⁻¹² Additionally, RAP can be continuously derived at the bedside in patients undergoing invasive ICP monitoring, making it a particularly suitable candidate for integration into TBI management protocols.

In modern neurocritical care, high-resolution physiologic monitoring plays a pivotal role in capturing dynamic changes in brain physiology, enabling timely interventions and more precise patient management. Such granular monitoring is essential in TBI, where secondary injuries often evolve rapidly and subtly. As a continuously computable metric, RAP can enable clinicians and researchers to track fluctuations in CC/CCR in near real-time, aligning well with the demands of data-driven, individualized care in clinical cases. This integration of RAP into the broader framework of high-resolution multimodal monitoring (MMM) holds promise for enhancing both bedside decision-making and advanced analytic approaches such as trajectory modeling and predictive analytics.

Despite its potential, the clinical adoption of RAP in TBI cases has been limited, largely due to an incomplete understanding of its characteristics.^{7,14-16} Currently, we have limited or no understanding of: A. the temporal statistical structure of the RAP index, including its artifact profile/management strategy, and B. the overall insult burden of impaired RAP in association with other cerebral physiology in moderate/severe TBI.

Considering these knowledge gaps regarding RAP, this thesis aims to address these knowledge gaps through the following objectives:

1. Exploring the temporal statistical relationships of RAP, characterizing its artifact profile, and providing insight into its management.
2. Characterizing the insult burden of impaired CC/CCR in moderate-to-severe TBI patients, in relation to other critical aspects of cerebral physiology in moderate-to-severe TBI patients.

Improved understanding in these areas is critical prior to future adoption of the RAP index into bedside monitoring, leveraging RAP data for patient trajectory modeling, and clinical interventional studies based on RAP values.

1.2 Aims and Hypotheses

Exploring the temporal statistical relationships of RAP, characterizing its artifact profile, and providing insight into its management.

To date, no studies have explored the temporal structure of RAP.^{7,14–16} Before RAP can be reliably applied in clinical settings, its inherent trends must be characterized, along with an assessment of whether it carries temporal information distinct from ICP and AMP. These insights will inform future modeling efforts involving RAP for clinical applications. Additionally, effective artifact management remains an unmet need; no established framework currently exists for identifying or managing artifactual RAP data. Without proper artifact management, data modeling efforts will be inaccurate or misleading. Identifying features that distinguish artifactual data from valid RAP signals will enable automated screening prior to using RAP in outcome prediction or patient trajectory models.

By leveraging the time series structure of RAP and its constituent signals, ICP and AMP, it is possible to characterize and compare their temporal features. RAP is expected to exhibit distinct time-series behaviour, as it reflects cerebral compliance and is influenced by broader cerebral dynamics beyond just ICP or AMP. Furthermore, by facilitating the time series structure, the artifacts can potentially be predicted after finding out the appropriate features. This will allow an automated method of artifact identification and management. Considering these, the following hypothesis was proposed:

Hypothesis #1: Viable RAP data streams will display a reproducible time-domain structure, highlighting the distinct information RAP conveys relative to its components, ICP and AMP. This will also facilitate the identification of artifacts and the development of semi-automated/automated methods of management.

Characterizing the insult burden of impaired CC/CCR in moderate-to-severe TBI patients, in relation to other critical aspects of cerebral physiology in moderate-to-severe TBI patients.

Continuous monitoring of RAP alongside other multimodal physiological parameters can potentially enable real-time assessment of CC/CCR and its interaction with key cerebral dynamics, facilitating earlier detection of secondary injury and more personalized, data-driven interventions in TBI management. However, prior works do not include such research, where the relationships between RAP and other physiologies can be comprehensively observed.^{7,14–16}

If analyzed, impaired RAP (i.e., positive RAP values) will be associated with increased ICP and AMP. Cerebral autoregulation (CA) measurements will be more positive in impaired RAP states. Furthermore, worsening RAP values (i.e., more positive values) will be associated with decreased CPP, mean arterial pressure (MAP), regional cerebral oxygen saturation (rSO₂), and PbtO₂. While these relationships are likely to be more apparent in higher-resolution data, similar trends should still be evident in lower-resolution datasets. It's because even when high-frequency fluctuations are averaged out in lower-resolution data, the

underlying patterns, such as shifts in physiologies associated with impaired compliance, remain preserved. Based on this rationale, the following hypothesis was proposed:

Hypothesis #2: Total insult burden of impaired RAP will vary based on the selected RAP thresholds. Consistent patterns of cerebral physiologies with relation to RAP will be evident across all the resolutions for different RAP thresholds.

1.3 Overview of Thesis Document

Chapter 2 presents a comprehensive literature review, beginning with the definition and classification of TBI injuries. This chapter then introduces the concept of CC/CCR, outlining its relevance to TBI pathophysiology. The discussion progresses to highlight the significance of MMM in neurological conditions and elaborates on how CC/CCR monitoring can be integrated into MMM to potentially improve patient outcome. Afterwards, various methods for assessing CC/CCR are reviewed, with an emphasis on continuous monitoring techniques. The chapter concludes by focusing on the central theme of this thesis, RAP, summarizing current knowledge and identifying key gaps in the literature. This chapter includes two comprehensive systematic reviews: one on existing continuous CC/CCR monitoring methods and the other on prior studies exploring the relationship between continuous MMM cerebral physiology and RAP in TBI patients.

Chapter 3 outlines the general methodological framework applied across the studies presented in the following chapters. It details the patient cohorts involved, including data sources and inclusion criteria, and provides an overview of the signal acquisition and processing methods used for high-resolution physiological data. This chapter also addresses the ethical approvals obtained for data collection and sharing, along with a summary of the statistical approaches commonly employed throughout the thesis. While each subsequent chapter presents study-specific methodologies, Chapter 3 serves to establish a cohesive foundation for the work that follows.

Chapter 4 explores the temporal characteristics of RAP alongside its constituent signals, ICP and AMP. This chapter also examines the possibility of identifying artifactual data in RAP with eligible features, utilizing the time series modeling of RAP, ICP and AMP. This study aims to address Hypothesis #1.

Chapter 5 analyzes the relationship between RAP and MMM cerebral physiology using summary measurements, various plots, and statistical comparisons across different established threshold ranges of different parameters. It further employs semi-supervised learning machine learning (ML) models to identify clustering patterns among the physiological variables, focusing on RAP. This chapter concludes with high-frequency temporal response analyses. This study addresses Hypothesis #2.

Chapter 6 summarizes various conclusions of the studies and their alignment with the thesis hypotheses. Chapter 7 outlines potential directions for future research.

2 Review of Literature

2.1 Definition of TBI

TBI can be referred to as a disruption in normal brain function or structural brain integrity resulting from an external mechanical force.¹⁷ It encompasses a wide range of severity, from mild concussions to severe injuries involving prolonged unconsciousness or death. TBI is typically classified into two major pathophysiological phases: primary injury and secondary injury.

Primary injury refers to the immediate mechanical damage that occurs at the time of trauma.¹⁸ This includes cerebral contusions, lacerations, intracranial hemorrhage, axonal shearing, and skull fractures. These injuries are often irreversible and set the stage for subsequent pathologic cascades.¹⁸

Secondary injury, in contrast, evolves over time, developing over minutes to days following the primary insult, and contributes significantly to morbidity and mortality in TBI.¹⁹ Secondary injury results from a complex interplay of biochemical, cellular, and physiological processes, including excitotoxicity, oxidative stress, inflammation, cerebral edema, ischemia, and impaired autoregulation.²⁰ These mechanisms often lead to increased ICP, decreased CPP, and ultimately, neuronal death.²¹

2.2 Definition of CC/CCR

CC/CCR is a fundamental physiological concept describing the brain's ability to accommodate changes in ICP without substantial increases in ICP. The intracranial compartment is a rigid, fixed-volume space enclosed by the skull, containing brain tissue, cerebrospinal fluid (CSF), and blood.²² According to the Monro-Kellie doctrine, the total volume of these components must remain constant; any increase in one component must be offset by a decrease in another to maintain normal ICP. Marmarou and colleagues published one of the earliest quantitative descriptions of CC/CCR in 1975,²² which quantifies CC/CCR as follows:

$$\frac{\text{resulting change in ICP } (\Delta P)}{\text{change in ICV } (\Delta V)}$$

CC/CCR reflects the elasticity or buffering capacity of this system. When compliance is high, small increases in ICV, such as those due to edema, hemorrhage, or increased cerebral blood volume (CBV), can be well tolerated with minimal rise in ICP. However, as compliance becomes exhausted, even minor volume shifts lead to steep increases in ICP, indicating decompensation and higher risk for secondary brain injury. This relationship results in a pressure-volume (P-V) curve from which the pressure-volume index (PVI) was derived. PVI is a foundation metric for assessing CC/CCR to date.

2.3 Importance of MMM of Cerebral Physiology in Neurological Illness

The management of acute neurological illnesses, particularly moderate-to-severe TBI, has evolved significantly over recent decades. While primary injury mechanisms are largely immutable following the initial insult, secondary injury cascades, including ischemia, excitotoxicity, oxidative stress, and intracranial hypertension, are modifiable and form the basis for current clinical interventions.^{19,21} The primary goal of intensive care management in this context is to prevent or attenuate secondary brain injury. Achieving this requires a comprehensive understanding of dynamic cerebral physiology, which has led to the increasing adoption of MMM techniques in neurocritical care.

MMM refers to the simultaneous and continuous monitoring of multiple intracranial and systemic physiological variables to guide individualized patient management.²³ This approach has become integral to modern neurocritical care, as it provides clinicians with real-time insight into complex, interacting physiological processes that extend beyond the limited scope of any single variable. Key monitored parameters typically include ICP, CPP, PbtO₂, CA, and cerebrovascular reactivity (CVR), among others.^{3–6,23}

2.3.1 ICP

ICP monitoring remains a cornerstone in the care of moderate-to-severe TBI. As the cranial vault is a rigid compartment, any increase in the volume of brain tissue, blood, or CSF can lead to elevated ICP and compromised cerebral perfusion. Contemporary guidelines recommend active intervention when ICP exceeds 22 mmHg due to its association with poor long-term neurological outcomes.^{3,4} Clinical management includes both medical therapies and surgical interventions (e.g., decompressive craniectomy or CSF diversion).³ Accurate and continuous measurement of ICP is essential in comatose or sedated patients, where neurological examination is not feasible.²⁴ Typically, strain-gauge parenchymal probes or external ventricular drains are used for this purpose.⁴

2.3.2 CPP

CPP is determined from the difference between MAP and ICP, that represents the driving pressure for cerebral blood flow (CBF). Ensuring adequate CPP is crucial to prevent cerebral ischemia. Both low CPP (<60 mmHg) and excessively high CPP (>70 mmHg) have been associated with adverse outcomes, including ischemia and cerebral edema, respectively.^{3,4} Although the Brain Trauma Foundation (BTF) and Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) recommend maintaining CPP between 60–70 mmHg,³ evidence supporting a universal target remains inconclusive.³ As

such, there is growing interest in developing individualized CPP targets guided by autoregulatory status, a strategy that may better accommodate patient-specific pathophysiology.

2.3.3 PbtO₂

Monitoring brain tissue oxygenation offers an additional dimension to ICP and CPP measurements by providing insight into the adequacy of cerebral oxygen delivery at the tissue level.²⁵ PbtO₂ monitoring, typically via an intraparenchymal probe, can guide therapeutic interventions such as increasing systemic blood pressure, optimizing ventilation, or transfusing red blood cells.^{5,26} While studies suggest improved outcomes with PbtO₂-guided management, limitations such as sampling bias, microtrauma from probe insertion, and limited spatial coverage highlight the need for cautious interpretation.^{27,28}

2.3.4 CA and CVR

CA is defined as the ability of cerebral vasculature to maintain stable CBF despite fluctuations in systemic arterial pressure.²⁹ It is critical in preserving brain homeostasis.²⁹ When autoregulation fails, the brain becomes vulnerable to hypo- or hyperperfusion, depending on systemic conditions.^{30,31} MMM allows for indirect, yet continuous assessment of autoregulatory capacity using metrics such as the pressure reactivity index (PRx) and the pulse amplitude index (PAX).^{32,33} These indices help identify “pressure-passive” states and can be used to tailor hemodynamic targets in an individualized manner.

2.3.5 Clinical Relevance of MMM

The importance of MMM lies in its ability to capture the complex and dynamic interplay between intracranial and systemic physiology. It enables clinicians to detect early signs of secondary injury, assess response to interventions, and develop individualized management strategies. For instance, persistent elevation of ICP, despite optimized CPP and PbtO₂ may indicate a failure of CVR, guiding consideration of alternative interventions. Additionally, the integration of autoregulation monitoring supports a shift toward personalized neurocritical care, where optimal CPP is derived based on patient-specific cerebral physiology rather than generic thresholds. Accumulating evidence and the continued development of standardized monitoring protocols suggest that MMM will play an increasingly central role in the future of neurocritical care.

2.4 Role of CC/CCR Monitoring in Human Health and Disease

While MMM has become integral to the care of patients with acute neurological injuries, CC/CCR remain relatively underexplored domains within this framework. The previous section highlighted common MMM

metrics, yet omitted CC/CCR, a reflection of the limited clinical integration and research attention it has received to date.

When the compensatory mechanism fails, even minor volume changes can trigger abrupt and dangerous increases in pressure, predisposing the brain to secondary insults such as ischemia and herniation.³⁴ Thus, monitoring CC/CCR is essential for understanding intracranial dynamics beyond static pressure measurements.

Integrating compliance monitoring into MMM could provide critical contextual information for interpreting standard metrics. For instance, persistent ICP elevation in the setting of optimized CPP and PbtO₂ may signal compliance failure rather than perfusion deficit. Without compliance data, such scenarios may be misinterpreted, potentially leading to suboptimal interventions.³⁵ Furthermore, compliance monitoring may serve as an early warning indicator of decompensation and a biomarker of treatment response, with particular relevance in conditions such as hydrocephalus, malignant stroke, or evolving traumatic mass lesions.

2.5 Methods of CC/CCR Monitoring

2.5.1 Intermittent Methods

Historically, CC/CCR was measured intermittently using techniques that assessed the ICP response to induced changes in ICV.^{34,36} One of the earliest and most widely recognized methods was the Marmarou infusion test, introduced in the 1970s.³⁴ In this approach, a known volume of fluid (typically saline or artificial CSF) was infused into the ventricular system or lumbar subarachnoid space at a constant rate, while ICP was continuously recorded during the infusion and subsequent plateau phases.³⁴ The PVI, a measure derived from this method, was calculated to quantify the brain's compensatory reserve and compliance capacity.³⁴ Another related method, the bolus injection technique, involved the rapid injection of a small volume of fluid into the intracranial compartment, with ICP changes analyzed to derive similar pressure-volume dynamics.³⁶ While these approaches provided foundational insight into cerebrospinal compensatory mechanisms, they were invasive, carried infection risk, required specialized equipment and personnel, and could not be repeated frequently or continuously due to the procedural burden they imposed on patients and clinicians.

These intermittent methods, although effective for discrete assessments, lacked the temporal resolution needed to capture the dynamic and evolving nature of CC/CCR, especially in critically ill patients where physiological parameters can shift rapidly. Furthermore, the assumptions underpinning these techniques,

such as constant cerebrospinal outflow resistance or steady-state conditions, often do not hold in acute pathologies like TBI or hydrocephalus.³⁷

Given these limitations, there is a clear clinical demand for continuous, non-invasive or minimally invasive methods that can track CC/CCR in real time. The need for continuous monitoring of CC/CCR arises from the dynamic and often unpredictable nature of cerebral pathophysiology, especially in conditions such as TBI, hydrocephalus, intracerebral hemorrhage (ICH), and other acute neurological insults. In such critically ill patients, key physiological parameters, including ICP, CBF, ABP, and brain oxygenation, fluctuate on a minute-by-minute or even second-by-second basis. These fluctuations can result in significant alterations in compliance, which may not be captured with intermittent measurements. Intermittent assessments risk missing important physiological transitions, such as the onset of CC/CCR exhaustion, a state where even minor volume increases can lead to dramatic ICP elevation and neurological deterioration.

Modern bedside technologies, those providing continuous high-resolution ICP waveforms, facilitate the derivation of methods or metrics which can serve as a surrogate for real-time compliance monitoring. These continuous indices overcome the temporal and logistical limitations of older infusion-based methods and offer far more granular, actionable information during critical care management.^{37,38}

2.5.2 Continuous Methods

This section summarizes the following systematic review:

- **Islam A**, Froese L, Bergmann T, et al. Continuous monitoring methods of cerebral compliance and compensatory reserve: a scoping review of human literature. *Physiol Meas* 2024;45(6); doi: 10.1088/1361-6579/ad4f4a.

In recent years, research has been conducted on the different approaches of continuous monitoring of CC/CCR aimed at objective quantification of patient state to get a more robust understanding, potentially leading to personalized routes of care. As time has advanced, the importance of monitoring CC/CCR in a continuous manner for critically head-injured patients has become evident. Recent advancements make this continuous monitoring of CC/CCR possible.^{39,40}

While RAP is the most popular metric for measuring continuous CC/CCR,⁴¹ the Spiegelberg Compliance Monitor comes closest to RAP in terms of directly measuring compliance.⁴² This method resembles fully invasive intermittent approaches but operates continuously.^{43,44} TCD-based measurements are also utilized to measure compliance, but these approaches do not directly estimate compliance but operate under the assumption that the ICP pulse waveform is the response to changes in cerebral arterial blood volume

(CaBV) within a single cardiac cycle.^{45–48} However, TCD-based measurements uniquely distinguish between cerebrospinal and arterial components of total cerebral compliance, a differentiation absent in RAP.^{46,48} Additionally, the P2/P1 ratio (i.e. the height of the peaks ICP pulse) and centroid metrics (i.e., the frequency of the ICP pulse) are also used to indirectly estimate compliance by analyzing characteristics of the ICP pulse shape.^{49,50} Combining these five principal approaches will present a persuasive depiction of the continuous measurement of CC/CCR.

Most prior studies primarily focused on defining these methods and the approach to measure continuous CC/CCR quantitatively. These analyses largely emphasized the relationships between these measurements and various physiological parameters or medical interventions, with some highlighting these methods' reliability in predicting patient outcome.

These analyses mainly focused on patients with TBI and hydrocephalus, with a few exceptions. To provide a more focused and comprehensive description, each method will be discussed in relation to specific patient populations. Accordingly, the description will be divided into three distinct sections, where applicable:

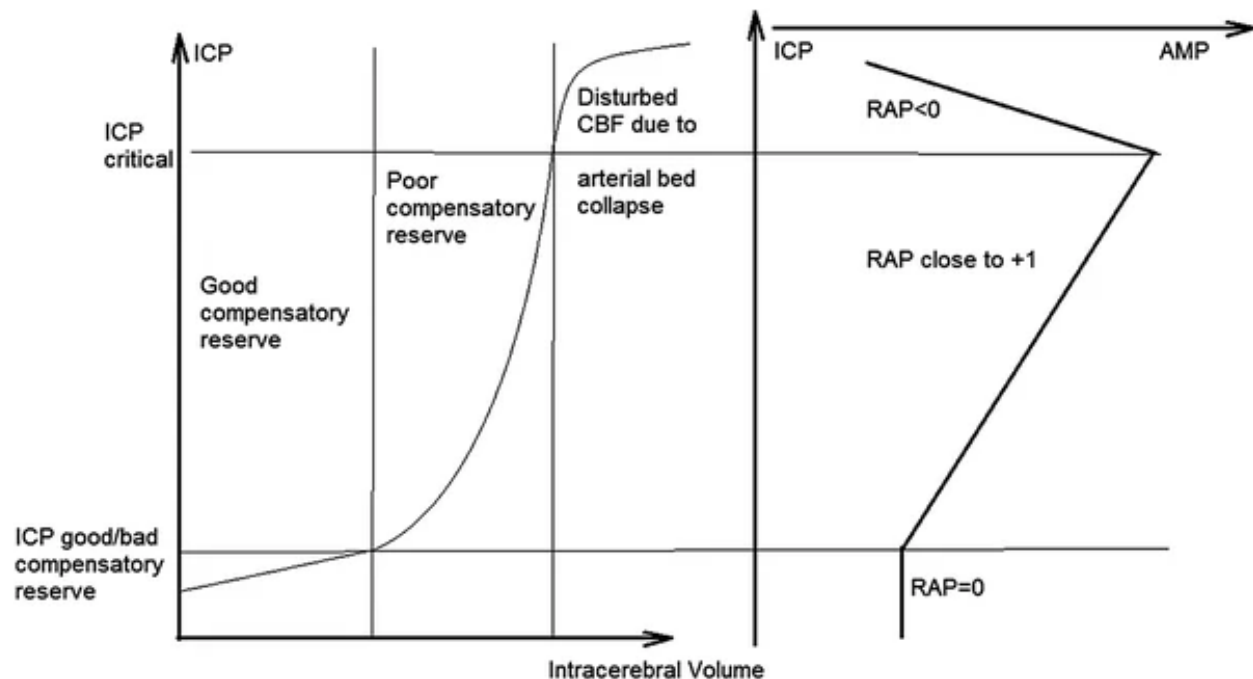
- Studies with TBI patients
- Studies with hydrocephalus patients
- Studies with other patients

2.5.2.1 CC/CCR index – RAP

Among all the methods, RAP is the most popular metric for measuring continuous CC/CCR. As mentioned earlier in section 1.1, RAP is calculated as a moving Pearson correlation coefficient between ICP and AMP, ranging from -1 to +1. Lower positive RAP values suggest that CC/CCR is still preserved, while increasingly positive or negative values indicate impaired and exhausted CC/CCR, respectively.

Figure 2.1 on the next page, collected from the study conducted by Calviello et al and colleagues,¹⁴ shows the relationship between RAP and its constituent signals. In the intact state, as ICP rises, an intact CVR mechanism prevents significant changes in AMP by controlling the constriction and dilation of the vessels. Therefore, RAP remains at close to 0. However, when ICP continues to increase and CVR becomes impaired, AMP also begins to rise, leading to a high positive RAP value (i.e., close to +1), which indicates compromised compliance. If ICP keeps increasing and exceeds a critical threshold, cerebral vessels reach a maximum vasodilation state and cerebrovascular function breaks down, leading to reduced transmission of pulse pressure, i.e., reduced AMP. This leads to a negative RAP value (i.e., $RAP < 0$), a characteristic of exhausted CC/CCR. A more detailed physiological explanation of RAP decreasing to a negative value is provided in a later section (section 2.7.3).

Figure 2.1 Schematic diagram of RAP, ICP and AMP relationship



The figure¹⁴ shows the relationship between RAP, ICP and AMP. Left: The extended shape of the pressure–volume (P/V) curve showing three zones: intact, impaired and exhausted CC/CCR. Right: The associated relationship between the AMP and mean ICP.

AMP, pulse amplitude of ICP; CBF, cerebral blood flow; ICP, intracranial pressure; RAP, index of cerebral compensatory reserve;

2.5.2.1.1 Studies with TBI patients

To assess CC/CCR of TBI patients, 26 studies used RAP metric.^{7,8,14–16,41,45,47,51–68} Among the studies that reported the age of the patients, in most cases, the mean age was between 30-50 years, except for three studies,^{58,59,65} where the mean age was 59.6, 55.7, and 53.2 years, respectively. The majority of these studies experimented and reported the association of RAP with other physiological factors, patient outcomes, and brain imaging.

Association with other physiologic parameters

Three studies^{14,41,61} demonstrated the relationship between ICP and RAP. Evident sign changes and significant variance of RAP were observed with the change of ICP. Moreover, when ICP was unchanged, RAP was found to be constant.^{14,41,61} This proves the future potential of RAP for predicting ICP events and patient outcome.

CPP also showed a noticeable trend with RAP.⁴¹ With the increase of CPP, RAP was reduced to zero. However, a steep increase was evident in RAP when CPP decreased towards the lower limit of autoregulation.⁴¹ This suggests both impaired RAP and impaired CA were associated with decreased CPP. Several studies reported their relationships.^{41,62,63} PRx is one of the CA measurements, which is derived from the moving Pearson correlation coefficient between slow waves of ICP and MAP.⁴¹ A negative or near-zero PRx suggests that even though MAP is changing, ICP remains the same; therefore, the brain is actively regulating its blood flow, a sign of good vascular reactivity and preserved autoregulation.^{41,62,63} A positive PRx suggests a “pressure-passive” state, where, with the change of MAP, ICP also changes, as cerebral vessels are no longer reacting appropriately to changes in MAP. This is associated with worsening outcomes.^{41,62,63} It was evident from the prior studies that positive PRx was associated with impaired RAP, i.e., impaired autoregulation was associated with impaired RAP.^{41,62,63} The same was observed with respect to another recently derived CA index – RAC, which is calculated as the moving correlation coefficient between AMP and CPP.⁴¹

Apart from these key physiological parameters, RAP also showed consistent patterns with many other cerebral and systemic physiological factors. The relation between respiratory oscillations (R waves) and RAP was researched by Haubrich and colleagues, and they found that an increase in RAP is associated with a decrease in GainFv (the transfer function gains of R waves between arterial blood pressure (ABP) and doppler flow velocity (FV)), i.e. reduction in R waves.⁵⁶ One study conducted research on the association of RAP with the transfer function of ABP to ICP at the fundamental cardiac frequency. This transfer function was denoted as MTF, and the result showed that RAP is positively correlated with MTF and negatively correlated in their variances.⁶³ In another experiment, after exploring the association of RAP with hyperventilation in TBI patients, the result showed that RAP was reduced due to hyperventilation and showed a significant correlation with hyperventilation-induced reduced ICP.⁴⁵ A different study showed that RAP decreased due to spindle waves, a distinctive pattern observed in Electroencephalogram (EEG) during the non-rapid eye movement (NREM) sleep stage.⁶⁵ This was evident in both scenarios – scenario 1, a comparison between the control and spindle wave group, and scenario 2, a comparison (within the spindle wave group) between during spindle wave occurrence and before and after the period of that occurrence.⁶⁵ Furthermore, a comparative analysis of the RAP metric between TBI and idiopathic normal pressure hydrocephalus (iNPH) patients was conducted by two studies.^{58,59} RAP baseline was not significantly different between the two groups.⁵⁸ Similarly, when comparing shunted post-traumatic hydrocephalus (PTH) vs non-shunted PTH, the difference was insignificant.⁵⁸ However, following continuous infusion tests, a notable increase in RAP of the PTH group was noticed.⁵⁹

The effect of surgery, medical treatment and agents on RAP was investigated in five studies.^{8,54,55,57,64} The association of RAP with decompressive craniectomy was observed in two studies.^{57,64} Both of the studies were aligned with the findings of decreasing RAP after decompressive craniectomy.^{57,64} In addition, Howells and collaborators studied RAP's association with thiopental treatment.⁵⁷ One of the major findings was that after thiopental treatment, a significant or marginally significant downward shift of RAP was noticed.⁵⁷ Another medical procedure, ventriculostomy, demonstrated reducing RAP.⁸ Two studies examined the impact of vasopressor and sedative agents on RAP.^{54,55} In both cases, their findings revealed that, overall, there was no significant change in RAP due to these medications. This was experimented with using mean hourly dose and incremental dose change protocols.^{54,55} However, sedation depth was examined, and a negative linear relation was revealed between the bispectral index (BIS) and RAP.⁵⁵

Lastly, three studies reported their subject as head-injured patients.⁶⁶⁻⁶⁸ One of the studies analyzed the impact of increasing ICP on R-waves based on RAP value.⁴⁸ RAP exceeding 0.85 reflects a substantial impact on R-waves gain with increasing ICP. Conversely, while RAP was below 0.85, it resulted in a lower impact on R-wave gain with rising ICP.⁴⁸ Haubrich and his group also studied the effect of RAP in response to mild hypocapnia. Their findings indicated a significant level of decrease below baseline in RAP, and hypocapnic ICP showed a positive correlation with baseline RAP.⁶⁷ The remaining study centred on the intensive care monitoring "plus" (ICM+) software and illustrated its usefulness in measuring the RAP metrics.⁶⁸

Association with Neuroimaging Features

The association of RAP with imaging was observed in one study.¹⁵ The relation of RAP with admission Computer Tomography (CT) injury characteristics was examined, and the integrated Area Under the Curve (AUC) was found to be statistically associated with CT markers of diffuse TBI across different RAP thresholds.¹⁵

Association with Patient Outcomes

Research was conducted to find out the association of RAP with patient outcome in four studies.^{14,52,53,61} Significant difference in RAP was found between the survivor and fatal outcome groups as well as between individuals with severe disability and those with a favourable outcome.¹⁴ In a different study, RAP illustrated a significantly lower value in patients with fatal outcome or patients in the vegetative state and RAP declined and oscillated towards 0 and negative value.¹⁶ Similarly, low RAP was identified in patients with severe intracranial hypertension.⁵³ This is because of the transitional phase of RAP, when large positive RAP starts to reduce due to the dysfunction of the cerebrovascular mechanism, which eventually goes to

negative. Another study investigated the potential of RAP in predicting cerebral hemodynamic instability and found RAP could identify unstable periods if it exceeded 0.6, providing a better distinguishing factor than ICP or AMP.⁶¹

2.5.2.1.2 Studies with hydrocephalus patients

The analyses of the RAP metric for patients affected with hydrocephalus were discussed in 11 studies.^{10,69–78} The majority of these subjects were elderly patients, more than 50 years old. However, two studies included children as their subjects.^{69,74}

Association Between RAP, Infusion Testing and Shunting:

The effect of CSF infusion on RAP was explored in six studies.^{10,69,71,76–78} The majority of the studies showed increased RAP during infusion of CSF. RAP was also shown to act as a marker of equilibrium before and during recovery following an infusion test.⁶⁹ In contrast, low RAP during infusion was observed in atrophic profiles, which could be caused by cerebrovascular or neurodegenerative diseases.

Experiments were conducted on NPH patients to assess the impact of shunting on RAP.^{10,73,74,77} Among patients with ventriculomegaly, RAP significantly improved (i.e., RAP decreased).^{10,73} Regarding shunting, patients with normal pressure hydrocephalus (NPH) and ventriculomegaly typically exhibited improved RAP (i.e., reduced RAP) following shunt placement.^{10,73,74,77} Furthermore, RAP demonstrated promise in detecting shunt malfunction, with significantly different values observed between patients with functioning shunts and those experiencing shunt failure.^{74,77}

Association with other physiologic measures:

Several studies investigated the association of RAP with other parameters and cases.^{10,70,72,75,76,78} For instance, exploring the relationship between RAP and the phase shift angle between fundamental harmonics of cerebral blood flow velocity (CBFV) and ICP illustrated a negative correlation.⁷² In another study, a strong positive correlation was observed between RAP and the resistance to CSF outflow (R_{CSF}), while a weaker correlation was observed with ventriculomegaly.¹⁰ Speil and collaborators conducted a study comparing RAP with both elastance (E) and PVI.⁷⁵ In this study, E and PVI were measured through a lumbar infusion test. However, no significant correlation existed between them.⁷⁵

In a different experiment, the association between cerebral hemodynamic indices (critical closing pressure (CrCP)), wall tension (WT), closing margin (CM)) was observed along with RAP.⁷⁶ No association between RAP and CrCP, WT or CM was found. However, it was suggested that CM at baseline pressure could be utilized as an indicator of RAP since it was negatively correlated with cerebrospinal elasticity.⁷⁶

Additionally, analysis was conducted to determine the relation between ICP pulse shape changes, CBFV, and intracranial compliance.⁷⁸ A new index called the ratio of pulse slopes (RPS) was introduced for this purpose, based on the inclinations of the ascending parts of the ICP and CBFV pulse waveforms.⁷⁸ The findings introduced a strong positive correlation of baseline RAP with intracranial elasticity and negative correlations with the height ratio of the first and second peaks of the ICP pulse (P1/P2) and RPS.⁷⁸

2.5.2.1.3 Studies with other patient populations

Aside from TBI and NPH patients, there are an additional six studies that include a diverse patient population investigating the RAP metric.^{37,79–83} The mean age across these studies varies from each other, since they explored different aspects within various types of patients.

Analysis of RAP in patients with intracranial hypertension was conducted in two studies.^{37,79} In the study of the comparison between patients with favourable and fatal outcomes, a progressive increase in RAP was observed over time, along with a sudden decrease when ICP started to increase in cases of patients who died.⁷⁹ In contrast, patients with a favourable outcome persistently showed a higher RAP.⁷⁹ Czosnyka and colleagues, while studying cerebrospinal dynamics, classified patients into group 1 with low RAP (good CC/CCR), group 2: RAP is high and increasing with decreasing CPP, and group 3: RAP is close to +1 (nearly exhausted RAP). Furthermore, RAP became negative when CPP dropped below 30 mmHg, indicating a critical disturbance in cerebral circulation.³⁷

Two studies analyzed patients with subarachnoid hemorrhage (SAH) and ICH.^{80,81} Combining RAP with ICP monitoring proved to be an effective marker in an experiment of SAH patients.⁸¹ The monitoring of the RAP index allowed an opportunity for implementing additional interventions to reduce ICP before clinical worsening, thus minimizing irreversible damage to brain tissue.⁸¹

Additionally, Moyse and collaborators examined states of RAP in the supratentorial and infratentorial compartments of a 70-year-old patient with acute cerebellar infarction and infratentorial mass effect.⁸² The correlation of RAP in the two compartments was strong, and their values did not align precisely but were close.⁸² In another study, observation of RAP in hypoxic ischemic brain injury (HIBI) patients showed impaired RAP along with normal ICP in most of the cases.⁸³

2.5.2.2 Spiegelberg Compliance Monitor-based continuous measurement

Recently, the Spiegelberg Compliance Monitor has emerged as a valuable and widely used tool for the continuous assessment of CC/CCR at the bedside. This device operates by inserting either an intraventricular or intraparenchymal catheter into the patient's brain, allowing for direct interaction with

intracranial dynamics. The monitor assesses CC/CCR by analyzing small ICP perturbations (ΔP) in response to a series of small, controlled volume additions (ΔV), which are typically generated through up to 200 brief inflation pulses. Based on the relationship $\Delta V/\Delta P$, the monitor calculates a real-time compliance value. Once the system achieves a stable average, it provides minute-by-minute measurements of CC/CCR, offering clinicians continuous insight into the brain's pressure-volume compensatory capacity. Thus, in this context, the interpretation of intact and impaired CC/CCR differs from that of RAP. A higher $\Delta V/\Delta P$ value indicates better cerebral compliance.

As with the previous section, the entire discussion is structured into three parts, each corresponding to a specific patient population.

2.5.2.2.1 Studies with TBI patients

Six studies conducted research with the TBI cohort that used the Spiegelberg Compliance Monitor-based CC/CCR.^{9,39,43,84–86} In regard to the relationships between physiological parameters, analysis was conducted on the potential of continuous CC/CCR to predict increased ICP.^{43,84} CC/CCR correctly predicted 37 increased ICP episodes from 225 episodes.⁴³ Furthermore, continuous CC/CCR and ICP had a scattered correlation (44), which reduced significantly with a rise in ICP.⁸⁴ In another study, the association of continuous CC/CCR with CPP was explored with a designated threshold of CPP = 60 mmHg. CC/CCR was significantly lower when CPP was below 60 mmHg.⁹ Though CPP exceeding 60 mmHg resulted in a higher CC/CCR, it dropped dramatically when CPP reached 100 mmHg.⁹ The relationship between continuous CC/CCR and the lactate/pyruvate (L/P) ratio was observed by Salci and team.⁸⁵ As CC/CCR decreased, the L/P ratio increased with or without high temperature. Notably, when the temperature was elevated, there was a greater increase in the L/P ratio.⁸⁵ Furthermore, the analysis revealed that individuals with lower CC/CCR were more susceptible to secondary hyperthermia.⁸⁵

Regarding the associations with other clinical factors, Abdullah and colleagues reported that, after undergoing decompressive craniectomy, CC/CCR improved substantially in all surviving patients.³⁹ Lastly, in two studies, a consistent association between CC/CCR and age was observed; as age increased, CC/CCR increased as well.^{43,86}

2.5.2.2.2 Studies with hydrocephalus patients

The application of the Spiegelberg Compliance Monitor to measure continuous CC/CCR in hydrocephalus patients was researched for different aspects in four studies.^{87–90} The performance and result of this continuous measurement method were compared with a manual volume injection /withdrawal method in one of the studies, where a strong positive correlation was found between them.⁸⁸ Their average

measurements were quite similar, with the continuous method showing a slightly higher value.⁸⁸ This further proves the validity of this method.⁸⁸

The exponentially-weighted moving average (ewma) method was introduced in another analysis, which utilizes a smoothing technique that assigns exponentially decreasing weights to past observations, giving greater emphasis to the most recent data while still retaining information from prior values. The result from ewma showed that it was more strongly correlated with ICP than the conventional Spiegel “rolling” method in terms of calculating continuous CC/CCR.⁸⁹ The functional and compliance improvement following CSF shunting was also investigated with the Spiegelberg Compliance Monitor measurement. Except for one, all the other patients had noteworthy improvement.⁹⁰ Lastly, in another study, continuous CC/CCR remained unchanged across different body positions.⁸⁷

2.5.2.2.3 Study with other patient populations

Other than research on TBI and hydrocephalus patients, Spiegelberg Compliance Monitor was also used in the case of patients with abnormal hematoma volume in one study.⁹¹ It was observed that performing ultrasound-guided aspiration in patients with abnormal hematoma volumes resulted in a sustained enhancement of intracranial compliance, along with a gradual decrease in ICP.⁹¹

2.5.2.3 TCD-based continuous measurement

In recent years, TCD ultrasound has emerged as a promising non-invasive method for assessing CC/CCR, particularly by examining the relationship between CBFV and the components of intracranial compliance—namely, cerebral arterial compliance (C_a) and cerebrospinal space compliance (C_i).^{44,92} Using TCD, CaBV can be derived from CBFV waveforms. C_a is then calculated as the ratio between the pulsatile amplitude of CaBV (AMP_{CaBV}) and the pulsatile amplitude of ABP (AMP_{ABP}). In contrast, cerebrospinal compliance (C_i) is estimated as the ratio of AMP_{CaBV} to AMP .⁹² These derived indices allow for real-time, non-invasive estimation of compliance dynamics, offering a valuable alternative in scenarios where invasive monitoring is not feasible.

2.5.2.3.1 Studies with TBI patients

Three studies analyzed TCD-based continuous measurement of CC/CCR, focusing on TBI patients.^{44,92,93} In one of the studies, Carrera and team investigated the changes of C_i and C_a induced by initial hyperventilation and observed an increase in C_i and a decrease in C_a . ICP was also reduced in this phase and correlated with C_a reduction.⁴⁴ The period of sustained hyperventilation was also observed, and though ICP was elevated and C_i was reduced, no noteworthy change in C_a was observed.⁴⁴ The state of C_a and C_i

was observed in a study regarding continuous monitoring of the Monro-Kellie doctrine.⁹² An index of CC/CCR was introduced, which was defined as a moving correlation coefficient between C_a and C_i , and denoted by ICC.⁹² Three phases were monitored – a. during arterial hypertension, b. during plateau waves, and c. during intracranial hypertension. C_a and C_i showed a negative correlation during arterial hypertension, leading to a negative ICC. During plateau waves, both C_a and C_i increased. In contrast, at the intracranial hypertension phase, both C_a and C_i were reduced, and a consistent and positive ICC was exhibited.⁹² Regarding outcome, the study also depicted that a higher ICC was associated with a higher mortality rate, indicating that a higher ICC suggests impaired CC/CCR.⁹² In addition, this defined ICC demonstrated a significant and positive correlation with PRx but none with ICP, mean ABP, or CPP.⁹² Alongside these findings, in another study, Kim and collaborators observed the compartmental compliance changes (i.e., the changes of C_a and C_i), focusing on plateau waves.⁹³ In the case of C_i , it reduced significantly during the plateau wave, followed by an increase. The opposite case was seen in terms of C_a since it increased during plateau waves and decreased afterwards.⁹³

2.5.2.3.2 *Studies with hydrocephalus patients*

TCD-based CC/CCR studies with hydrocephalus patients were found in three studies.^{48,94,95} Among which, CSF infusion tests were performed in all involving hydrocephalus patients. All of the tests demonstrated poorer compliance during the plateau phase of infusion, characterized by an elevated value of C_a , whereas a reduction in C_i and other discussed cerebral compliance indices.^{48,94,95} In one of the studies, after a total of 50 infusion tests, a strong negative correlation was found between C_a and cerebrovascular response as well as between C_a and CPP.⁹⁴ However, no correlation was noted between C_a and any CSF compensatory parameters – R_{CSF} , elasticity or ICP baseline.⁹⁴ In another infusion test study, brain elasticity was positively correlated with C_i , which was evident when comparing values from the baseline to the plateau phase and during the plateau phase itself.⁹⁵

In a comparative study where three CC/CCR measurement methods were evaluated, all of them were found to be strongly correlated with each other. These three methods – C_{CSF} , C_{CaBV} , and $C_{P1/P2}$ represented the cerebrospinal compliance and were derived from Marmarou's model of CSF dynamics, changes in C_{aBV} , and the amplitudes of peaks P1 and P2 of the ICP pulse waveform, respectively. Comparing their values between the baseline and plateau phase of the infusion test revealed that all of them reduced, with C_{CaBV} exhibiting the largest change, whereas $C_{P1/P2}$ had the smallest.⁴⁸

2.5.2.3.3 *Studies with other patient populations*

Aside from the TBI and hydrocephalus cohorts, two studied normal subjects^{46,96} and the remaining one involved patients with internal carotid artery disease.⁹⁷ Carrera and collaborators researched patients with internal carotid artery disease for predicting ischemic events.⁹⁶ Their findings encompassed a lower value of C_a for the diseased group during baseline, hyperventilation, and 5% CO_2 inhalation. Additionally, C_a and the degree of stenosis exhibited a reciprocal characteristic at baseline.⁹⁶ In addition, a comparative analysis was conducted on normal subjects, examining the differences between normo-, hypo- and hypercapnia.⁴⁶ While comparing with normocapnia, C_a was eminently lower in hypocapnia; however, in terms of hypercapnia, there was no difference between them. Furthermore, C_a was associated with CVR in an inversely changing manner, evident in both hypo- and hypercapnia.⁴⁶ Another study was conducted on healthy subjects, experimenting with the effect of sublingual sodium nitroglycerin protocol and hypercapnia protocol.⁹⁷ In both cases, cerebrovascular compliance decreased, with hypercapnia protocol associated with a comparatively higher reduction.⁹⁷

2.5.2.4 *HFC/HHC-based continuous measurement*

Another approach for estimating CC/CCR continuously is the use of two centroid metrics: A. The high frequency centroid (HFC), determined as the average power-weighted frequency within the 4 to 15 Hz frequency range of the ICP power density spectrum.^{49,98} B. The higher harmonics centroid (HHC), defined as the center of mass of the ICP pulse waveform harmonics from the 2nd to the 10th.^{51,99} The distribution of oscillatory energy across frequencies reflects the damping capacity of the intracranial system. In states of preserved compliance, arterial pulsations are buffered, resulting in lower relative contributions of higher-frequency components. Conversely, with impaired compliance, pulsations are transmitted more directly, amplifying higher-frequency harmonics and shifting the spectral centroid upward, thereby offering a physiologically meaningful surrogate of CC/CCR.^{51,99}

Five studies demonstrated the measurement method of continuous CC/CCR using HFC or HHC.^{49,51,98–100} All of the studies concentrated on TBI patients. In the study conducted by Contant and colleagues, though a direct association of HFC with CC was not mentioned, it was found that HFC decreased during the refractory ICH changes.⁹⁸ In contrast, it increased during the transient changes. Since the pulse amplitude of ICP (referred to as PAICP in the study) showed an inverse relation with CC/CCR and demonstrated an increased value in refractory ICH (not significant), it can be said that, probably, HFC and CC/CCR had a positive association, i.e., with the increase of HFC, CC/CCR increased.⁹⁸ However, the association of HFC with compliance is not straightforward since two other studies found that HFC was significantly greater in the group that met the fatal outcome, which was associated with poor CC/CCR.^{49,51} Regarding HHC, a

negative correlation was reported with PRx, indicating a negative correlation between CA and CC.⁹⁹ Additionally, Lang and the team found from their experiment that a non-invasive measurement of HFC results was similar to the invasively measured HFC, concluding the possibility of measuring CC/CCR by HFC non-invasively.¹⁰⁰

2.5.2.5 P2/P1 ratio-based continuous measurement

Distinct peaks from the ICP pulse wave, namely P1 (percussion wave) and P2 (tidal wave), were observed to be utilized for assessing continuous CC/CCR, as alterations in the P2/P1 ratio can indirectly indicate changes in CC/CCR.^{50,101} The measurement of continuous CC using the P2/P1 ratio was examined in six studies.^{50,101–105} Among the studies, three specifically targeted TBI patients, two focused on patients with hydrocephalus,^{104,105} and one examined patients with type 2 diabetes.¹⁰³ In an approach to assess CC/CCR utilizing ICPW, an increase in P2/P1 ratio was observed, which was associated with impaired CC/CCR in the patients with craniectomy.⁵⁰ Another parameter derived from the P2/P1 ratio, known as the Brain Compliance Index (BCI), demonstrated a higher value (i.e., impaired compliance) in the early death (ED) group.¹⁰² Furthermore, P2/P1 was higher in patients with ICH.¹⁰² Conversely, in the group with type 2 diabetes mellitus, no significant change in the P2/P1 ratio (i.e., no substantial change in CC/CCR) was observed compared to the control group.¹⁰³ However, a significant decrease in the P2/P1 ratio was noticed due to active postural change only in the group with type 2 diabetes mellitus.¹⁰³ A different study by Kuramoto and colleagues illustrated the influence of P2 in bulk compliance.¹⁰⁴ They observed that after the infusion test, P1 was smaller than P2 in the case of subdural hematoma cases, whereas P1 and P2 were either constant or hard to identify in hydrocephalus cases. Additionally, they noted an increment of P2 compared to P1 during the rapid eye movement (REM) period.¹⁰⁴

Special cases

Two studies focused on identifying real-time P1, P2 and P3 peaks from ICPW.^{51,105} Using a clustering method, 95.3%, 87.8%, and 87.5% accuracy was obtained for P1, P2 and P3, respectively.⁵¹ Meanwhile, Nucci and the team used artificial neural network to classify AMP into different classes and found a match of 88.3% of cases between their result and an expert examiner's observation.¹⁰⁵ These classes ranged from class I to class IV. A progressive increase in average elasticity index values was noted with the advancement of morphological class.¹⁰⁵

2.5.2.6 Other approaches for continuous measurement

Aside from RAP, Spiegelberg Compliance Monitor, TCD, HFC/HHC, and P2/P1 ratio, few other methods have been utilized to measure CC/CCR continuously. Two such studies are included in this systematic review focusing on patients with TBI.^{106,107}

The potential of representing continuous CC/CCR from a PV curve was experimented with. An indicator “a” was derived from a parabolic regression model, expressed initially from the PV curve but without a conclusive statement.¹⁰⁶ PCI is another index defined as the moment-to-moment correlation between ICP change and end-tidal CO₂ change. Throughout most of the observation period, PCI remained within the range of 0.1-0.2, where $PCI \approx 0$ suggests good compliance and $PCI \approx 0.2$ suggests poor compliance.¹⁰⁷

2.5.2.7 Conclusion

A majority of the studies discussing continuous methods of monitoring CC/CCR focus on TBI and hydrocephalus patients, whereas most of the hydrocephalus cases encompass infusion studies and analysis on the effect of the shunt. Another crucial aspect highlighted in this discussion is the numerous associations between these metrics and various physiological parameters, as well as patient outcomes, underscoring the utility of continuous CC/CCR in diverse medical contexts and its potential clinical applications.

2.6 Current Understanding of RAP

As outlined in Section 2.5.2.1, several studies have incorporated the RAP metric within broader investigations and have reported its associations with a variety of physiological parameters and clinical interventions. While these studies have contributed valuable insights into the potential significance of RAP, it is important to note that RAP was not the primary focus in any of these works. Instead, it was typically included as a secondary or supplementary measure within studies centred on broader topics, such as ICP dynamics, CA, or MMM. To date, no dedicated or systematic research effort has been undertaken that specifically targets RAP as the principal subject of inquiry. To potentially apply RAP in clinical practice, at least we need to have a clear understanding of the temporal characteristics of RAP and its constituent signals (i.e., ICP and AMP), develop approaches for RAP artifact management, and understand its association with other key cerebral physiologies within an MMM framework.

2.6.1 Current Understanding of the Temporal Profile of RAP

Since RAP is calculated as a moving Pearson correlation coefficient between ICP and AMP over time, it is inherently sensitive to fluctuations in these signals. These fluctuations can arise from physiological sources, such as cardiac and respiratory cycles, or from external artifacts like sensor noise, patient movement, or

procedural interventions. Without a clear understanding of the expected time-domain behaviour of RAP, it becomes difficult to distinguish between meaningful physiological changes and transient noise. It is essential to determine whether RAP contains any inherent trends across different time scales. If such characteristics are present, they could significantly affect the interpretation and modeling of RAP, especially in contexts where temporal stability is assumed. Without properly accounting for these potential features, future efforts in physiologic modeling that incorporate RAP may yield inaccurate or misleading results.

Moreover, it is equally important to evaluate the degree to which RAP is dependent on its constituent signals, ICP and AMP. If RAP demonstrates a relatively low physiological dependency on either or both of these signals, it will indicate that RAP represents a distinct physiological metric, rather than merely a derivative or reflection of its inputs. This distinction is critical because it implies that understanding RAP cannot be fully achieved by analyzing ICP and AMP in isolation. Rather, RAP must be analyzed with respect to other key physiologies. To this end, comparing the temporal characteristics of RAP with those of ICP and AMP can offer valuable insights into their interrelationships.

To date, no study has comprehensively examined the temporal characteristics of RAP alongside its constituent signals, ICP and AMP. Despite RAP's growing use as an index of CC/CCR, the literature remains notably silent on how this metric and its underlying components behave over time. This represents a significant knowledge gap, as the absence of such foundational insight limits both the interpretability of RAP in clinical settings and its integration into advanced physiological models. Before applying RAP in clinical settings, this major knowledge gap needs to be addressed.

2.6.2 Current Understanding of the RAP Artifacts

Accurate identification and distinction of artifacts from the true RAP signal are critical for reliable assessment of CC/CCR and intracranial dynamics. Artifacts, which may arise from patient movement, sensor displacement, or external interference, can introduce sudden fluctuations that significantly distort RAP measurements. If not properly recognized and managed, these artifacts can lead to erroneous interpretations of brain compliance status, potentially compromising clinical decision-making. Moreover, the presence of artifacts adversely affects the statistical properties and modeling of RAP time series, undermining the validity of predictive models and impairing the detection of subtle physiological changes.

However, research into artifact identification and management within RAP signals remains notably absent, similar to the lack of progress observed in the study of its temporal profile. To ensure the precision of RAP-based interpretations, it is essential to develop systematic approaches for distinguishing artifacts from physiological fluctuations. One possible solution is to leverage the temporal characteristics inherent in RAP

signals, such as their autoregressive structures, stationarity patterns, or correlation dynamics, to construct automated methods for artifact detection.

2.6.3 Current Understanding of the relationship between RAP and MMM cerebral physiology

This section and section 2.7 summarize the following systematic review:

- **Islam A**, Marquez I, Froese L, et al. Association of RAP Compensatory Reserve Index with Continuous Multimodal Monitoring Cerebral Physiology, Neuroimaging, and Patient Outcome in Adult Acute Traumatic Neural Injury: A Scoping Review. *Neurotrauma Rep* 2024;5(1):813–823; doi: 10.1089/neur.2024.0058.

As previously noted, although several studies have incorporated RAP in their research, it was not the central focus in all cases. Nonetheless, these studies provide insight into some associations between RAP and continuous MMM of cerebral physiology. A preliminary discussion of these relationships was presented in Section 2.5.2.1. However, that discussion addressed broader clinical contexts and various patient populations. To better support the objectives of this thesis, the following section presents a more focused examination of RAP's association with other MMM cerebral physiological parameters, specifically in adult TBI patients.

The change in different continuous MMM cerebral physiologic parameters with the change in RAP in TBI patients had been analyzed in 11 studies.^{8,14,15,41,53,64,66,108–111} These observations are based on diverse perspectives and conditions. However, researchers mainly mentioned these values without explicitly demonstrating the direct association of these parameters with RAP, but rather signifying the different conditions. In the sub-sections to follow, we aim to outline the RAP and MMM associations during these condition states.

2.6.3.1 Plateau Waves – RAP and MMM Associations

Four studies explored the values of physiologic parameters and RAP during plateau waves of ICP.^{14,108–110} Sustained and elevated periodic increases in ICP alongside a decrease in CPP can be observed in TBI patients. These periodic waves are known as plateau waves of ICP, characterized by a gradual elevation to peak pressure, sustained for an extended duration and then gradually returning to baseline afterward.¹⁰⁸

Two studies found increased RAP during the plateau wave, which indicated poor CC/CCR.^{108,110} However, instances with higher ICP values during the plateau wave resulted in a lower RAP,^{14,109} from 0.77 ± 0.18 to 0.44 ± 0.19 , as mentioned in the study conducted by Czosnyka and colleagues.¹⁰⁹ This result suggests a state of maximum vasodilation.^{14,109} Specifically, when ICP reached 52.3 mmHg, a reduced positive RAP

during the wave was noted,¹⁰⁹ whereas in cases with even higher ICP levels leading to fatal outcomes, RAP was found to be negative.¹⁴ Following the occurrence of plateau waves, RAP reverted to its initial state in the majority of observations,^{109,110} except one, where RAP remained the same.¹⁰⁸

While comparing the parameters during three stages of the plateau waves (before, during and after plateau waves), it was observed that impaired RAP was associated with increased ICP and PRx and a decreased CPP and PbtO₂.^{108–110} They returned close to their previous states after the wave.^{108–110} Additionally, one of the indices of autoregulation, Mx, and pulsatility index (PI) increased during the plateau wave with a decreased RAP, signifying disturbed autoregulation and increased vascular resistance, respectively.¹⁰⁹ A decrease in CBFV was observed during the wave, indicating a diminished ability of cerebral blood vessels to dilate, resulting in higher cerebrovascular resistance. This led to impaired autoregulation.¹⁰⁹ No significant change in ABP, amplitude of Slow vasogenic waves of ICP (Slow), brain temperature, and PAX was found.^{108–110}

Furthermore, in the research conducted by Castellani and colleagues, when comparing patients with and without plateau waves, higher RAP (i.e., poor CC/CCR) associated with slightly higher ICP were observed in the patients with plateau waves.¹⁰⁸ However, PRx, CPP, ABP and outcome (expressed by the Glasgow outcome scale (GOS)) had no significant change.¹⁰⁸

2.6.3.2 General ICP Fluctuations – RAP and MMM Associations

The analysis of three studies involved comparing parameters based on the ICP range.^{15,41,53} An increase in ICP was associated with a positive increase in RAP within a specific range of ICP.^{15,41,53} Exceeding that range led to a gradual decrease in RAP.^{15,53} As reported in two studies, RAP exhibited a gradual decrement characteristic when ICP > 50 mmHg.^{15,53}

In addition, other parameters, including ABP and PRx, increased progressively with both higher and lower RAP. Conversely, CPP, CVR, and PbtO₂ decreased.^{15,41,53} In one study, an increase in PAX was also observed in lower RAP.⁴¹ Regarding MAP, two studies reported an increment in MAP in both states of RAP (i.e., higher and lower RAP;^{41,53} however, one study reported the reduction of MAP with progressive arterial hypertension when RAP was exhausted, i.e. when RAP was decreasing.¹⁵

2.6.3.3 Impact of Operative Interventions – RAP and MMM Associations

Comparison of parameters based on different operative approaches is evident in three studies.^{8,64,111} Two studies observed parameter values before and after decompressive craniectomy.^{64,111} Both analyses reported an improved CC/CCR, i.e. lower RAP with a small positive value following craniectomy. A reduced ICP,

MAP, PRx and Slow were associated with lower RAP. However, CPP and ABP did not exhibit significant changes.^{64,111} The third study focused on the ventriculostomy, which led to a rapid reduction in RAP, signifying improved CC/CCR similar to that achieved with decompressive craniectomy.⁸ Similar to craniectomy, a decrement in ICP and MAP was associated with reduced RAP. Unlike craniectomy, an increase in CPP was associated in the case of ventriculostomy, while no significant change in the PRx index was noticed. Additionally, PbtO₂ increased, whereas the change in brain temperature was not significant.⁸

2.6.3.4 Considerations for RAP range in MMM Associations

One study analyzed the values of parameters in two different RAP ranges while observing the respiratory oscillations in CBFV.⁶⁶ When RAP exceeded 0.85, ICP, ABP, and FV were higher, and CPP was lower compared to cases where RAP was below 0.85. For both RAP ranges, ICP, ABP, Mx and PI were higher on day 4 compared to day 1 after sedation and mechanical ventilation, whereas CPP was lower on day 4. The increment in Mx and PI was more significant for RAP < 0.85.⁶⁶

2.6.3.5 Association of RAP with Patient Outcomes and Neuroimaging

In addition to RAP's associations with MMM physiological parameters, its relationship with patient outcomes and neuroimaging findings can provide valuable context for interpreting the physiological state of patients at varying RAP levels. This perspective can enhance our understanding of how and why specific physiological variables respond to changes in specific ranges of RAP, offering a more integrated view of cerebral dynamics in different clinical conditions.

2.6.3.5.1 Association with Neuroimaging Features

The association of RAP with neuroimaging was studied in one study, where research was focused on admission CT characteristics.¹¹² The analysis was conducted over two distinct time frames – the first 10 days of recording, and the first 48h of recording. In the context of the first 10 days of recording, certain CT characteristics exhibited a significant association with the AUC for RAP, where higher RAP was observed with an increase in those CT characteristics. These are – cortical gyral effacement, lateral ventricle compression, bilateral contusions, cortical SAH extent, cortical SAH thickness, and subcortical diffuse axonal injury (DAI).¹¹² On the contrary, while comparing with RAP, Marshall computed tomography (CT) grade, Rotterdam CT grade, Helsinki CT grade, and Stockholm CT grade – these CT grade systems were not significantly associated, whereas, Midline shift, number of DAI lesions, and total contusion volume were the non-significant continuous CT variables.¹¹²

The AUC for RAP was calculated for each patient by integrating the RAP signal over time using a sequential linear interpolation approach.¹¹² In the first 48h of recording, higher RAP AUC values were associated with the presence of subcortical and corpus callosal DAI lesions. However, none of the continuous CT variables were significantly associated.¹¹²

2.6.3.5.2 Association with Patient Outcomes

The relationship between RAP and patient outcome was investigated in nine studies^{16,37,59,61,65,113–116}. In these analyses, observations were conducted regarding the association of RAP with outcome, as well as the association with other parameters in different physiological conditions or outcomes that patients met.

Association in the comparison of survival vs. fatal group

Four studies analyzed the association of RAP with survival vs fatal outcomes.^{16,114–116} In all cases, RAP was significantly lower in the group that met the fatal outcome, which was less than 0.5 for all studies,^{16,115,116} except one, which reported 0.53 for the fatal outcome.¹¹⁴ The study conducted by Czosnyka and colleagues reported that $RAP < 0.5$ associated with $ICP > 20$ mmHg differentiated the two groups most significantly in their analysis.¹⁶

Concerning the relation of RAP with physiologic parameters in the context of comparing survival outcomes with the fatal group, lower values of ICP was evident with higher RAP values in the survival group.^{16,114} In contrast, one study observed no significant statistical difference in mean ICP or mean RAP in this comparison. Instead, the dominant ICP pulse type was significantly associated with RAP.¹¹⁶ Additionally, in moderate cases, $RAP > 0.5$ was associated with relatively higher CPP than the persistent vegetative state cases.¹⁶ On the contrary, this study did not identify a significant difference in ABP between the groups that experienced survival and fatality. The set threshold for the comparison was $ABP < 70$ mmHg. However, it is noteworthy that this specific threshold was effective in distinguishing the group with severe disability from both the survival and fatal groups.¹⁶

Association with other post-TBI Outcomes

Beyond RAP's association with survival vs fatal outcome, five studies investigated the association of RAP with outcome from other perspectives.^{37,59,61,65,113} While comparing PTH and atrophy groups, following continuous infusion tests, a notable positive increase in RAP of the PTH group was noticed, which was higher than that of the atrophy group.⁵⁹ For both of the cases, RAP increased during infusion. However, only the PTH group exhibited depleted CC/CCR.⁵⁹ Another study investigated the potential of RAP in predicting cerebral hemodynamic instability, characterized by abnormal rises in ICP following brain injury.

It was found that RAP exceeding 0.6 could identify unstable periods with an average positive predictive value of 74%.⁶¹ Asgari and team categorized the patients into ‘good,’ ‘intermediate,’ and ‘poor’ states utilizing the unsupervised training of the Hidden Markov model characterized by ICP, CPP, RAP and PRx.¹¹³ A ternary state variable assigned these categories, which were learned through the proposed Hidden Markov model training. RAP showed a gradual decrease from a good to a poor state, ending with a mean value of 0.39 in the latter.¹¹³ In another investigation, based on the values of AMP, RAP, mean ICP, and mean CPP, four states of the TBI patients were defined: state 1, state 2, state 3 and state 4.³⁷ RAP was close to zero and did not change with the increase in ICP at state 1, significantly positive at state 2, close to +1 at state 3, and switched to negative at state 4 with a further increase in ICP, marking the terminal stage of the patients.³⁷ Zhu and colleagues experimented with the effect of spindle waves in TBI patients, defined as a distinctive pattern observed in EEG during the NREM sleep stage.⁶⁵ It was found that RAP was significantly lower in the spindle wave group than in the control group.⁶⁵ A similar trend was observed with the Glasgow outcome scale extended (GOSE), with a lower value in the spindle group. In addition, while observing different periods of spindle wave, it was found that RAP during the spindle wave was significantly lower than before and after the spindle wave.⁶⁵

Additionally, shedding light on the association of parameters in these observations revealed that a higher value of ICP at base and R_{CSF} was associated with an elevated value of RAP in the possible PTH group than in the atrophy group.⁵⁹ However, in terms of detecting unstable cerebral hemodynamic periods, parameters other than RAP did not exhibit significant changes during stable versus unstable periods.⁶¹ In the two manuscripts, where different physiological states were described, one had three categories, and the other had four.^{37,113} The first study demonstrated a gradual decrement of RAP from good to poor state, which was associated with increased ICP and PRx.¹¹³ CPP also illustrated a higher value in the intermediate state. However, a lower value was found in the poor state.¹¹³ In the second analysis with four states, higher RAP was observed in states 1 and 2, followed by a lower values in states 3 and 4, even reaching a negative value in state 4.³⁷ With this variation in RAP, a rise in ICP and a decrease in CPP were associated across these four states. In state 4, ICP exceeded 65 mmHg, and CPP was lower than 30 mmHg.³⁷ Lastly, in the analysis involving the spindle wave, no significant difference was detected in ICP in the comparison of the spindle wave group to the control group.⁶⁵ However, ICP was lower during the occurrence of the spindle wave compared to the periods before and after the wave.⁶⁵

2.7 The definition of RAP states

Following the review of the current understanding of RAP, a notable observation emerged: specific RAP ranges appeared to correspond with consistent patterns in various MMM cerebral physiological signals and

clinical outcomes. Although some earlier studies defined physiological states based on different parameters, they did not focus exclusively on RAP as a defining metric. As the analysis progresses toward investigating the temporal characteristics of RAP, it will be interesting to explore whether RAP exhibits distinct temporal features across different ranges. Additionally, assessing how RAP correlates with other MMM physiological parameters within different ranges can reveal whether such associations remain consistent across different patients. Identifying varying patterns of association across RAP ranges could also enhance our ability to evaluate the severity of patient conditions and improve outcome prediction.

Therefore, to facilitate the objectives of this thesis, three distinct RAP states are proposed. These states are characterized by variations in RAP relative to primarily ICP and AMP, followed by other key physiological factors, as reported in previous literature.

2.7.1 Consistent pattern of continuous MMM cerebral physiology across RAP ranges

It's evident from the past studies that in most cases, when ICP surpasses 20 mmHg, RAP begins to decline.^{41,64,66,108,113,114} Prior to this threshold, RAP generally increases with rising ICP values^{41,64,66,108,113,114}. Considering this transition, the three states are defined (i.e., state 1, state 2, and state 3). When patients exhibit low and relatively stable RAP levels with minimal changes as ICP increases, this corresponds to state 1. When RAP exceeds 0.4 as a consequence of the increment in ICP, that condition falls into state 2. As RAP surpasses 0.4 due to ICP elevation, the condition is classified as state 2. Lastly, when ICP continues to rise beyond 20 mmHg, resulting in lower RAP^{41,64,66,108,113,114}, the condition falls into state 3.

If we consider other MMM physiology and patient outcomes, we would find consistent patterns across these particular ranges of RAP, which were more thoroughly analyzed and experimented with in later studies. So, based on the prior studies, the states can be defined as follows:

State 1: RAP is close to zero and exhibits minimal variation with the increase in ICP. State 2: a positive increase in RAP alongside increasing ICP, and has a considerable positive value. In this state, RAP exceeds 0.4 and can be seen close to +1. State 3: RAP decreases with the increase in ICP, potentially reaching a negative value when ICP surpasses a critical ICP threshold.

Firstly, in the context of the plateau wave, RAP reached state 2 during the wave.^{108,110} However, if ICP reached a sufficiently high level, state 3 of RAP was observed.^{14,109} Additionally, state 2 was associated with elevated ICP and PRx, along with lower values of CPP and CVR during the wave. The positive value of PRx indicated impaired autoregulation.^{108,110} Conversely, in state 3, similar associations were noted for ICP, PRx, CPP, and CVR, as observed in state 2. Additionally, disturbed autoregulation and increased vascular resistance were reported as well, since increased Mx and PI were observed during the wave.¹⁰⁹

When comparing patients with and without plateau waves, both groups exhibited elevated RAP, which was positioned in state 2. However, the group experiencing plateau waves had a higher RAP.¹⁰⁹

Secondly, in studies focusing on the ICP range, higher RAP was observed with the increase of ICP range, i.e. state 2 of RAP,^{15,41,53} and after exceeding a specific value of ICP, RAP kept decreasing, i.e. state 3 of RAP,^{15,53} a pattern reminiscent of findings observed during plateau waves. Regarding other physiologic parameters, RAP in state 2 was associated with an increase in MAP, ABP, and PRx and a decrease in CPP, CVR, and PbtO₂.^{15,41,53} Therefore, these findings, alongside resembling impaired autoregulation as observed in plateau waves, also indicated a reduction in oxygen delivery to brain tissue and impaired CVR in state 2 of RAP. A similar association was observed in state 3 of RAP,^{41,53} with an accompanying increase in the PAX'.⁴¹

Thirdly, significant improvement in RAP (i.e., lower RAP with lower ICP) was observed through surgical interventions such as decompressive craniectomy and ventriculostomy, as they were able to shift RAP from state 2 to state 1.^{8,64,111} During this transition, reductions in ICP, MAP, PRx and Slow were observed in the case of decompressive craniectomy. Reduced PRx and Slow indicated improved CA.^{64,111} On the contrary, although ventriculostomy did not yield a significant improvement in PRx, the maintenance of CPP within the normal range suggested an improvement in autoregulation.⁸ Additionally, improved oxygen in brain tissue was observed.⁸

Fourthly, while comparing survivor and deceased groups of TBI patients, state 3 of RAP was noticed in the latter.^{16,115,116} Higher ICP and non-invasive Slow (nSlow) with a lower CPP were associated with the state 3 of RAP in the fatal outcomes, aligning with findings from previous analyses such as plateau waves, ICP range, and operative approaches.^{16,114} Furthermore, in the comparison of the PTH group with the atrophy group, the PTH group showed a RAP value belonging to state 3, associated with higher R_{CSF}.⁵⁹ In the case of detecting unstable hemodynamics, state 2 of RAP (greater than 0.6) played an important role,⁶¹ while the presence of spindle waves was found to shift RAP to state 1.⁶⁵ Aside from these studies, two more examined the patients based on their physiologic conditions and revealed increased ICP, PRx^{37,113} and decreased CPP were associated throughout both state 2 and state 3.³⁷

Finally, one study analyzed the association of neuroimaging with RAP.¹¹² This analysis revealed that towards the conclusion of the initial 10 days of recording, higher values of certain CT characteristics were linked to state 2 of RAP. Furthermore, at the end of the first 48 h of recording, the existence of subcortical and corpus callosal DAI lesions was also associated with the state 2 of RAP.¹¹²

2.7.2 The definitions

Overall, based on the findings from the review of the past studies, consistent patterns in certain RAP ranges were evident. According to these patterns and RAP values, three states of RAP can be defined as follows:

State 1: RAP was close to zero. ICP, MAP, PRx, and Slow were the lowest, while PbtO₂ and CPP (balanced) were the highest. These parameter values suggested good CC/CCR, CA, and ample brain tissue oxygen. This state was observed in TBI patients during the spindle wave.

State 2: RAP showed a significant positive value. ICP, MAP, PRx, ABP, and Slow demonstrated higher values than state 1 but lower than state 3. Conversely, CPP, CVR and PbtO₂ showed smaller values than state 1 but higher than state 3. These parameter values indicated poor CC/CCR and CA, inadequate brain tissue oxygen, and impaired CVR. Unstable hemodynamics were detected in this state, and interventions like decompressive craniectomy and ventriculostomy could shift RAP from State 2 to State 1. Moreover, specific CT characteristics demonstrated elevated values, and the presence of subcortical and corpus callosal DAI lesions was noteworthy in this state.

State 3: RAP was lower than state 2, and with the increase of ICP, RAP reduced and could reach negative values at one point. ICP, MAP, PRx, ABP, and Slow demonstrated the highest values among the states, whereas CPP, CVR and PbtO₂ showed the lowest. Alongside these, Mx, PI, PAX, and R_{CSF} were higher than state 2. These parameter values represented exhausted CC/CCR, disturbed CA, impaired cerebrovascular resistance, insufficient brain tissue oxygen, and compromised CVR. These impairments are more severe than those observed in state 2. Fatal outcomes and PTH outcomes were associated with this state.

2.7.3 The physiological understanding of the transition from State 2 to State 3 of RAP

The transition from State 2 to State 3, where RAP becomes negative and AMP decreases after ICP exceeds a critical threshold, can be understood physiologically. In State 1, CA and CVR are intact.^{14,16,109} With the increase of ABP, the cerebral arterial bed constricts to decrease ICP so that CA remains intact (i.e., negative PRx) and vice versa.⁸ However, in State 2, there will be the presence of impaired CA and CVR.^{37,64} Physiologically, there is likely increased resistance in cerebral blood vessels, leading to poorer perfusion (i.e., reduced CPP) and brain tissue oxygenation (i.e., reduced PbtO₂).^{108,109,115} The vessels gradually lose their capability to dilate in response to the change of ABP (i.e., positive PRx).^{108,115} With the further increment of ICP and crossing the critical ICP threshold (i.e., state 3), alongside the decrement of CPP, the cerebral arterioles' capacity to dilate is exhausted.^{14,108,115} Consequently, they collapse passively.^{108,115} This is associated with the discontinuity of CBF, which leads to a further decrement in PbtO₂.¹⁴ This is the maximal vasodilation state of the vessels since the CVR is exhausted.^{16,109,115} This signifies a final

breakdown in cerebrovascular function, leading to reduced transmission of pulse pressure from the arterial system to the intracranial space.¹¹⁵ That's why, even though ICP increases, AMP decreases in this state, and the RAP value becomes negative.

2.8 Limitations of the Literature and Thesis Rationale

Considering the review of the literature presented in this chapter, the hypotheses introduced in Chapter 1 can now be clearly rationalized.

First, prior studies have illustrated the need for continuous monitoring over intermittent approaches.^{108,110} Among the available continuous metrics/methods, RAP was outlined as the most popular indicator of CC/CCR.^{41,42,117} Therefore, this thesis places its focus on RAP to build on its clinical relevance and widespread application.

Second, the temporal structure of RAP remains poorly characterized. No study has investigated whether it follows any autoregressive trends or if it exhibits stationarity.^{42,117} A clear understanding of these temporal properties is crucial for developing accurate predictive models and for integrating RAP into long-term monitoring frameworks. Furthermore, the dynamic relationship between RAP and its constituent signals, ICP and AMP, has not been sufficiently explored.^{42,117} While RAP is mathematically derived from the moving correlation between ICP and AMP, it is still unclear whether RAP reflects its own temporal behaviour or simply mirrors changes in its inputs. Without distinguishing RAP's unique dynamics, clinicians and researchers may misinterpret its variations. By leveraging the time series structure of RAP, ICP, and AMP, this concern can be effectively addressed.

Third, and perhaps most critically, the issue of artifacts in the RAP signal remains largely unaddressed.^{42,117} Artifacts can arise from various sources, including patient movement, sensor disconnections, and clinical procedures. These distortions can lead to inaccurate assessments of CC/CCR, thereby compromising data integrity, model performance, and clinical decision-making. To date, no established methodology exists for the identification or mitigation of RAP artifacts, and this represents a significant barrier to its clinical adoption.

Fourth, although RAP is one of the most widely used metrics for assessing CC/CCR,^{41,42,117} it has rarely been the central focus of investigation in TBI studies. While several studies have demonstrated strong correlations between RAP and other physiological parameters^{64,66,108} and illustrated its potential as a predictor of patient outcomes,^{113,114} RAP has typically been treated as a secondary variable, used to support other primary research objectives.^{64,66,108} To date, no study has comprehensively explored RAP's associations within the broader physiological context or positioned it as the primary subject of analysis.

Additionally, among the existing literature, some literature examined small data or excluded too many subjects due to more constrained conditions, which could introduce the lack of generalizability of the findings, as the study sample might not be representative of the broader population.^{16,61,113} The lack of generalizability is also applicable to the case of single-center data, which could also introduce regional biases.^{65,108} Furthermore, even though some studies found promising associations and results, there is uncertainty regarding their application in the clinical sector.^{41,53} Additionally, some studies deviated from the common findings, presenting exceptions to the majority.^{113,116} These limitations in the current literature raise concerns about the reliability of existing RAP observations, highlighting the need for a thorough analysis of RAP using a multicenter dataset with a robust patient population.

Thus, based on the past limitations outlined in the above review of literature, in combination with the advent of newer high-frequency MMM, the following thesis Chapters (Chapters 4 and Chapter 5) explore the specific hypotheses (outlined in Chapter 1) related to the RAP's time series structure, artifact management and association with other cerebral physiologies through novel original contributions to the field.

Therefore, considering the previously discussed review of literature, with the availability of newer high-frequency MMM data, the thesis chapters, Chapters 4 and 5, investigate the specific hypotheses introduced in Chapter 1. It focuses on RAP's time-series behaviour, artifact management, and its relationships with other cerebral physiologies, offering original and novel contributions to the field.

3 General Methodology

To achieve the objectives of this thesis, two comprehensive studies were conducted, one focusing on RAP's temporal characteristics and artifact profile management, and the other exploring RAP's relationships with other cerebral physiologies. This chapter provides a comprehensive overview of the common methodologies employed across these two studies. Given the complexity and unique nature of each study, while detailed descriptions of the study-specific statistical approaches are provided within their respective chapters, this section outlines the general framework. Included here are descriptions of the patient populations studied, approaches to high-resolution physiological monitoring, techniques for signal acquisition and processing, derivation of different physiological metrics, ethical considerations, and common components of the statistical analyses that facilitate the objectives of this thesis.

3.1 Patient Populations

Two different TBI patient datasets were employed across the two studies. The first, the Winnipeg Acute TBI Database, represents a single-center cohort, whereas the second, the CANadian High Resolution TBI (CAHR-TBI) Database, includes a multicenter, international patient population. Notably, the single-center dataset is a subset of the larger CAHR-TBI cohort. All raw physiological data were collected prospectively and analyzed retrospectively for the purposes of these analyses. In the studies, certain participants may have been excluded based on inclusion criteria specific to each study's design.

3.1.1 Winnipeg Acute TBI Database

The Winnipeg Acute TBI Database represents a single-center observational cohort of moderate-to-severe TBI patients admitted to the intensive care unit (ICU) at the Health Sciences Centre (Shared Health Manitoba), University of Manitoba. Moderate and severe TBI were defined according to admission Glasgow Coma Scale (GCS) scores of 9–12 and ≤ 8 , respectively. Patients were managed according to contemporary BTF guidelines for ICP and CPP management. Some mild TBI patients (GCS 13–15) who clinically deteriorated following admission were also included if they underwent invasive neuromonitoring in the ICU.

Invasive monitoring of ICP was performed using either intraparenchymal or intraventricular devices, consistent with BTF recommendations. ABP was continuously monitored through a radial arterial catheter, zeroed at the level of the tragus in accordance with consensus standards. All patients received standard ICP- and CPP-targeted therapies with treatment goals of ICP < 20 mmHg and CPP between 60–70 mmHg. These interventions included head-of-bed elevation, sedation, osmotic therapy with mannitol (0.5–1 g/kg) or

hypertonic saline (typically 140 mL of 7.33% NaCl), CSF drainage when applicable, and short periods of controlled hyperventilation. For patients with refractory intracranial hypertension, escalated therapies such as barbiturate coma, therapeutic hypothermia (to 33°C), neuromuscular blockade, or decompressive craniectomy were used.

Vasopressor agents, including norepinephrine, phenylephrine, or vasopressin, were employed to maintain CPP within target ranges. Electrolyte abnormalities and glycemic control were managed in accordance with standard ICU protocols. A subset of patients was also enrolled in parallel prospective observational studies that included additional non-invasive neuromonitoring modalities, such as near-infrared spectroscopy (NIRS)-based rSO₂, depending on eligibility and protocol alignment (REB protocols B2018:103, B2019:065, and B2023:001).

Demographic variables (e.g., age, biological sex), injury severity indices (e.g., GCS, pupil reactivity), and radiologic findings (e.g., Marshall CT classification, presence of subdural or epidural hematomas, contusions) were collected as part of routine data abstraction. Metabolic and pharmacologic parameters were extracted from bedside records. All physiological signals were recorded at high temporal resolution and subsequently anonymized for analysis. No additional clinical record access was performed post-discharge. Data collection spanned from January 2018 to March 2023.

Ethical approval for data acquisition and retrospective analysis was obtained from the University of Manitoba Health Research Ethics Board. As all data were de-identified and collected under prospective protocols, patient consent for secondary analysis was waived.

3.1.2 CAHR-TBI Database

The CAHR-TBI Database is a multicenter, international collaborative dataset comprising moderate-to-severe TBI patients admitted to ICUs at four major university-affiliated medical centers: Foothills Medical Centre, University of Calgary (2011–2021); Health Sciences Centre Winnipeg (Shared Health Manitoba), University of Manitoba (2019–2024); Maastricht University Medical Center, University of Maastricht (2017–2022); and Vancouver General Hospital, University of British Columbia (2014–2019). This retrospective database is maintained prospectively under the leadership of the Multi-omic Analytics and Integrative Neuroinformatics in the HUMAN Brain (MAIN-HUB) Lab at the University of Manitoba and captures detailed clinical, physiological, and outcome data across participating centers.

Inclusion in the database required invasive monitoring of both ICP and ABP. Patients were managed according to contemporary BTF guidelines, with treatment directed at maintaining ICP < 20 mmHg and CPP within the target range of 60–70 mmHg. While all patients received core monitoring, subsets of patients

also underwent advanced cerebral monitoring such as NIRS-based rSO₂ and/or brain tissue oxygenation (PbtO₂) monitoring, depending on local clinical protocols and availability. PbtO₂ probes were placed in viable brain regions as identified by neuroimaging or intraoperative assessment. rSO₂ values were not used for clinical decision-making. Although detailed patient-specific treatment data were not available across sites, comparable classes of vasopressors, sedatives, and hyperosmolar or hypertonic agents were administered across all participating centers, ensuring a reasonable level of treatment standardization across the cohort.

Physiological data were collected at high temporal resolution, including variables such as ICP, ABP, CPP, MAP, PRx, P_{Ax}, RAC, RAP, rSO₂ (left and right hemispheres), cerebral oximetry indices (COx and COx-a), and PbtO₂, where available. Demographic characteristics (e.g., age, sex), clinical severity indicators (e.g., GCS, pupil reactivity), radiologic findings (e.g., Marshall CT classification), and outcomes (e.g., GOS or GOSE at 3-, 6-, and 12-month follow-up) were also documented.

3.2 Physiologic Monitoring

3.2.1 ICP Monitoring

ICP was measured using either intra-parenchymal strain gauge probes or external ventricular drains (EVDs). Intra-parenchymal probes (Codman ICP MicroSensor, Codman & Shurtleff Inc., Raynham, MA, USA; or NEUROVENT-P-TEMP) were typically placed in the frontal lobe, while EVDs were inserted into the lateral ventricles when clinically indicated. Placement of all devices was confirmed using postoperative CT scans. No corrections were applied for long-term signal drift.

3.2.2 ABP Monitoring

ABP was monitored invasively using radial, brachial, or femoral arterial lines connected to fluid-filled pressure transducers (Baxter Healthcare Corp. CardioVascular Group, Irvine, CA, USA). The transducers were zeroed at the level of the tragus to approximate CPP. This setup enabled high-fidelity ABP waveform capture, which was essential for synchronized MMM and the calculation of derived indices such as CPP, PRx, and RAP.

3.2.3 NIRS-based rSO₂ Monitoring

Regional cerebral oxygen saturation (rSO₂) was assessed through near-infrared spectroscopy (NIRS) oximetry, targeting the left (rSO₂_L) and right (rSO₂_R) frontal lobes using the INVOS 5100C or 7100 systems (Covidien-Medtronic, Minneapolis, MN, USA).^{118,119} This measurement was performed in a subset of patients where viable rSO₂ signal channels were available. Viable channels were defined as those

unaffected by underlying lesions, hematomas, or scalp abnormalities. Channels were validated against lesion annotations to confirm that only NIRS signal streams from unaffected regions were included in the analysis.^{118,119}

3.2.4 PbtO₂ Monitoring

Where available, brain tissue oxygenation (PbtO₂) was measured using the Licox Brain Tissue Oxygen Monitoring System (Integra LifeSciences Corp., Plainsboro, NJ, USA). The initiation of PbtO₂ monitoring was determined by the treating clinical team and, as such, was not uniformly applied across all patients or centers.^{118,119} When placed, it was typically colocalized with the ICP monitor in the frontal lobe.

3.3 Signal Capture and Processing

All physiologic signals in the CAHR-TBI dataset were recorded at high temporal resolution using either direct digital data transfer or real-time analog-to-digital (A/D) conversion. Where necessary, A/D converters (DT9803, DT9804, DT9826; Data Translations, Marlboro, MA, USA) were employed to digitize analog outputs from bedside monitors and devices. As an exemplar in Manitoba, within the ICU setting, ICP and ABP signals were sampled at 100 Hz from analog outputs of Spacelabs Xprezzon monitors (scaling: 0–5 V = 0–200 mmHg for ICP, 0–5 V = 0–500 mmHg for ABP), then digitized using A/D converters. Other device outputs (e.g., rSO₂) were captured via direct digital export using serial data interfaces. All data streams were time-aligned and stored as high-frequency time series using ICM+ software (Version 8.5, Cambridge Enterprise Ltd., Cambridge, UK).

Signal processing was conducted using ICM+ as well. All recordings were manually inspected by trained personnel for artifact removal, with cleaning performed blinded to patient demographics or outcomes. Following cleaning, signals were decimated using 10-second, non-overlapping moving average filters to extract slow-wave cerebral physiology, in line with established practices. ICP, ABP, and rSO₂ were each summarized into 10-second epochs. CPP was computed as the difference between MAP and ICP at this same resolution, and AMP was calculated as the fundamental Fourier amplitude of each ICP pulse waveform over 10-second windows, updated every 10 seconds. This approach allowed for subsequent analysis of CC/CCR metric (i.e., RAP) and CA indices.

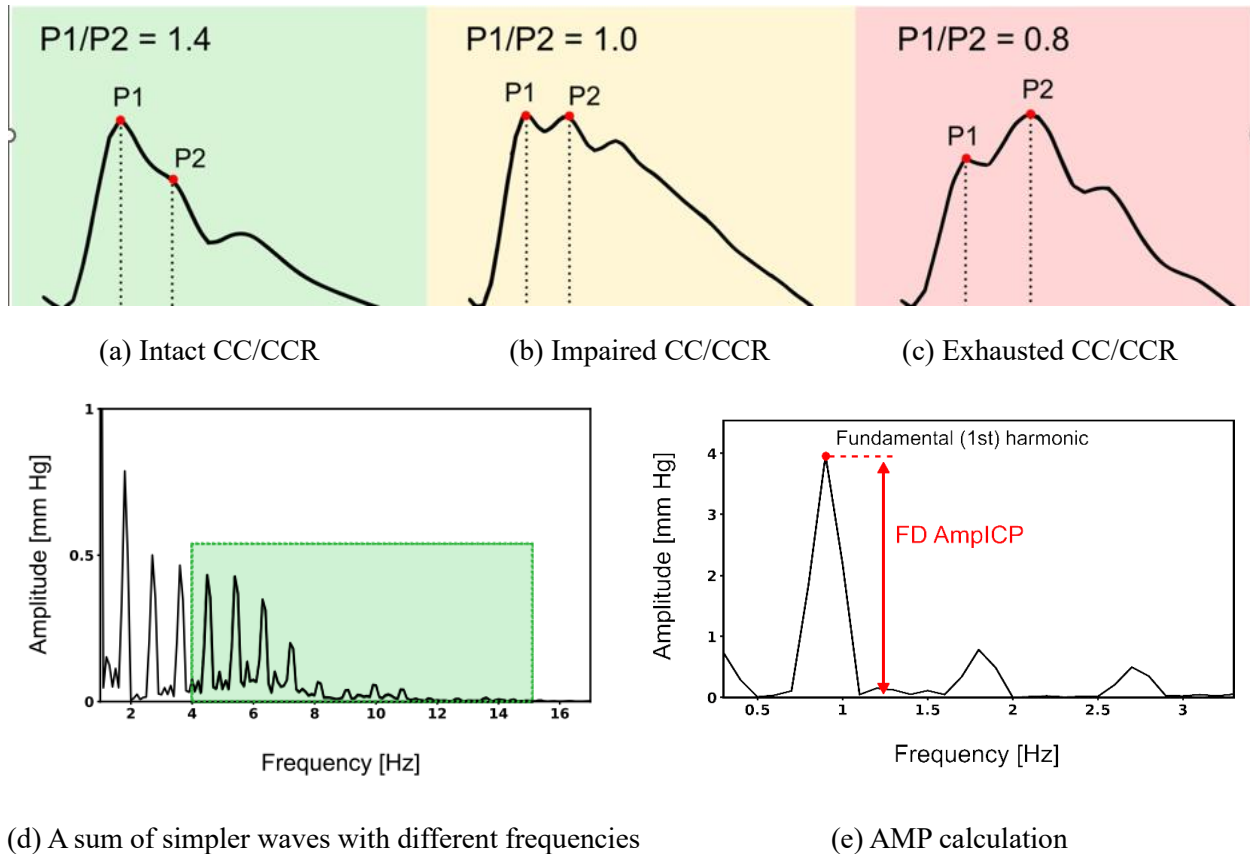
Additionally, to enable a comprehensive analysis and assess the effects of reduced temporal resolution, the dataset was subsequently down-sampled using non-overlapping time windows. This was accomplished with the *resample* function from the *Pandas* library¹²⁰ of Python. The original data, calculated at a minute-by-minute resolution, was down-sampled to 5-minute, 10-minute, 30-minute, and 1-hour intervals.

3.4 Derived Physiologic Measures

3.4.1 AMP

AMP is one of the two components of RAP. It is the pulse amplitude of the ICP waveform. As shown in Figure 3.1(a to c), ICP has complex waveforms,¹²¹ making it challenging to calculate AMP accurately. Therefore, Fast Fourier analysis was used, which converted the complex ICP waveform into a sum of simpler waves with different frequencies (Figure 3.1(d)). Among them, the wave with the lowest frequency represents the fundamental or first harmonic component of the wave, which also represents the base frequency of the waveform. AMP was calculated as the magnitude of this component (Figure 3.1(e)). By extracting the amplitude of the fundamental harmonic, we got a clean and consistent measure of the pulsatile part of the ICP signal, which is exactly what AMP is meant to reflect. Therefore, this method was applied to derive AMP.

Figure 3.1 Extraction of the fundamental component from the pulsatile ICP waveform



The figure¹²¹ shows the overall process of the derivation of AMP starting from the pulsatile ICP waveform at different CC/CCR states: (a) intact CC/CCR state, (b) impaired CC/CCR, and (c) exhausted CC/CCR state. It also illustrates the result of applying Fast Fourier analysis to this complex ICP waveform, in (d), which represents a sum of simpler waves with different frequencies. Lastly, it shows the calculation of AMP from the fundamental harmonic in (e).

AMP, pulse amplitude of ICP;

3.4.2 CC/CCR Index – RAP

RAP is derived from moving Pearson correlation coefficients between ICP and AMP over 30 consecutive 10-second mean windows (i.e., a 5-minute analysis window), updated every minute.^{33,41,122,123}

3.4.3 CA indices

All continuous indices of CVR were derived using a moving Pearson correlation approach, applied to slow-wave fluctuations extracted from 10-second, non-overlapping mean values of relevant physiological signals. These indices quantify the dynamic relationship between cerebral physiology and systemic driving pressures. If Z is a CA index, the following is an example of how it is calculated, with identical calculation methods utilized for all the indices: Z is calculated as the moving correlation coefficient between X and Y, where X and Y are two other constituent signals for Z. This is calculated using 30 consecutive 10-second windows of X and Y, generating a total of five minutes of data, with the Z index updated every minute, similar to the calculation method of RAP. This leads to an 80% overlap in data between successive Z measures. Following is a table illustrating the derived CA indices from their constituents.

Table 3.1 Calculation of the continuous CA indices

CA Index	Constituent Signals	Signal Averaging (sec)	Pearson Correlation Coefficient Calculation Window (sec)	Index Calculation Update Frequency (sec)
PRx	ICP and MAP	10	300	60
PAx	AMP and MAP	10	300	60
RAC	AMP and CPP	10	300	60
COx_L	rSO ₂ _L and CPP	10	300	60
COx_R	rSO ₂ _R and CPP	10	300	60
COx-a_L	rSO ₂ _L and MAP	10	300	60
COx-a_R	rSO ₂ _R and MAP	10	300	60

_L = left side, _R = right side, AMP = pulse amplitude of ICP, CPP = cerebral perfusion pressure, ICP = intracranial pressure, MAP = mean arterial pressure, min = minute, rSO₂ = regional brain oxygen saturation, sec = second.

3.5 Data cleaning

Several missing data points were present across the datasets, which were excluded from the analysis.^{119,124,125} Although artifacts were removed by experts prior to the calculation of derived parameters, some unrealistic values persisted. To ensure data quality, further filtering was applied: for ICP-ABP-derived parameters, data points were excluded if any of the following criteria were met: ICP > 100 mmHg or < 0 mmHg, MAP > 200 mmHg or < 0 mmHg, or AMP > 30 mmHg.^{119,124,125} For NIRS-derived parameters, visual inspection of scatterplots revealed a cluster of data points at rSO₂ values below 20, particularly around or equal to 0, indicating likely recording errors. As a result, a threshold of 20 was established for rSO₂, and all data points below this value were excluded from the NIRS-derived parameters-related analyses. This process was carried out using custom Python scripts (version 3.7.16).

3.6 Ethical Considerations

All data gathered through the Winnipeg Acute TBI Database were fully approved by the University of Manitoba Health and Biomedical Research Ethics Board (HREB and BREB; H2017:181, H2017:188, H2020:118, B2018:103, B2023:001, H2024:266), as well as the Health Science Centre/Shared Health Impact Committees. Due to the critical nature of the patient population, lack of study intervention (ie. purely observational study), and de-identified nature of data collection, both HREB/BREB approved a waiver of consent model for such data collection.

For patients involving in CAHR-TBI database, ethical approval for all aspects of data collection and anonymized data sharing across participating centers was obtained from the respective institutional research ethics boards: University of Manitoba Biomedical Research Ethics Board (BREB; protocols H2017:181, H2017:188, H2020:118, H2024:266), University of Calgary Conjoint Health Research Ethics Board (CHREB; protocol H20-03759), University of British Columbia Clinical Research Ethics Board (CREB; protocol REB20-0482), and the Medical Ethics Committee of Maastricht University (protocol 16-4-243). Given that all data were fully anonymized and retrospectively accessed, approval was granted to conduct the study under a waived consent model.

3.7 Statistical Analysis

Statistical analyses employed throughout the two studies varied considerably across the diversity of research objectives, data types, and analytical frameworks. Consequently, detailed descriptions of statistical approaches are provided in the methods sections of the respective chapters. Despite differences between studies, several common analytical methods were employed throughout them, as outlined below.

In general, all statistical procedures were conducted using Python custom scripts (version 3.7.16). For computationally intensive tasks, multiprocessing was applied using the *multiprocessing*¹²⁶ Python library. Given the predominance of non-normally distributed physiological data, no assumption of normality was made. As such, non-parametric tests were the primary analytical tools, including the Mann-Whitney U test for two-group comparisons and the Kruskal-Wallis test for multi-group comparisons. All hypothesis testing was conducted with a significance threshold of $p = 0.05$. No corrections for multiple comparisons or power calculations were applied, as the majority of the work was exploratory in nature. Where applicable, simple linear models and visual tools such as scatter plots and bar plots were used to explore relationships between variables.

For time-series modeling of cerebral physiology estimation and forecasting, autoregressive integrated moving average (ARIMA) and vector autoregressive integrated moving average (VARIMA) models were implemented. These models were assessed and compared using the autocorrelation function (ACF), partial ACF (PACF), Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and log-likelihood (LL) values. The stationarity analysis of the signals was conducted using the Augmented Dickey-Fuller (ADF) and Kwiatkowski-Phillips-Schmidt-Shin (KPSS) tests.

As outlined in Section 3.3, both studies were performed at different temporal resolutions to assess whether any variations occurred across these different scales. Additionally, analyses were conducted across the distinct RAP states defined in Section 2.7 to explore potential relationships within the various RAP value ranges. All corresponding figures and tables are provided in full detail within the published and submitted manuscripts.

4 RAP Signal Patterns, Temporal Relationships, and Artifact Profiles

The study described in chapter 4 can also be found in detail in the following publication, and addresses Hypothesis #1 of this thesis:

- **Islam A**, Sainbhi AS, Stein KY, et al. Characterization of RAP Signal Patterns, Temporal Relationships, and Artifact Profiles Derived from Intracranial Pressure Sensors in Acute Traumatic Neural Injury. *Sensors* 2025;25(2):586; doi: 10.3390/s25020586.

4.1 Introduction

Although recent hydrocephalus studies have demonstrated the utility of RAP in predicting shunt failure^{10-12,42}, its application in moderate-to-severe TBI remains underexplored. Particularly, the lack of knowledge of the temporal characteristics of RAP and its constituent signals presents a significant barrier to the development of patient-specific data modeling approaches for clinical use. To date, no prior research has investigated the temporal dynamics of RAP.^{14,16} Furthermore, without effective identification and management of artifacts within the RAP signal, any modeling efforts risk being inaccurate or potentially misleading. No studies have addressed the identification and management of RAP artifacts either.

Therefore, this study aims to explore: A. the general description of RAP signal patterns and behaviours, B. the temporal statistical profile of RAP, and C. the characterization of RAP artifact profiles. Gaining more profound insights into these aspects is essential for advancing the future integration of the RAP index into bedside monitoring, enhancing patient trajectory modeling, and supporting clinical intervention studies based on RAP values.

4.2 Materials and Methods

4.2.1 Study Design

The data were retrospectively obtained from the prospectively maintained TBI database maintained at the Multi-omic Analytics and Integrative Neuroinformatics in the HUMAN Brain (MAIN-HUB) Lab at the University of Manitoba. This study included patient data collected from January 2018 to March 2023. All patients in this cohort are aged 17 or older and have experienced moderate-to-severe TBI (GCS < 12). Invasive ICP and ABP monitoring were conducted as per BTF guidelines.³

4.2.2 Data Acquisition and Signal Processing

As described in sections 3.2, 3.3, and 3.4, signal data was collected and processed. For this study, demographic information at admission was extracted according to existing prognostic models in TBI. The collected demographic data included age, biological sex, admission pupillary response (bilaterally reactive, unilaterally reactive, or bilaterally unreactive), Marshall CT grade, and GOSE grade.

4.2.3 Analysis of the patterns and behaviours of RAP

Alongside RAP, the analysis also included ICP, MAP, AMP, and CPP signals since ICP and AMP were used to derive RAP,^{10,117} while MAP and CPP helped establish standard thresholds used in RAP analysis in this field.^{3,123} Firstly, *Panda's* (a Python library)¹²⁷ *describe* function¹²⁸ was used to find the summary measurements for each signal in all patients. Following this, a custom script was executed to find the time spent of RAP within certain threshold ranges (0.4 to 1, 0 to 0.4, and -1 to 0), based on a systematic review study previously conducted by our lab.¹¹⁷ Afterwards, a comparative sub-group analysis was conducted based on age, biological sex, pupillary response, Marshall CT grade, outcome (GOSE grade), ICP, AMP, and PRx values. Threshold lines for these comparisons were established using commonly referenced values from prior studies^{41,57,76,84} in related fields as follows:

- Age: less than 40 years, between 40 to 60 years, and above 60 years
- Pupillary response: bilateral reactive, bilateral unreactive, and unilateral unreactive
- Marshall CT grade: grade II, grade III, grade IV, and grade V
- Outcome GOSE grade: alive/dead (2 or higher vs. 1) and favourable/unfavourable (5 or higher vs. 4 or less)
- ICP thresholds: below 20 mmHg and above 22 mmHg
- AMP thresholds: below 1, between 1 and 3, and above 3
- PRx thresholds: less than 0 vs greater than 0 and less than 0.25 vs greater than 0.25

Mann Whitney U-test was utilized for the formal comparison since none of the groups showed normal distributions. Kruskal-Wallis test was used to compare more than two groups. To run this operation, Python's *mannwhitneyu*¹²⁹ and *kruskal*¹³⁰ functions from *scipy.stats* library were used respectively.

4.2.4 Analysis of RAP time-series structures

4.2.4.1 Application of ARIMA model

An ARIMA model is a widely used statistical method for time-series forecasting.^{131–134} It works by combining three main components: autoregression (AR), differencing to make data stationary (I for Integrated), and a moving average (MA). The model aims to capture the underlying patterns in time-series data and predict future values based on historical observations.^{131–134} The AR part is controlled by the

parameter p , representing the number of lagged observations in the model. It refers to the regression of the variable on its own lagged (previous) values. The parameter d represents the number of times the data needs to be differenced to achieve stationarity. The MA part is controlled by parameter q , representing the number of lagged error terms in the model. It refers to modeling the error (or residual) term as a linear combination of previous error terms.^{131–134} An ARIMA model is usually written as ARIMA(p, d, q). Assuming the signal is stationary (d -order = 0), a general autoregressive moving average model for a physiological signal, X , can be represented by Equation 1. In this model, p is the autoregressive order, q is the moving average order, X_t is the signal at time t , X_{t-i} is the signal at time $t-i$, ε_t is the error at time t , ε_{t-j} is the error at time $t-j$, φ is the autoregressive coefficient at time $t-i$, and θ is the moving average coefficient at time $t-j$.¹³⁵

Equation 1:

$$X_t = c + \varepsilon_t + \sum_{i=1}^p \varphi_i X_{t-i} + \sum_{j=1}^q \theta_j \varepsilon_{t-j}$$

This ARIMA model was employed to capture the structure of time-series signals. ARIMA was chosen since it provides interpretability in terms of temporal dependencies (p, d, q), making it particularly suited for understanding signal dynamics, comparing temporal structure among signals and identifying artifacts. According to previous works from the lab, both the p -order and q -order for determining the optimal ARIMA model were varied from 0 to 10.^{135,136} The analysis was run on the differenced data (discussed in section 4.2.4.3), and therefore, the d -order was set to 0, which effectively acted as d -order=1. The *ARIMA* function from the *statsmodels* module¹³⁷ of Python was used for this analysis. Each combination of the orders was evaluated to find the optimal model for each signal and each patient.

4.2.4.2 Statistical metrics for ARIMA analysis

AIC, BIC, and LL were calculated to assess whether the models effectively captured the structure of the signal. These are statistical metrics used to evaluate the quality and goodness-of-fit of an ARIMA model, helping to assess how well the model captures the underlying structure of the time-series data.^{135,138,139} Each of these metrics has its own characteristics and significance in model selection. AIC measures the goodness-of-fit of a model while penalizing for model complexity (the number of parameters). It balances model fit and complexity to avoid overfitting. BIC is similar to AIC but applies a more substantial penalty for models with more parameters, making it more conservative in terms of model complexity. LL measures the likelihood that the model could have generated the observed data. It reflects the fit of the model without penalizing for complexity. Lower AIC and BIC values indicate a better model, while higher LL values indicate a better fit.^{135,138,139}

According to a previous study from our lab, BIC is more stringent than AIC and LL.¹³⁵ On the other hand, models based on LL were more complex and could potentially overfit the data, leading to higher residuals.¹³⁵ Given this, AIC was considered the most balanced option for model selection, as it strikes a middle ground between the stringency of BIC and the leniency of LL. For this reason, AIC was chosen to find the optimal ARIMA models for the signals.

4.2.4.3 Stationarity analysis

Since the ARIMA model is built on the assumption of the stationarity of time series, the data needs to be stationary to apply an ARIMA model. Hence, stationarity analysis was carried out. Like the previous work from our lab,¹³⁵ ADF and KPSS tests were used to check the stationarity of all the signals. The ADF test indicates whether a time series is trend-stationary, while the KPSS test determines if the series remains stationary around a linear trend.^{132,140} If the p-value from the ADF test is less and the p-value from the KPSS test is higher than a certain threshold, the time series is considered stationary. In line with previous studies,¹³⁵ the threshold was set at 0.05 for both tests. The *adfuller* and *kpss* functions from the *statsmodels* module¹³⁷ in Python were used to perform the tests at the patient level. Additionally, due to the ADF and KPSS test results on the original data (discussed in section 4.3.4), these tests were performed on each patient's 1st order differenced data. It is noteworthy that the differenced data was achieved after temporal resolution.

4.2.4.4 Generation of different temporal resolutions of data

ICP, AMP, and RAP were calculated across various temporal resolutions for a comprehensive analysis and to examine the impact of temporal resolution reduction on the results. Subsequently, the optimal ARIMA model at the patient level was calculated for each parameter for every temporal resolution. The temporal resolutions applied in this study included minute-by-minute, 10-minute intervals, 30-minute intervals, and hour-by-hour intervals. The primary derived data was at minute-by-minute intervals. Afterward, Panda's *resample* function¹²⁰ was used to reduce the resolution. The primary data's (i.e. minute-by-minute resolution) mean of 10-minute data points was determined as a single non-overlapping point in the 10-minute intervals. Similarly, for the 30-minute and 1-hour intervals, the mean of 30 consecutive data points and 60 consecutive data points, respectively, were used to represent each interval.

4.2.4.5 Evaluation tools

After getting the optimal ARIMA model for each patient, the median optimal ARIMA model for each signal was calculated based on those models (i.e. median p-order and median q-order values were calculated). The choice of median value for optimal models across the whole population ensured a more representative

summary across the examples while reducing the impact of outliers. To confirm the adequacy of the median optimal ARIMA models, the magnitude of residuals, ACF, and PACF plots of residuals were examined by comparing the raw data to the modeled data.^{132,135} Residuals represent the differences between actual data points and model-predicted values. The ACF measures the relationship between a time series and its past values, while the PACF indicates the correlation between a time series and its lagged values, excluding the effects of intermediate lags. For a well-fitted ARIMA model, residuals should be minimal, and the ACF and PACF plots should show no significant spikes at any lags, indicating that the model has captured the underlying structure.^{132,135} Additionally, this analysis included the calculation of the overall variance in data, the residual variance, and the count of significant spikes to justify that the data had been modeled well.

4.2.5 RAP artifact segment analysis

4.2.5.1 Separating true artifact segments

For this section, true artifacts were required to be calculated. Previously, to obtain clean and artifact-free data, artifacts were manually detected and removed from the raw collected data by experts in cerebral physiologic signal analysis and neurophysiology. Therefore, while comparing clean data with non-clean data, any additional data present in the non-clean version but absent in the clean version should represent artifacts. This step was performed by comparing timestamps of clean and non-clean data. Afterwards, identified artifact segments were saved into different comma separated value (CSV) files.

4.2.5.2 Analysis of clean data and artifact segments

The optimal models for the clean signal were already obtained in the previous section. The optimal models for the artifact segments were calculated for each signal of each patient using the same methodology. Finally, a comparison between clean data and artifact segments based on temporal structure was conducted using various statistical techniques. The temporal resolutions applied in this analysis included minute-by-minute and 10-minute intervals. The remaining resolutions were excluded from this analysis because, at such low resolutions, the quantity of artifact data would be insufficient to yield significant results in this section.

This analysis focused on three key areas:

- i) Comparing optimal ARIMA models: The optimal models for clean data would have been obtained as described in the previous section (i.e. section 4.2.4). The optimal models for the artifact segments were also computed for each signal of each patient using the same methodology. These models for clean data and artifact segments are expected to differ, resulting in varying p-orders and q-orders between the two groups for each patient. A formal comparison of the groups' ARIMA orders for each

signal was conducted using the Mann-Whitney U test, with scatterplots provided for visual representation.

- ii) Comparing the residuals: Using the median optimal ARIMA model calculated for clean data, residuals for clean and artifact segments were computed and formally compared at the patient level. The results are expected to indicate significant differences in the mean residuals and variance of residuals between the clean and artifact groups.
- iii) Comparing the cross-correlation of residuals: If cross-correlation is calculated between RAP residuals and ICP/AMP residuals, the expectation is that the maximum correlation value between clean RAP and clean ICP/AMP residuals would be higher than that between clean RAP and artifact ICP/AMP residuals. Since RAP is derived from ICP and AMP, their residuals should naturally show a strong correlation. However, this correlation is expected to decrease when considering the artifact segments of ICP/AMP, as these segments do not accurately represent true ICP/AMP values. The *correlate* function from the *Numpy* library was used to calculate the cross-correlations, and it measured the similarity between two signals (or datasets) as a function of the time lag applied to one of them (i.e. calculated dot product).

4.2.5.3 Evaluating identified features

After analyzing the data to identify features with the potential to effectively distinguish artifacts, a simple sliding window approach was applied to the non-clean data to assess the success rate of these features in identifying artifacts within the signal. The success rate of capturing artifacts within the signal was calculated as (captured artifacts / true artifacts) * 100%.

4.3 Results

4.3.1 Patient demographics

As reported in Table 4.1, 109 TBI patients were included in this study, with a median recording duration of 4125.13 minutes. The median age of the patients was 43 years (interquartile range (IQR): 29 to 57), and 89 of the patients were male (81.65%). The median GCS score was 7 (IQR: 4 to 8), while the median motor sub-score was 4 (IQR: 2 to 5).

Table 4.1 Demographic data

Variable	Median (IQR) or Number (%)
Duration of recording (minutes)	4125.13 (1714.99-7250.14)
Number of Patients	109
Age (years)	43 (29-57)
Sex (Male)	89 (81.65 %)
GCS	7 (4-8)

GCS Motor	4 (2-5)
Pupils	
Bilateral Reactive	65 (59.63 %)
Unilateral Reactive	25 (22.93 %)
Bilateral Unreactive	19 (17.43 %)
Marshall CT Score	
V	55 (50.46 %)
IV	20 (18.34 %)
III	31 (28.44 %)
II	3 (2.75 %)

CT, computerized tomography; GCS, Glasgow Coma Score; IQR, interquartile range

4.3.2 General RAP patterns and behaviours

4.3.2.1 Summary Measurements

There were some unrealistic values of ICP and MAP in the data that could lead to erroneous CPP, AMP, and RAP values since they are derived from them. Therefore, according to the previous studies,¹⁴¹ data points with ICP > 100 mmHg or < -15 mmHg and MAP > 200 mmHg or < 0 mmHg were excluded from this analysis. Afterwards, summary measures of the aforementioned parameters were calculated and depicted in Table A.1 of Appendix A. Notably, RAP had a mean of 0.632 ± 0.483 .

Based on our previous study, RAP was classified into three distinct states according to its value¹¹⁷, which were: i) state 1, representing a healthy condition, was characterized by small positive RAP values close to zero; ii) state 2, which was most commonly observed in TBI patients, reflected impaired intracranial compliance and compensatory reserve, with elevated RAP values (RAP > 0.4), and iii) state 3, occurred in more severe conditions, indicating further deterioration of CC/CCR, CVR, and CA. This state was associated with a significant number of fatal outcomes and was marked by declining RAP values, including, in some cases, negative RAP.¹¹⁷ Based on the mean RAP obtained in this study, it can be stated that the mean RAP fell into state 2, indicating impaired cerebral compliance and compensatory reserve. This finding was consistent with our previous study, where state 2 was also the most commonly observed condition among TBI patients.¹¹⁷

4.3.2.2 Time spent within thresholds

According to the threshold ranges outlined in section 4.2.3, the percentage of time spent within each range was calculated for all patients and is presented in A.2. So, using the RAP index, the highest percentage of time spent was in the impaired state (ranging from RAP of 0.4 to 1), which was 78.091% and corresponds to state 2 as previously defined.¹¹⁷

4.3.2.3 Sub-group analysis

All the results from the sub-group analysis are presented in Appendix A, from Table A.3 to A.15. In the age groups analysis, for the first age comparison (i.e. age above and below 40 years), only ICP showed a significant difference ($p=0.048$) between the two groups, with AMP having a near-significant p -value of 0.065227, as depicted in Table A.3. In the second age comparison (age below 40 years, 40 to 60 years, and above 60 years), AMP and RAP were significantly different ($p=0.046$, $p=0.005$), while ICP showed no significant difference ($p=0.284$) (Table A.4).

In the M/F sex groups, only CPP ($p=0.008$) was significantly different (Table A.5). For pupillary response, none of the parameters showed significant difference (Table A.6). In Marshall CT grade groupings, ICP, AMP, and RAP were significantly different across groups ($p=0.002$, $p=0.0003$, $p=0.00001$) (Table A.7). RAP increased from grade II to IV, but at grade V, it decreased. A similar case was observed for ICP and AMP.

For outcome comparison, the GOSE grade was assessed at 1-month and 6-month intervals (Table A.8 to Table A.11). In the alive/dead comparison, for both cases, AMP significantly differentiated the groups in both intervals ($p=0.003$, $p=0.01$), while ICP and CPP were only significant in the 1-month GOSE results ($p=0.033$, $p=0.032$). However, RAP was not significant in either case. In the favourable/unfavourable cases, ICP, CPP, and AMP were significantly different for both intervals, but RAP again showed no significant difference in either case ($p=0.294$, $p=0.403$).

In the subgroup analysis for ICP, all parameters showed significant differences between the two groups (p =close to 0 for both groups). The group with ICP > 22 mmHg had higher RAP and AMP values than the other group. Similarly, in the AMP analysis, both ICP and RAP increased as AMP rose, reflecting the findings from the ICP subgroup analysis, with all parameters displaying significant differences.

Finally, in PRx analysis, the first comparison showed that RAP had a lower mean value when PRx > 0 compared to PRx < 0, though ICP and AMP were higher. This finding suggested that impaired CVR (PRx > 0) was associated with reduced RAP, aligning with the results of our systematic review.¹¹⁷ This decrease in RAP corresponded to state 3 of RAP,¹¹⁷ as defined in section 4.3.2.1. Similarly, in the second comparison, using a PRx threshold of 0.25, a comparable pattern emerged, with lower RAP being associated with higher PRx values (i.e. PRx > 0.25). Similar to ICP and AMP threshold analysis, all parameters demonstrated significant differences between sub-groups in the PRx threshold analysis (p =close to 0 for all cases). The results of these three threshold analyses are presented in Tables A.12 to A.15.

4.3.3 Optimal ARIMA structure analysis

4.3.3.1 Stationarity Assessment

As discussed in section 4.2.4.3, ADF and KPSS tests were performed for each patient and signal to check the stationarity of the signals. Initially, these tests were applied to the original data. The p-values for each patient's test results at the minute-by-minute data resolution can be found in the Appendix of the published manuscript.¹²⁴ Additionally, Tables B.1 and B.2 of Appendix B show the summarized results. As shown in the tables, while most of the signals appeared stationary according to the ADF tests, the KPSS test indicated that most were non-stationary. This suggests that the signals are largely trend-stationary but likely non-stationary around a linear trend. However, for ARIMA model analysis, the data needs to be stationary in terms of both cases. Therefore, a 1st order difference was applied to the original data after temporal resolution. The p-values for each patient's test results at the minute-by-minute data resolution can be found in the Appendix of the published manuscript. The resulting outcomes are summarized in Table B.3 and Table B.4.

As evident from the tables, after applying first-order differencing, nearly all the data, with a few exceptions, were assessed as stationary in both tests. Therefore, this differenced data was suitable for ARIMA model analysis.

4.3.3.2 Determination of optimal ARIMA models

Appendix C provides the optimal ARIMA models for each signal at each resolution for each patient, detailing the p, d, and q-orders along with their AIC values. Based on these results, the population global median optimal models in each resolution were calculated and shown in Table 4.2. As shown in the table, the models for each signal were quite similar in the case of 10-minute resolution and below.

Table 4.2 Global population median optimal models for each resolution

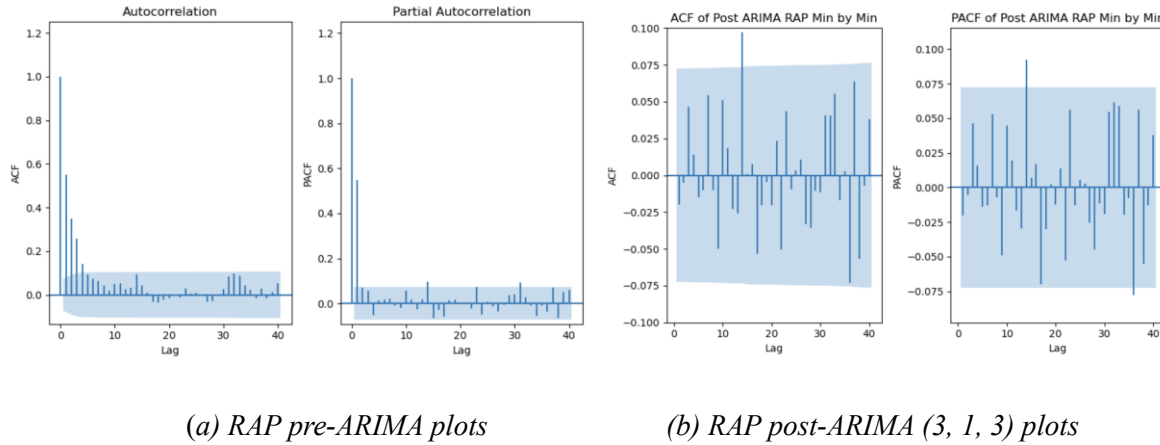
Temporal Resolution	ICP	AMP	RAP
Minute-by-minute	5, 1, 1	3, 1, 5	3, 1, 3
10-minute-by-10-minute	2, 1, 2	2, 1, 3	1, 1, 1
30-minute-by-30-minute	2, 1, 2	2, 1, 2	1, 1, 1
Hour-by-hour	2, 1, 2	1, 1, 1	1, 1, 1

AMP, pulse amplitude of ICP; ICP, intracranial pressure; RAP, compensatory reserve index

4.3.3.3 Evaluation of optimal ARIMA models

With the median optimal ARIMA models now determined, the quality of these models can be assessed using residuals, ACF, and PACF plots of residuals. Figure 4.1 represents a patient example of the ACF and PACF plots of residuals for RAP at 1-minute intervals for pre- and post-ARIMA modeled data.

Figure 4.1 ACF and PACF plots at minute-by-minute temporal resolution – patient example



The figure corresponds to the residuals of the RAP signal (a) before and (b) after ARIMA. Original plots had significant spikes both in ACF and PACF plots while post-ARIMA (3, 1, 3) showed mostly were within 95% confidence interval, indicating that the model moderately accounts for the RAP structure.

ACF, autocorrelative function; ARIMA, autoregressive integrated moving average; PACF, partial autocorrelative function; RAP, compensatory reserve index.

Figure 4.1(a) corresponds to the original RAP data since the orders were set to zero (ARIMA (0, 0, 0)). Figure 4.1(b) utilizes the median optimal ARIMA model for RAP (ARIMA (3,1,3)). It is evident that the ACF plot of the residuals using the original data had a gradual decay, while the PACF plot had significant spikes at various lags, indicating that the ARIMA (0, 0, 0) model did not effectively capture the signal's structure. On the contrary, after applying the median optimal ARIMA model for RAP (3, 1, 3), only two significant spikes were present at lag 15 and another after lag 30 in the PACF plot. Otherwise, most of the ACF and PACF values fell within the 95% confidence interval, implying that any autocorrelation left in the residuals is not statistically significant and suggests that the calculated ARIMA model successfully captured the structure of the signal.

Figure D.1 and Figure D.3 of Appendix D illustrate a patient example of ACF and PACF plots with this comparison for ICP and AMP signals and demonstrate similar results, proving the calculated median optimal ARIMA model captures the time-series structure with moderate performance.

While visually, the performance of the optimal ARIMA model is satisfactory, the global population median of residuals was compared to provide a better description between the original data and post-optimal ARIMA model application state for all signals, as reported in Table 4.3.

Table 4.3 Global population median residuals of the signals

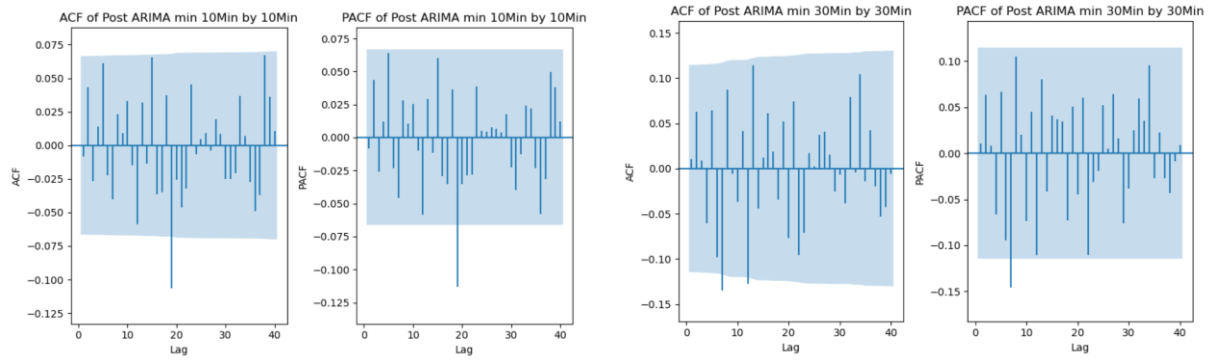
Parameter	Original	Optimal ARIMA Model
ICP	0.63008	0.17941
AMP	0.49329	0.13549
RAP	0.32493	0.12564

AMP, pulse amplitude of ICP; ARIMA, autoregressive integrated moving average; ICP, intracranial pressure; RAP, compensatory reserve index

While calculating, the absolute value of the residuals of each data point was taken for the betterment of the calculation. The median residual of the optimal ARIMA model was substantially less than that of the original data for all signals, which further emphasizes the ARIMA model's success in capturing the signal structure. Additionally, the variance of the overall data, variance in the residuals, and the number of significant spikes were calculated and shown in Table D.1. It can be seen that the variance of the residuals was smaller than that of the original data. Furthermore, both ACF and PACF plots for the modeled data had only one significant spike, in contrast to the original ACF and PACF plots, which had seven and two spikes, respectively. These values align with the results from Figure 4.1 and Table 4.3, further justifying that the data is being modeled. The values of these parameters were calculated for each signal of each patient at the minute-by-minute resolution, as shown in Tables D.3 through D.5. Subsequently, the means and medians were determined, as presented in Tables D.6 and D.7. The attribute values in these tables indicated that the data was adequately modeled. The values of the variance in the residuals and the number of significant spikes in ACF and PACF plots were much smaller than those of the original data.

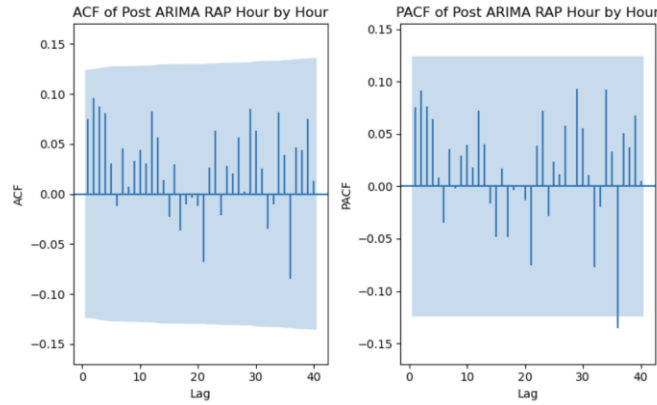
A similar analysis was performed at different temporal resolutions for the same patients. Figure 4.2 shows a patient example of the ACF and PACF plots of the residuals for RAP at the remaining temporal resolutions. Even though all the lags were within the 95% confidence interval at all the resolutions (which was also justified by the result in Table D.2), the ACF and PACF plots exhibited comparatively significant spikes with higher magnitude than those at the minute-by-minute temporal resolution (depicted in Figure 4.1(b)). This indicates that while the optimal ARIMA model captures the time-series structure in both cases, it is more successful at the minute-by-minute resolution than at the other lower temporal resolutions. Figure D.2 and Figure D.4 present these comparative figures for ICP and AMP at the 10-minute, 30-minute and hour intervals, which also displayed similar characteristics in the ACF and PACF plots of the residuals.

Figure 4.2 ACF and PACF plots at different resolutions – patient example



(a) At 10min-by-10min resolution with ARIMA (1, 1, 1)

(b) At 30min-by-30min resolution with ARIMA (1, 1, 1)



(c) At hour-by-hour resolution with ARIMA (1, 1, 1)

The figure documents the ACF and PACF of the residuals of RAP-mapped ARIMA structure in the (a) 10 minute-by-10 minute, (b) 30 minute-by-30 minute, and (c) hour-by-hour relationships.

ACF, autocorrelative function; *ARIMA*, autoregressive integrated moving average; *PACF*, partial autocorrelative function; *RAP*, compensatory reserve index.

4.3.4 Assessment of the features for identifying artifacts

4.3.4.1 Comparing optimal ARIMA models

Initially, the optimal ARIMA model for the artifact segments for each signal of each patient was calculated. The result is depicted in Table E.1 of Appendix E. Afterwards, the median and mean of the orders of the ARIMA models for the two groups were calculated. Table E.2 and Table E.3 contain the median and the mean results for the 1-minute and 10-minute temporal resolution. D-order was not included in the analysis,

as it was set to 1 across all cases. While calculating optimal models for the artifact segments of 10-minute data, five examples (i.e. patients) could not provide any result because of the inadequacy of data (i.e. artifact segments). As both tables show, the median and mean orders of all clean and artifact data parameters differed significantly, particularly for the minute-by-minute data. The Mann-Whitney U test was conducted on these two groups of orders would provide a clear statistical comparison. The resulting p-values are as follows:

Table 4.4 A comparative analysis between clean and artifact segments' optimal ARIMA models (p-values from Mann Whitney U-test)

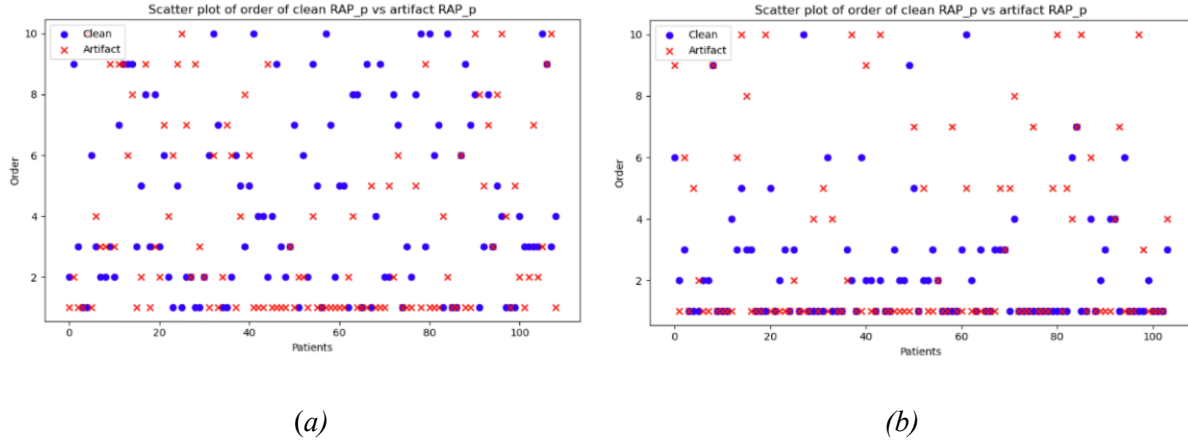
Parameter	Minute-by-minute		10-minute-by-10-minute	
	p-order	q-order	p-order	q-order
ICP	0.60996	0.00058	0.49778	close to 0
AMP	0.00501	0.20620	0.23175	0.00032
RAP	close to 0	0.01526	0.88808	0.94798

AMP, pulse amplitude of ICP; ARIMA, autoregressive integrated moving average; ICP, intracranial pressure; RAP, compensatory reserve index

Since p-value < 0.05 indicates a significant difference between the two groups, it can be concluded that in the case of minute-by-minute data, both the p-orders (p=close to 0) and q-orders (p=0.01526) of the RAP ARIMA model can serve as effective indicators for distinguishing artifact segments from clean data. However, only the q-order of ICP (p=0.00058) and the p-order of AMP (p=0.00501) demonstrated a significant difference between the two groups. For the lower-resolution data, RAP did not appear to show any notable differences across any orders. However, the q-orders of ICP (p=close to 0) and AMP (p=0.00032) exhibited significant differences.

To visually represent the data, scatterplots comparing the orders of the two groups are shown in Figure 4.3. As seen in the figure, there are only a few patient examples where the clean and artifact segment orders overlap in the minute-by-minute resolution (Figure 4.3(a)). The majority of them differ, confirming that the optimal models for the parameters of clean and artifact segments are quite distinct. In the case of the 10-minute resolution data, although many instances show non-overlapping orders, there are more examples of overlap compared to the minute-by-minute resolution. Scatterplots for RAP q-order and the rest of the signals are demonstrated in Appendix E from Figure E.1 to Figure E.3. They also displayed similar results, with both of the orders differing between the two groups and the minute-by-minute resolution showing a more pronounced distinction.

Figure 4.3 Scatterplots for RAP p-orders at different resolutions for each patient



The figure demonstrates the values of the p-orders from the ARIMA model of the clean vs artifact for each patient at (a) minute-by-minute resolution and (b) 10-minute-by-10-minute resolution. The blue circles correspond to the p-orders of the cleaned data, whereas the red crosses represent the p-orders of the artifact segment. If a red cross overlaps a blue circle, the value of the order for that patient is the same. If they don't overlap, the values differ.

ARIMA, autoregressive integrated moving average; RAP, compensatory reserve index.

As seen from the figures, there are only a few patient examples where the clean and artifact segment orders overlap in the minute-by-minute resolution (Figure 4.3(a)). The majority of them differ, confirming that the optimal models for the parameters of clean and artifact segments are quite distinct. In the case of the 10-minute resolution data, although many instances show non-overlapping orders, there are more examples of overlap compared to the minute-by-minute resolution. Scatterplots for RAP q-order and the rest of the signals are demonstrated in Appendix E from Figure E.1 to Figure E.3. They also displayed similar results, with most of the orders differing between the two groups and the minute-by-minute resolution showing a more pronounced distinction.

To assess the success rate of artifact identification, the sliding window method was applied at the patient level. For minute-by-minute data, a window size of 100 with a sample size of 50 was used, while for 10-minute-by-10-minute data, a window size of 50 with a sample size of 25 was employed. Within each window, the optimal ARIMA model was calculated, and artifacts were identified in the window if any of the calculated orders (p, d, or q) differed more than three from those of the clean data's optimal model. Using this approach, the average success rates for artifact identification were 65.258% for ICP, 65.258% for AMP, and 84.038% for RAP at the minute-by-minute resolution. The average success rates for artifact identification at the 10-minute-by-10-minute resolution were 55.336% for ICP, 54.128% for AMP, and

43.089% for RAP. Tables F.1 and F.2 of Appendix F depict the average success rates for artifact identification in both temporal resolutions.

4.3.4.2 Comparing the residuals

Using the median optimal model described in the table, the residuals of clean data and artifact segments were calculated for all patients. The difference between the two groups was determined using the Mann-Whitney U test for each patient. The result was summarized below where significant corresponds to $p < 0.05$, and insignificant is otherwise.

Table 4.5 Significant and insignificant count after a Mann-Whitney U test between clean and artifact residuals

Parameter	Minute-by-Minute		10-minute-by-10-minute	
	Significant	Insignificant	Significant	Insignificant
ICP	63	45	17	79
AMP	64	45	22	74
RAP	65	44	8	96

AMP, pulse amplitude of ICP; ICP, intracranial pressure; RAP, compensatory reserve index

As seen from the table, most cases showed significant differences at the minute-by-minute resolution while comparing clean residuals with artifact residuals. On the contrary, the result was the opposite in the 10-minute temporal resolution, with the majority of examples belonging to the insignificant group.

While calculating residuals, a few patient examples had inadequate data points; one patient at the minute-by-minute data resolution for ICP and 13 patients at the 10-minute data resolution across all signals. Consequently, the residuals for those patients could not be calculated, and the analysis was carried out excluding them.

Additionally, to consider residuals as a feature to identify artifacts, the residuals of all the clean data should be low. In other words, they need to be consistent and should be fitted by the median optimal ARIMA model calculated for the clean data. To check this, the variance of the residuals of each patient was calculated. The same was done for the artifact data (whose expected variance should be higher). The median and mean values of variance of each group were calculated as follows:

Table 4.6 Medians and means of the variance of the residuals

Parameter	Minute-by-Minute				10-minute-by-10-minute			
	Median		Mean		Median		Mean	
	Clean	Artifact	Clean	Artifact	Clean	Artifact	Clean	Artifact
ICP	1.41843	24.83865	2.00069	266.45723	4.56886	35.47967	10.2683	1837.70208
AMP	0.04842	0.61611	0.08891	2.29946	0.11453	0.09194	0.27448	3.60461
RAP	0.10523	0.20676	0.10882	0.21222	0.08715	0.10794	0.09471	0.11736

AMP, pulse amplitude of ICP; ICP, intracranial pressure; RAP, compensatory reserve index

As shown in the table, the expected outcome was observed for both resolutions. Particularly, ICP showed the largest difference among the signals. However, the median results of AMP at the 10-minute-by-10-minute data resolution deviated from the expected result.

The sliding window method was applied at the patient level to evaluate the success rate of artifact identification for this feature. A window size of 50 with a sample size of 25 was used for both minute-by-minute and 10-minute-by-10-minute resolution. At first, the variance of residuals within each window was calculated, and artifacts were identified if the variance of residuals exceeded the median variance of the total data for a single patient. Using this method, the average success rates for identifying artifacts across the entire population were 70.212% for ICP, 56.916% for AMP, 91.666% for RAP at the minute-by-minute resolution, and 85.092% for ICP, 74.264% for AMP, 84.411% for RAP at the 10-minute-by-10-minute resolution as illustrated in Table F.1 and Table F.2.

4.3.4.3 Comparing the cross-correlation of residuals

The groups for this analysis were formed as outlined in Section 4.2.5.2. After calculating the cross-correlation of total signals for each case and patient, the maximum values from the results were recorded. Next, the median and mean values of the maximum cross-correlation between RAP and ICP/AMP residuals were calculated across the total population for both the clean and artifact cases, as follows:

Table 4.7 Medians and means of the maximum cross-correlations of residuals

Parameter	Minute-by-minute				10-minute-by-10-minute			
	Median		Mean		Median		Mean	
	Clean and Clean	Clean and Artifact	Clean and Clean	Clean and Artifact	Clean and Clean	Clean and Artifact	Clean and Clean	Clean and Artifact
RAP-ICP	14.48875	23.01389	77.319716	46.14512	26.92	32.46088	36.9293	121.002

RAP-AMP	137.63467	28.61530	415.91384	51.74234	4.4332	1.55919	5.83130	3.97946
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Clean and clean refer to the cross-correlation between clean RAP and clean ICP (RAP-ICP) or clean RAP and clean AMP (RAP-AMP). Whereas clean and artifact refer to clean RAP and artifact ICP (RAP-ICP) or clean RAP and artifact AMP (RAP-AMP).

AMP, pulse amplitude of ICP; ICP, intracranial pressure; RAP, compensatory reserve index

Table 4.7 demonstrates that for the minute-by-minute data, the maximum RAP-AMP cross-correlation of residuals was expectedly higher in clean-clean cases compared to that of clean-artifact cases based on both median and mean values. However, this was not the case for RAP-ICP; even though the mean value of clean-clean cases was slightly higher, the median was lower. On the other hand, for the 10-minute-by-10-minute data, none of the clean-clean cases had considerably higher values in RAP-ICP (median and mean) cross-correlation. In contrast, RAP-AMP cross-correlation showed higher values in clean-clean cases both in median and mean.

A Mann-Whitney U test was subsequently performed to compare the two groups: maximum cross-correlation of clean RAP residuals with clean ICP/AMP residuals vs clean RAP residuals with artifact ICP/AMP residuals. For RAP-ICP, the p-values were 0.02809 for the minute-by-minute resolution and 0.31919 for the 10-minute resolution. In contrast, for RAP-AMP, the p-values were close to 0 for both resolutions.

Additionally, the maximum cross-correlations of the two groups (i.e. RAP-ICP clean-clean residuals vs clean-artifact residuals and RAP-AMP clean-clean residuals vs clean-artifact residuals) were compared at the patient level. The expected result was that the clean-clean maximum cross-correlation of residuals should be greater than the clean-artifact maximum cross-correlation of residuals, as explained in Section 4.2.5.2. The number of patients (out of 108 patients in total) in each case that showed greater values in clean-clean cases: i) RAP-ICP, 34 cases and ii) RAP-AMP, 95 cases at the minute-by-minute resolution, whereas i) RAP-ICP, 41 cases and ii) RAP-AMP, 69 cases at the 10-minute-by-10-minute resolution.

The outcome of this analysis aligns with the findings of the overall (median and mean) result presented in Table 4.7, which is only the RAP-AMP cross-correlation at the minute-by-minute resolution demonstrated a majority number of patients (95 cases) with higher values of maximum cross-correlation in clean-clean cases, alongside RAP-AMP cross-correlation at the 10-minute-by-10-minute resolution demonstrating 69 cases. On the contrary, RAP-ICP failed to achieve such large numbers at both resolutions.

In the success rate findings of this feature, RAP-ICP and RAP-AMP cross-correlations were calculated within each window. The window size and sample size were similar to the previous feature (i.e. 50 and 25, respectively). Artifacts were predicted within a window if the maximum cross-correlation was lower than the median of the maximum cross-correlation values between clean and artifact groups of the total recording for a single patient. Using this method, the median success rates for identifying artifacts across the entire population were 37.011% for RAP-ICP and 61.6% for RAP-AMP cross-correlation at the minute-by-minute resolution, whereas at the 10-minute-by-10-minute resolution, they were 6.512% and 35.829%, respectively.

4.4 Discussion

We set out to explore the RAP compensatory reserve index, derived from ICP pressure sensors, to better understand some critical aspects of such cerebral data streams and address Hypothesis #1 of this thesis. First, we comprehensively characterized the general nature of RAP signals with respect to other cerebral physiologic parameters, including subgroup analysis. Second, we outlined the time-series statistical structures of RAP in relation to its constituent signals (ICP and AMP). Finally, we leveraged our enhanced understanding of the time-series structures of RAP data streams to explore signal artifact detection. Throughout this process, some important aspects of RAP and the use of such sensor data streams deserve to be highlighted.

4.4.1 RAP's patterns and behaviours

First, based on the results in Appendix A, TBI patients generally demonstrated an impaired compensatory reserve, as they spent most of their time within the range of 0.4 to 1 as measured by the RAP index (illustrated in Table A.2), corresponding to state 2 of RAP,¹¹⁷ as defined in section 4.3.2.1. Regarding age comparison, Tables A.3 and A.4 indicated that RAP increased with age. For Marshall CT grades, grades I through IV represent progressively worsening brain injuries;¹³⁶ thus, RAP would be expected to increase from grade I to IV, as supported by the analysis in Table A.7. In grade V, patients underwent brain surgery where mass lesions were removed.¹³⁶ This may or may not have resulted in a higher RAP than grade IV, depending on the surgery's outcome and can explain the reduced RAP value observed in grade V.

4.4.2 Time series structure analysis

Second, during time series analysis, it was clear that RAP signal sources were non-stationary and carried substantial trend features inherent within their data streams. We were able to demonstrate this across two different temporal resolutions of RAP data, emphasizing that this was present even at low temporal

resolutions. This is critical for future use of RAP in physiologic modeling, as not accounting for such a trend would lead to model inaccuracies, where most work in the field to date ignores such features.

RAP data streams displayed inherent autoregressive features, consistent with optimal ARIMA models with non-zero autocorrelative and moving average orders (p-orders and q-orders, respectively). Also of interest, the optimal ARIMA model orders for RAP differed from both ICP and AMP, and its constituent signals, highlighting that RAP contains different information compared to ICP or AMP alone. This was the case across the population, highlighting again the need to not just account for data trend, but also more complex autoregressive features in future modeling using temporally resolved RAP data. However, it must be noted that the median optimal model calculated for the dataset may not accurately represent all patients. For instance, RAP at minute-by-minute resolution had a median optimal ARIMA model of (3, 1, 3). However, one patient individually obtained an optimal ARIMA model (8, 1, 3). Hence, applying the ARIMA (3, 1, 3) model to this patient's RAP signal may not effectively capture the data's structure due to the substantial difference in the p-order. Examining this patient's ACF and PACF plots from Figure D.5 reveals spikes between lags 0 to 5 that fall outside the confidence intervals, highlighting further limitations of using the median optimal ARIMA model. Nevertheless, the spikes out of the confidence intervals had very small magnitudes compared to the spikes seen in the ACF and PACF plots from the original data. Therefore, the median optimal ARIMA model obtained in this analysis could contribute to the identification of the features that helped distinguish clean data from artifact segments.

4.4.3 Comparison among different resolutions

Third, during ARIMA model generation, including stationarity tests, some examples failed to return a p-value due to insufficient data points, which were most commonly observed at the hour-by-hour temporal resolution. Similarly, most of the non-stationary results were also found at this lowest resolution in both the original and differenced data. Additionally, while calculating the optimal ARIMA model for each signal of each patient, some cases failed to yield results due to insufficient data, mainly at lower resolutions. These observations highlight the critical role of data point quantity in each step of determining the optimal ARIMA model. It also suggests that lower resolutions may be associated with higher residuals, indicating a comparatively less accurate model. The median of the residuals for each resolution were calculated with the results summarized in Table D.8 of Appendix D. All of these findings emphasize the importance of a proper understanding of the statistical structures of such data streams from pressure sensors and their derived metrics (such as RAP). Throughout Table 4.2, the loss of RAP lags can be observed in the median optimal ARIMA models for lower resolutions (i.e. order numbers are smaller). Additionally, Table 4.5 and Table 4.6 show the less importance of artifact management since the difference between clean and artificial

groups was not significantly different in lower resolution. This suggests that the lower resolutions lose the dynamic aspects of the data (ICP/AMP/RAP).

This trend can also be observed in Table C.1, which details the optimal model for each signal and resolution for each patient. Lower resolutions tend to have simpler optimal models with lower order (p, d, q) values, leading to underfitting. This occurred because the ARIMA analysis, constrained by fewer data points, could not find a suitable model to capture the data fully. In contrast, higher resolutions, with more data points, yielded better results. The presence of spikes with higher magnitudes in the ACF and PACF plots of residuals at lower resolutions from Figure D.2 further supports this statement.

4.4.4 Identifying artifacts

Finally, building on the results from the time-series modeling of RAP, ICP, and AMP, we aimed to identify potential features capable of distinguishing artifacts from clean data. To qualify as a potential identifier of artifact profiles, a feature must show significant differences between the clean and artifact groups in every case; for instance, in a Mann-Whitney U-test analysis, the p-value between the two groups should be less than 0.05. Firstly, according to Table 4.4, the p-values for ICP q- order, AMP p-order, and RAP p-orders and q-orders were less than 0.05 (i.e. significant difference) while comparing optimal ARIMA models of clean and artifact data at the minute-by-minute resolution, suggesting that these orders are strong candidates for identifying artifacts. Conversely, ICP p-orders and AMP q-orders from the optimal models could be excluded as potential features due to insignificant differences between the clean and artifact groups (p-value > 0.05). However, at the 10-minute-by-10-minute data resolution, only the q-order of optimal ARIMA models of ICP (p-value = close to 0) and AMP (p-value = 0.00032) proved to be a potential distinguishing factor, while other orders showed no significant differences.

Secondly, while comparing the residuals of clean and artifact profiles at the patient level, Table 4.5 shows that the majority of cases exhibited significant differences for each signal at the minute-by-minute resolution. Specifically, significant differences were observed in 63, 64, and 65 cases out of 108 for ICP, AMP, and RAP, respectively. In contrast, at the 10-minute-by-10-minute resolution, most cases showed no significant differences for all signals. This indicates that though residuals could be a strong feature for distinguishing artifact profiles at the minute-by-minute resolution, they are less effective at the 10-minute resolution. Table 4.6 further supports this finding, as the median and mean of the variance of residuals across the population were consistently lower for clean data and higher for artifact segments at both resolutions. This consistency suggests that clean data were moderately well-modeled. Therefore, residuals could be considered as a reliable feature for artifact identification.

The third and final analysis focused on comparing the maximum cross-correlation of residuals between clean-clean and clean-artifact combinations for RAP-ICP and RAP-AMP. This analysis was conducted in three parts. It was hypothesized that the maximum cross-correlation between clean RAP and clean ICP/AMP residuals would be higher than that between clean RAP and artifact ICP/AMP residuals, as RAP is derived from ICP and AMP, and their residuals are expected to exhibit strong correlations. Firstly, the medians and means of the maximum cross-correlations were calculated. Among these, only the RAP-AMP cross-correlation consistently showed higher values in clean-clean cases for both median and mean. Thus, the RAP-AMP maximum cross-correlation emerged as a potential feature for both minute-by-minute and 10-minute-by-10-minute resolutions. Secondly, a Mann-Whitney U test was performed across the entire population to compare the groups. The test revealed significant differences ($p < 0.05$) between clean-clean and clean-artifact residuals for each case except RAP-ICP at the 10-minute-by-10-minute resolution. Finally, maximum cross-correlations were compared at the patient level, with the expectation that clean-clean maximum cross-correlations would be greater than clean-artifact correlations. This was confirmed for RAP-AMP cross-correlation at both the minute-by-minute and 10-minute-by-10-minute resolutions, where the majority of patients exhibited higher clean-clean values. In conclusion, combining these three parts, between RAP-ICP and RAP-AMP, the cross-correlation of the latter at both resolutions could serve as a strong feature for identifying artifacts.

Finally, while the success rate of capturing artifacts showed promising results, some non-artifact data points were mistakenly identified as artifacts (i.e. false positives). The number of false positives at each parameter and each analysis is demonstrated in Table F.1 and Table F.2. Removing these non-artifact data points could result in the loss of valuable information from the signal. Further work is needed to address this issue, either by refining the thresholds and parameters in the sliding window approach or by utilizing ML methods and incorporating these identified features into the model.

4.5 Limitations

The population sample size is relatively small despite representing the largest study to date comprehensively characterizing RAP data features. Such small sample sizes limit the ability to extrapolate such findings to other populations where ICP sensor technology is applied, and RAP can be measured. For instance, as discussed in the previous section, the median optimal model identified for the clean data may not fully represent all patients. Secondly, the number of data points for each patient constrains the results at lower resolutions. The reduction in data points at lower resolutions, due to calculation methods, led many optimal models at these resolutions to return ARIMA (1, 1, 1), indicating insufficient data points to capture the signal structure and resulting in underfitting. This is supported by the table showing higher residuals at

lower resolutions (Table D.7). Additionally, several examples failed to return optimal ARIMA models, residuals, or p-values in the Mann-Whitney U test, further decreasing the data size at lower resolutions. Moreover, it remains unclear why RAP at lower resolutions did not show significant order differences between clean and artifact groups, while RAP at higher resolutions did. This could be due to RAP's derivation method, which results in 80% overlapping data, or due to insufficient data points at lower resolutions. Thirdly, the heterogeneity in TBI characteristics and the diversity of treatments administered could have influenced the physiological response observed in the signals, which might make it difficult to identify consistent patterns and draw generalized conclusions. Fourthly, a detailed treatment based subgroup assessment is required. This analysis did not include the effect of different therapeutic interventions, such as decompressive craniectomy, pCO₂ changes or mannitol infusion. Though ICP treatments have an immediate impact on ICP (the minutes after treatment), their long-term impact on ICP modeling and other derived ICP measures (like PRx) is quite limited. Therefore, when modeling and assessing RAP physiological factors over larger periods of time and over whole populations, ICP treatment factors can likely be largely ignored. However, when robust minute-by-minute RAP is being modeled (looking at individual moments of patient state); these factors should be considered. Finally, the data originates from a single-center archive, limiting generalizability, as findings may not apply to other centers with different patient populations, treatment protocols, or equipment.

4.6 Future directions

Future work on ICP pressure sensor-based signal sources, including RAP, needs to include larger multi-center high-frequency signal databases. With improved sample sizes, validation of the above general RAP behaviour, its time-series structure, and artifact detection methods need to occur. Such future work could include non-linear methods and future sub-group analysis based on injury or disease patterns. Further, artifact detection methods could be enhanced to include not just time-series methods explored within this manuscript but layered approaches, including signal morphological assessments, wavelet decomposition methods, and ML techniques. Finally, for RAP data to be temporally modeled, a proper understanding of its time-domain statistical features is key. Such larger multi-center studies would be optimally positioned to define RAP statistical features more robustly.

4.7 Conclusion

RAP signals, derived from ICP sensor technology, displayed reproducible and characteristic patterns in this population of moderate/severe TBI patients, with most displaying features of impaired compensatory reserve. The time-series statistical features of RAP demonstrated inherent autoregressive features and data trends, regardless of temporal resolution, which are distinct from its constituents, ICP and AMP. Such time-

domain statistical features of RAP signals can be used to identify artifactual segments in RAP data streams. Future work is required in larger populations to validate such findings.

5 Relationship Between RAP and Multi-Modal Cerebral Physiological Dynamics

The study described in chapter 5 can also be found in detail in the following submitted manuscript, and addresses Hypothesis #2 of this thesis:

- **Islam A**, Stein KY, Griesdale D, et al. Relationship Between RAP and Multi-Modal Cerebral Physiological Dynamics in Moderate/Severe Acute Traumatic Neural Injury: A CAHR-TBI Multivariate Analysis. Bioengineering (Basel) 2025. (Under Review)

5.1 Introduction

Despite its potential, the clinical adoption of RAP in TBI cases has been limited, largely due to an incomplete understanding of its characteristics.^{7,14–16} The previous study has focused on characterizing the temporal dynamics of RAP and its constituent signals, ICP and AMP, as well as addressing artifact management strategies.¹²⁴ However, there remains a notable gap in the literature regarding the broader cerebral physiology context and the injury burden of impaired RAP in association with other continuous MMM cerebral physiology.¹²⁴ Section 2.6.3 highlighted that various MMM physiological indices consistently exhibited distinct patterns across different states of compliance (i.e., intact, impaired, exhausted) in TBI patients, emphasizing the potential for a more granular analysis of how RAP aligns with these physiologic parameters.¹¹⁷

Therefore, this study aims to characterize the insult burden of impaired cerebral compensatory reserve in moderate/severe TBI patients in relation to other critical aspects of cerebral physiology by A. describing general descriptive associations between RAP and other physiologic signals, B. exploring multivariate covariance patterns using semi-supervised ML techniques, and C. assessing high-resolution RAP responses to dynamic changes in related variables. The broader objective is to understand the overall burden of impaired RAP in the context of cerebral physiology, thereby laying the groundwork for its future use in bedside monitoring, patient trajectory modeling, and interventional clinical studies.

5.2 Materials and Methods

5.2.1 Study design

This retrospective investigation utilized archived human subject data from the Canadian High-Resolution Traumatic Brain Injury (CAHR-TBI) Research Collaborative.¹⁴² Patients were included in the database if they met all of the following criteria: they were 18 years of age or older, had a diagnosis of moderate-to-

severe TBI with a GCS score of less than 13, were admitted to the ICU of a participating hospital, underwent both invasive ICP and ABP monitoring, and had data collection initiated within 24 hours of clinical presentation.^{118,119}

In addition to high-resolution physiological data, the dataset included demographic details (such as age, sex), admission-related characteristics (including admission GCS score and pupillary reactivity), and imaging findings (e.g., Marshall CT score).

5.2.2 Data Acquisition and Signal Processing

As described in sections 3.2, 3.3, and 3.4, signal data were collected, processed and derived using ICM+.

5.2.3 Analysis of general descriptive relationships

Based on the results of our previous systematic review, the entire population was categorized into three groups according to three RAP threshold ranges: [-1, 0], [0.4, 1], (1, 0.4).¹¹⁷ These threshold ranges were established based on cerebral physiological states (i.e., exhausted, intact, and impaired states of cerebral compliance) and transitions inferred from RAP values.^{117,124} Afterwards, general descriptive relationships between RAP and other physiology were explored across the three segments. Initially, different plots were created for visualization, including scatterplots with piecewise linear regression and boxplots across the entire population. Subsequently, the medians of the cerebral physiological parameters were observed to explore how RAP values affect other physiological measures. Given the non-parametric nature of the data and the presence of more than two groups, the Kruskal-Wallis test was selected to perform a formal comparison among the groups.^{118,143} Finally, the percentage time spent of different ranges of other parameters within different RAP states was observed. For formal comparisons and percentage time calculations, the median value across each patient's entire recording was used.

Next, a reverse analysis was carried out using the thresholds of other physiological parameters, examining how RAP changed in response. Similarly, this was analyzed using the median measurements and statistical comparisons. Furthermore, the percentage time spent of RAP within different RAP states at these threshold ranges was examined. The thresholds for various parameters were as follows: ICP (20 mmHg, 22 mmHg)^{3,123}, CPP (60 mmHg, 70 mmHg),³ rSO₂ (60, 70, 80, 90),^{144,145} PbtO₂ (15 mmHg, 20 mmHg),^{146–148} PRx (0, +0.25, +0.35), PAx (0, +0.25), RAC (0),^{38,123} COx/COx-a (0, +0.20).¹⁴⁵ Threshold values for these parameters were determined based on commonly referenced values from previous studies in related fields. For statistical comparisons, the Mann-Whitney U-test was applied, given the number of groups and non-parametric nature of the data.^{118,119,124}

5.2.4 Application of semi-supervised ML methods for parameter clustering

To quantify covariance patterns in multivariate space for the discussed physiological parameters, semi-supervised ML methods, namely agglomerative hierarchical clustering (AHC), principal component analysis (PCA), and K-means clustering (KMCA), were utilized.^{125,136,145}

AHC is an ML algorithm used for hierarchical data grouping. The method works by initially treating each data point as an individual cluster, and then iteratively merging the closest clusters based on a defined distance metric. This process continues until all data points are clustered into a single group.^{149,150} In this study, the Euclidean distance metric was employed, and dendrograms were generated for visualization of the output. By examining the clustering and merging distances in the dendrogram, it became possible to identify patterns of similar behaviour among parameters across various instances, as well as to uncover inherent subgroups within the data that displayed comparable dynamics. This analysis was conducted using the *hierarchy* submodule from the *SciPy* library, with adequacy of fit of the resulting dendrogram quantified using cophenetic correlation coefficients.¹⁵¹

Next, PCA was employed, which is a statistical technique that reduces the dimensionality of multivariate data while retaining as much variance as possible. PCA transforms the original set of variables into a new set of orthogonal components, known as principal components, ranked by the amount of variance they capture.^{152,153} In this study, a PCA biplot was constructed using the first two principal components (PC1 and PC2), with the directional vectors of the physiological parameters projected onto this reduced space. Parameters that exhibited alignment in a similar direction within the biplot were interpreted as being positively correlated, indicating that they share similar variance structures and contribute in a comparable manner to the principal components. Furthermore, to assess the contribution and effectiveness of the principal components, scree plots of the explained variance ratio and cumulative explained variance were analyzed. This analysis was performed using the *PCA* class from the *scikit-learn* library.¹⁵⁴

Lastly, KMCA is a widely used semi-supervised learning algorithm that partitions data into k distinct clusters by iteratively assigning points to the nearest centroid and updating centroids based on a similarity measure.^{155,156} In this analysis, the Euclidean distance was used as the similarity measure, and the elbow method was applied to identify the optimal number of clusters (k). This technique involved plotting the within-cluster sum of squared errors (WCSS) against varying values of k . As k increased, WCSS typically decreased; however, after a certain point, the rate of decrease sharply diminished. The "elbow" point on the plot, where the curve starts to level off, indicated the optimal number of clusters. The *KMeans* class from the *scikit-learn* library was used to carry out this analysis.¹⁵⁷

To execute these algorithms, it would be necessary to include all parameters and remove any missing values, which would require excluding the entire dataset of a patient, even if a single parameter was absent. However, as seen in Section 5.3.1, out of 379 patients, only 133 and 116 patients had available data for both NIRS-derived parameters (rSO_2_L , rSO_2_R , COx_L , COx_R , $COx-a_L$, $COx-a_R$) and $PbtO_2$, respectively. Therefore, using all parameters would have left insufficient data, reducing analysis efficiency. To overcome this, the population was divided into three groups: (a) ICP-ABP-derived parameters (ICP, AMP, MAP, CPP, PRx , Px , RAC), (b) ICP-ABP-derived parameters with NIRS-derived parameters, and (c) ICP-ABP-derived parameters with $PbtO_2$, and separate analyses were conducted on these groups to ensure a more comprehensive and effective approach.

The analysis was initially conducted on the original data (i.e., minute-by-minute). Later, the entire analysis was repeated on lower-resolution datasets. Afterwards, the whole dataset was divided into three segments based on three RAP states (intact, impaired, severely impaired) as defined in our previous systematic review,¹¹⁷ and the analysis was conducted on these sub-groups across all the resolutions.

5.2.5 High-frequency temporal analysis of RAP vs. MMM relationships

In the context of our research goal, high-frequency temporal analysis of RAP vs MMM relationships would enable us to capture the dynamic, time-resolved interactions between RAP and other parameters. This section of the analysis includes VARIMA, impulse response function (IRF) plots with corresponding quantitative evaluations, Granger causality testing and cross-correlation analysis.

The analysis was conducted on the minute-by-minute, 5-minute, and 10-minute resolution data. Other lower-resolution data were excluded, as the mentioned methods' effects on these datasets would be minimal and would not provide sufficient observations for meaningful conclusions. This is because at lower resolutions, they don't adequately capture short-term variability and result in few data points for robust analysis, as important signal dynamics are smoothed out, reducing the sensitivity of the methods.

The entire analysis in this section was also extended to the sub-group level. For Granger causality testing and cross-correlation analysis, each patient's recording was divided into three segments based on predefined RAP thresholds, and each segment was analyzed separately. However, this segmentation approach was not feasible for IRF analysis involving VARIMA models, as the $RAP < 0$ and $0 \leq RAP \leq 0.4$ segments in most cases lacked sufficient data to reliably fit the optimal VARIMA models for many patients. To address this, the median RAP value across the entire recording period was calculated for each patient, and patients were then grouped into the three RAP states based on these median values.

5.2.5.1 Application of VARIMA IRF

VARIMA is a multivariate time series modeling approach that extends the ARIMA framework to capture temporal dependencies and interactions across multiple variables.^{136,145,158} It accounts for both autoregressive and moving average components, along with differencing to ensure stationarity. Impulse Response Function (IRF) analysis was then applied to the fitted VARIMA models^{136,145} to quantify the effect of a one-time impulse in a given physiological variable (e.g., ICP, MAP) on RAP over subsequent time points, allowing for the temporal propagation of influence to be assessed.

To determine the optimal AR order (i.e. p-order) and MA order (i.e. q-order) of the VARIMA model, first, the optimal ARIMA orders needed to be determined. For the ARIMA application, the data needed to be stationary. As ARIMA modeling requires stationarity, and prior analyses confirmed that the dataset was non-stationary,^{118,119,124} first-order differencing was applied to achieve stationarity. Optimal ARIMA models were then selected for each patient using the AIC, which was preferred over the BIC and LL due to its balanced trade-off between model fit and complexity.^{118,124,136} Since the objective was to assess the influence of other physiological parameters on RAP, pairwise VARIMA models were computed for each RAP-X combination, where X denotes a secondary physiological variable. The VARIMA p-order for each RAP-X pair was determined by multiplying the respective ARIMA p-orders of RAP and X,^{125,136,159} and the VARIMA q-order was computed by summing the individual ARIMA q-orders,^{136,159} following approaches established in previous work. This modeling procedure was implemented at the patient level.

While determining the optimal orders for the VARIMA model, p- and q-orders were capped at 10. This constraint was applied to prevent overfitting and to preserve the practical applicability of the model for real-time monitoring. Moreover, prior studies have demonstrated that limiting the model orders to 10 did not change the results significantly.¹²⁵

Afterwards, the IRF coefficients were derived from the fitted VARIMA model for each RAP-X pair at the individual patient level. These coefficients were then used to generate IRF plots, offering a graphical depiction of the effect of a one-unit orthogonal impulse of first-order differenced X (ΔX) on first-order differenced RAP (ΔRAP) over time. To estimate the population-level confidence intervals, a bootstrapping approach was employed.^{136,160} This involved repeatedly sampling subsets of the data and recalculating the IRF, with a standard percentile-based bootstrap interval generated from a number of iterations to quantify variability and uncertainty in the response estimates.^{136,160} In this study, 100 iterations were used.

Given the high variability across IRF plots and the limitations of relying solely on visual interpretation in large datasets, a simplified classification approach was adopted to distinguish between “more responsive”

and “less responsive” models.¹³⁶ This involved normalizing each impulse response relative to its original variable. A response was considered “more responsive” if its absolute value exceeded 0.001 (i.e., a $\geq 0.1\%$ change in the normalized scale) within steps 11 to 15, consistent with thresholds used in prior studies.^{125,136} The observation in these steps was effective since immediate responses might reflect noise or autoregulatory transients, while sustained changes after a short delay are more likely to reflect true, biologically meaningful interactions. Additionally, observing steps after 15 could reduce the practical utility of the analysis for real-time monitoring.

The *VARMAX* class from the *statsmodels* library was employed to fit the VARIMA optimal model.¹⁶¹ While the *VARMAX* class facilitates the implementation of VARIMA models, it does not include a specific argument for the differencing component (i.e., d-order).¹⁶¹ To address this, first-order differenced data was used as input, effectively setting the differencing order (d-order) to 1 during the VARMAX operation. In this manner, the VARIMA model was successfully fitted. The IRF analysis was carried out using the *IRAnalysis* class from the *statsmodels* library.¹⁶²

5.2.5.2 Application of Granger causality testing

To assess potential directional relationships between RAP and other physiological parameters, Granger causality testing was employed. This method determines whether past values of one time series contain statistically significant information that helps predict the future values of another series, beyond the information contained in its own past values.^{163,164} The test was conducted at the patient level for each $\Delta X \rightarrow \Delta \text{RAP}$ pair, where associated p-values and F-statistics were calculated and compared against those from the corresponding $\Delta \text{RAP} \rightarrow \Delta X$ direction. Initially, p-values were assessed for each $\Delta \text{RAP} - \Delta X$ pair. If only one direction yielded a statistically significant p-value ($p < 0.05$), that direction was considered to represent Granger causality for the pair. In cases where both directions were significant, the direction with the higher F-statistic was selected as the causal direction. If neither p-value was significant, the observation was classified as having no Granger causal directionality. First-order differenced data were used as inputs to ensure stationarity, a prerequisite for performing Granger causality testing.^{125,136}

This analysis was also applied across the discussed resolutions and sub-groups. The *grangercausalitytests* class from the *statsmodels* library was used to conduct the test.¹⁶⁵

5.2.5.3 Application of cross-correlation

Cross-correlation is a statistical method used to measure the similarity or degree of association between two time series as a function of the lag of one relative to the other. In physiological data analysis, it helps

to identify whether changes in one signal precede, follow, or occur simultaneously with changes in another signal.^{166,167}

To perform this analysis, each variable was first mean-centred to ensure a zero mean, preventing biased cross-correlation results that could otherwise occur due to offset signals. The resulting cross-correlation values were then normalized by dividing by the product of the standard deviations of the mean-centred signals and the signal length. This standardization confined the correlation values within the range of -1 to 1, comparable to Pearson’s correlation, and eliminated the influence of differing signal scales between RAP and the corresponding variable. Finally, the entire analysis was performed on first-order differenced data to prevent misleading correlation results and to more accurately capture the true lagged relationships between the variables. The lag position of the peak correlation provided insight into the temporal relationship between the signals: a peak near lag 0 suggested synchronous changes, a positive lag that the other variable preceded changes in RAP, and a negative lag indicated RAP preceded changes in the other signal. Additionally, the magnitude of the peak correlation reflected the strength of the association.

This analysis was performed at the population level across three different data resolutions. For each patient, the maximum cross-correlation value and the corresponding absolute lag value at which this maximum occurred were recorded. Median values of these metrics were then calculated across all patients to provide a summarized overview of the results. Subsequently, this was conducted at the sub-group level across all the resolutions. The *correlate* class from the *scipy* library was used to conduct cross-correlation.¹⁶⁸

5.3 Results

5.3.1 Patient demographics

A total of 379 patients were included in the study. Of these, 295 were male. The median age was 38 years, with an interquartile range (IQR) of 24 to 55 years. Additional key demographic and clinical characteristics of the patient cohort are summarized in Table 5.1. This table also presents the number of patient population for NIRS-derived parameters and PbtO₂, along with the median percentage of each RAP state at the patient level.

Table 5.1 Patient demographics

Variable	Median (IQR) or Number (%)
Duration of recording (minutes)	5811.23 (2872.90%—9951.18%)
Number of Patients	379
Age (years)	38 (24—55)
Sex (Male)	295 (77.83 %)
GCS	6 (3—7)

GCS Motor	4 (1—5)
Pupils	
Bilateral Reactive	250 (65.96 %)
Unilateral Unreactive	63 (16.62%)
Bilateral Unreactive	56 (14.77 %)
Marshall CT Score	
VI	6 (1.58%)
V	104 (27.44 %)
IV	43 (11.34 %)
III	90 (23.74 %)
II	118 (31.13 %)
Parameter groups	
Patient with ICP-ABP-derived parameters	379 (100 %)
Patient with combined NIRS-derived parameters	133 (35.09 %)
Patient with PbtO ₂	116 (30.60 %)
RAP states	
RAP < 0	4.78% (2.52%—9.72%)
0 ≤ RAP ≤ 0.4	10.91% (5.97%—17.19%)
RAP > 0.4	84.31% (72.17%—91.29%)

ABP, arterial blood pressure; CT, computerized tomography; GCS, Glasgow Coma Score; ICP, intracranial pressure; IQR, interquartile range; NIRS, near-infrared spectroscopy, PbtO₂, brain tissue oxygenation; RAP, index of cerebral compensatory reserve;

5.3.2 Graphical Relationships between RAP and MMM Cerebral Physiologic Variables

After dividing the data according to three RAP threshold ranges ([0.4, 1], (0, 0.4), and [-1, 0]), scatterplots were drawn with the piecewise linear regression for all the parameters, which is illustrated in Figure G.1 of Appendix G. For this figure, minute-by-minute resolution was used. The slope of the straight line for each threshold range obtained from the linear regression is illustrated in Table 5.2.

Table 5.2 Slope of the piecewise linear regression

Parameters	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4
ICP	-3.43	0.92	3.73
AMP	-0.24	1.09	1.81
MAP	1.85	-1.05	2.25
CPP	5.38	-1.95	-1.5
PRx	-0.08	0.0	-0.59
PAx	0.23	0.21	-0.25
RAC	-0.12	-0.08	-1.09
rSO ₂ _L	-2.51	0.14	-3.24

rSO ₂ _R	-1.57	1.44	-2.59
COx_L	0.02	-0.03	-0.21
COx_R	-0.05	0.03	-0.19
COx-a_L	-0.12	-0.02	-0.05
COx-a_R	-0.12	-0.02	-0.03
PbtO ₂	-2.43	-1.22	9.58

AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; P_{ax}, pulse amplitude index; PbtO₂, brain tissue oxygenation; PR_x, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

As presented in the table and figures, ICP and AMP displayed similar slope signs (i.e. positive/negative slopes) across all segments. The significant positive slopes of ICP and AMP in the RAP positive range indicate that both parameters increased as RAP increased, consistent with the theoretical understanding of RAP. However, in the RAP < 0 state, AMP showed a slightly smaller negative slope (-0.24). Regarding MAP and CPP, the reduction in their values in the RAP < 0 state was evident in both figures. Furthermore, CPP decreased with the increase of RAP in its positive range.

Theoretically, as cerebral compliance worsens, CA indices should increase and remain positive, indicating impaired CVR. This pattern was observed in the RAP < 0 state for most CA indices (PR_x, RAC, COx_R, COx-a_L, COx-a_R), where regression lines were in the positive region and showed an upward trend as RAP decreased toward -1. However, interestingly, the opposite occurred in the RAP > 0.4 state, where all CA indices decreased toward negative values as RAP increased. Additionally, at the 0 ≤ RAP ≤ 0.4 state, most slopes (RAC, COx_L, COx-a_L, COx-a_R) suggested that reactivity worsened as RAP decreased, with regression lines remaining in the positive region. These findings suggested that impaired reactivity was associated with lower values of RAP. This was due to the transitional phase of cerebral compliance when it worsens from an impaired to an exhausted state. A more detailed explanation regarding this is given in section 5.4.1.

The NIRS-derived rSO₂_L and rSO₂_R showed a decrement with the increase of RAP towards +1, indicating reduced oxygen saturation. Interestingly, a decrement in rSO₂_L and rSO₂_R as RAP moved

towards -1 from 0. However, in the case of PbtO₂, it was increasing at the RAP > 0.4 state. In the other two states, the change rate was minimal, i.e. the slopes were much smaller (-2.43 and -1.22).

Figure G.2 presents boxplots for all parameters across the entire population. The patterns observed align with those in the scatterplots, with most parameters exhibiting consistent increases or decreases within specific RAP states. This further validates the findings of the plots.

5.3.3 Comparison of MMM Cerebral Physiology Across RAP Threshold Categories

Afterwards, the median values of different physiological parameters, along with IQR were calculated across the three RAP states and presented in Table G.1. This table also includes the p-values obtained from the Kruskal-Wallis test conducted across the three RAP states. Furthermore, the percentage time spent of different parameters within different RAP states was also included in this table. Most of these median values were consistent with the findings illustrated in Figures G.1 and G.2. However, while ICP was expected to have higher median values in the RAP < 0 state and CPP was anticipated to be lower compared to the $0 \leq \text{RAP} \leq 0.4$ state, the results contradicted these expectations. This discrepancy was likely due to uneven data distribution, particularly the limited availability of data in the RAP < 0 state, which might have caused unexpected shifts in median values. Furthermore, consistent with previous figures, the median values of all CA indices indicated that impaired autoregulation (i.e., higher CA index values) was associated with lower RAP values, with the exception of PAX. Regarding PbtO₂, the $0 \leq \text{RAP} \leq 0.4$ state exhibited the lowest median PbtO₂ value, while the other two RAP states showed increasing trends, with the RAP > 0.4 state having the highest PbtO₂ value.

In the formal statistical comparison analysis, ICP, AMP, MAP, PRx, and RAC demonstrated significant differences ($p < 0.05$) across the RAP states, based on the Kruskal-Wallis test. The % time spent of these RAP states across predefined thresholds of different physiological parameters was also depicted in the table, which showed a similar trend to these findings.

5.3.3.1 Comparison of RAP Behaviour Across Different MMM Critical Thresholds

Next, a reverse analysis was conducted with other physiological thresholds. First, the median values for each parameter across the segments were calculated, along with the corresponding p-values obtained from the Mann-Whitney U-test (for two groups) and the Kruskal-Wallis test (for three or more groups), enabling a formal comparison between the groups. These results are presented in Table G.2. Furthermore, this table also contains the % time spent of RAP within different RAP states at the threshold ranges.

As shown in the table, while higher RAP was associated with higher ICP and CPP threshold ranges, for the rest of the parameters, higher RAP was associated with lower threshold ranges of the parameters. In terms of CPP thresholds, the association of higher RAP with higher CPP threshold contradicted the previous observations from the RAP-CPP scatterplots (Figure G.1(d)), boxplots (Figure G.2 (d)), median values from Table G.1. This discrepancy is likely because the scatterplots and table provided a more continuous representation of the data, capturing localized variations or specific trends within RAP states.

From the analysis of the percentage of time spent across different RAP threshold ranges, it was evident that the $RAP < 0$ state was associated with a higher proportion of time spent at elevated ICP levels. Specifically, for $ICP \geq 20$ and $ICP \geq 22$, the percentages were 6.25% and 6.21%, respectively, compared to 4.69% and 4.66% for their corresponding lower thresholds. This suggests that an exhausted RAP state (i.e., $RAP < 0$) was more frequently associated with elevated ICP values ($ICP \geq 20$ and $ICP \geq 22$), consistent with the previous findings in this study. A similar trend was observed across most CA indices, where higher CA index values corresponded to greater percentages at higher threshold ranges. In the $RAP < 0$ state, the percentage for $PRx \geq 0$ was 6.12%, whereas it was 3.12% for $PRx < 0$.

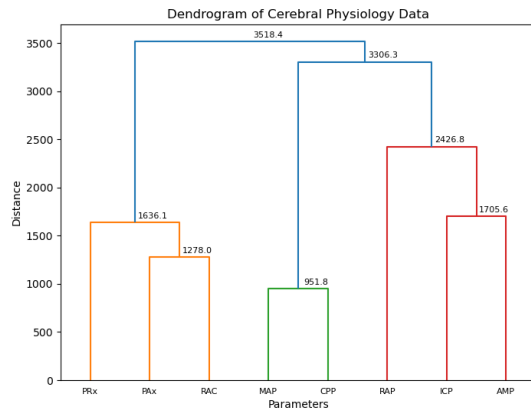
Furthermore, in the formal comparison analysis across the different thresholds of the parameters, RAP showed significant differences for PRx (thresholds 0, +0.25, +0.35), RAC (threshold 0), rSO_2_L (threshold 70), rSO_2_R (thresholds 80, 90), COx_L (threshold 0), as reported from Table G.2.

5.3.4 Clustering of the parameters

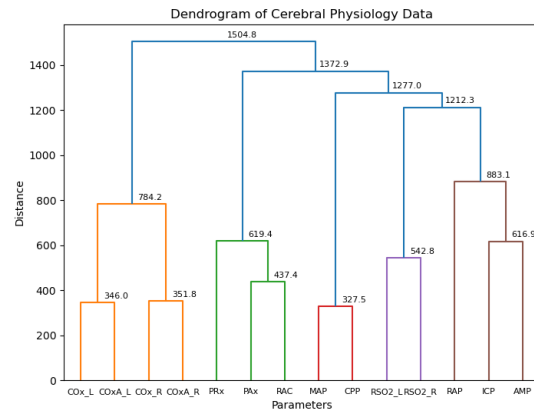
5.3.4.1 Agglomerative hierarchical clustering (AHC)

As mentioned in section 5.2.4, all the semi-supervised ML approaches were conducted separately for three segments of data across different resolutions to ensure a more comprehensive analysis. Initially, AHC was applied to the minute-by-minute resolution data, and the resulting dendrograms are presented in Figure 5.1.

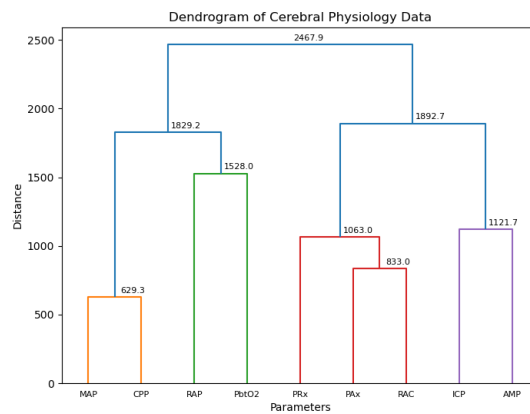
Figure 5.1 Dendrograms at minute-by-minute resolution across whole population



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

The figure demonstrates the dendrograms obtained by AHC applications at minute-by-minute resolution to (a) ICP-ABP-derived parameters, (b) ICP-ABP-derived and NIRS-derived parameters, and (c) ICP-ABP-derived parameters with PbtO₂. Among all the parameters, ICP, AMP and PbtO₂ (in (c) dendrogram) were in the same clusters with RAP. rSO₂_L and rSO₂_R were in the next closest clusters to RAP(in (b) dendrogram).

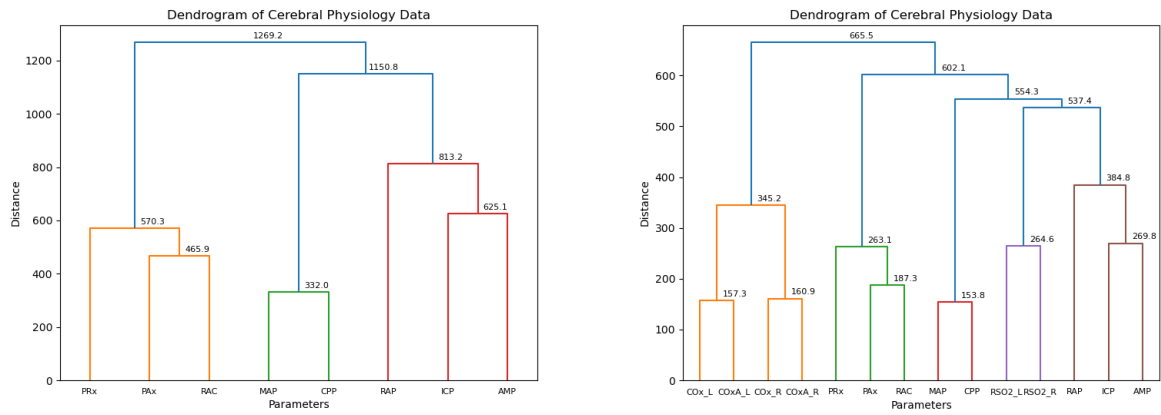
ABP, arterial blood pressure; *AMP*, pulse amplitude of ICP; *COx_L*, cerebral oxygenation index of left hemisphere; *COx_R*, cerebral oxygenation index of right hemisphere; *COx-a_L*, COx with ABP of left hemisphere; *COx-a_R*, COx with ABP of the right hemisphere; *CPP*, cerebral perfusion pressure; *ICP*, intracranial pressure; *MAP*, mean arterial pressure; *NIRS*, near-infrared spectroscopy; *PAX*, pulse amplitude index; *PbtO₂*, brain tissue oxygenation; *PRx*, pressure reactivity index; *RAC*, a cerebral autoregulation index; *RAP*, index of cerebral compensatory reserve;

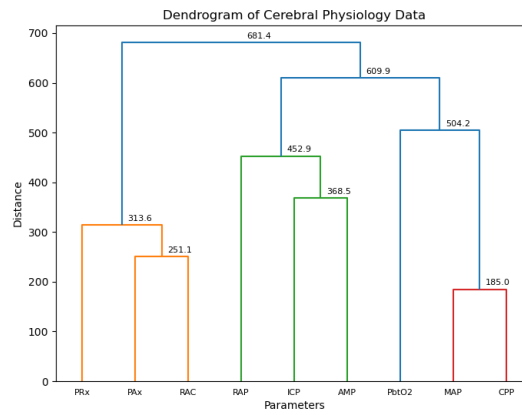
rSO_2_L , regional cerebral oxygen saturation of left hemisphere; rSO_2_R , regional cerebral oxygen saturation of the right hemisphere.

As illustrated in the figure, for the ICP-ABP-derived parameters, ICP-AMP-RAP first clustered with MAP-CPP to form a large group, which then merged with the PAX-RAC-PRx cluster, completing the dendrogram as shown in Figure 5.1(a). When NIRS-derived parameters were included, the ICP-AMP-RAP cluster joined with rSO_2_L - rSO_2_R , along with MAP-CPP, to form a larger cluster. This cluster subsequently merged with the PAX-RAC-PRx group, and finally with the COx_L-COx_R-COx-a_L-COx-a_R cluster to complete the dendrogram, as depicted in Figure 5.1(b). This structure closely resembled the previous dendrogram, with the only notable difference being the addition of rSO_2_L and rSO_2_R to the ICP-AMP-RAP-MAP-CPP cluster. In the last dendrogram shown in Figure 5.1(c), incorporating PbtO₂ into the ICP-ABP-derived parameters led to RAP clustering with PbtO₂, which then grouped with MAP and CPP to form a large RAP-PbtO₂-MAP-CPP cluster. This was later joined by the PAX-RAC-PRx-ICP-AMP cluster to complete the dendrogram.

This analysis was also conducted across different data resolutions, with the resulting dendrograms presented in Figures 5.2–5.5.

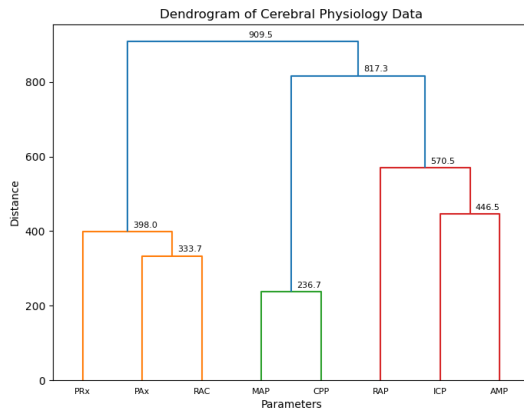
Figure 5.2 Dendrograms at 5-minute-by-5-minute resolution across whole population



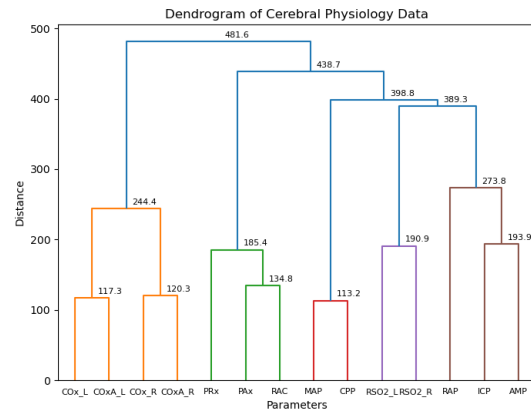


(c) ICP-ABP-derived parameters and PbtO₂

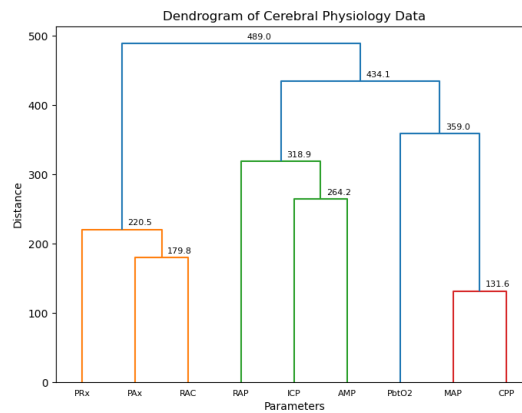
Figure 5.3 Dendrograms at 10-minute-by-10-minute resolution across whole population



(a) ICP-ABP-derived parameters

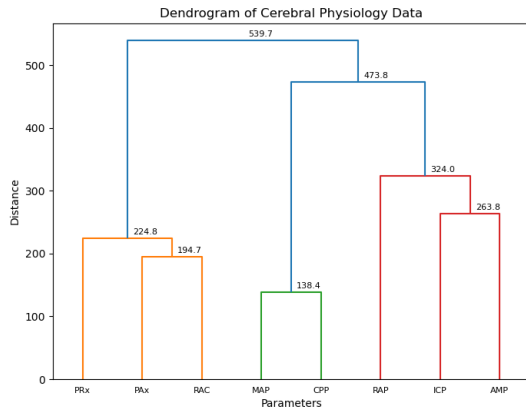


(b) ICP-ABP-derived and NIRS-derived parameters

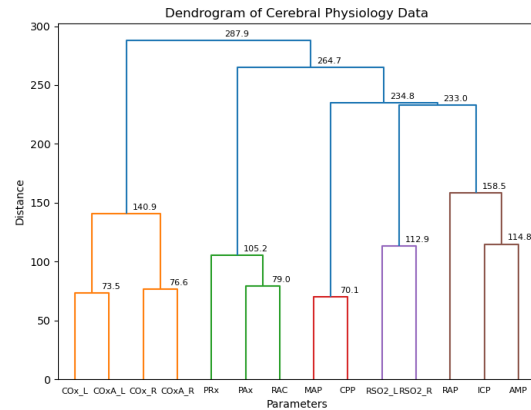


(c) ICP-ABP-derived parameters and PbtO₂

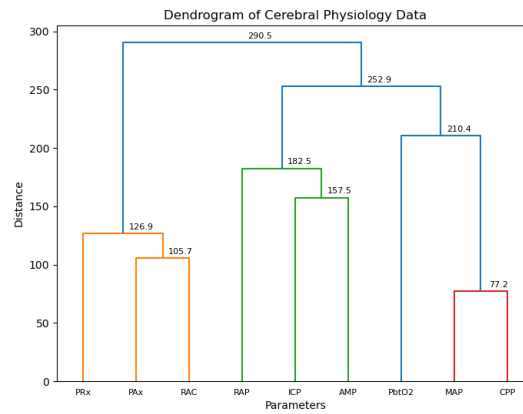
Figure 5.4 Dendrograms at 30-minute-by-30-minute resolution across whole population



(a) ICP-ABP-derived parameters

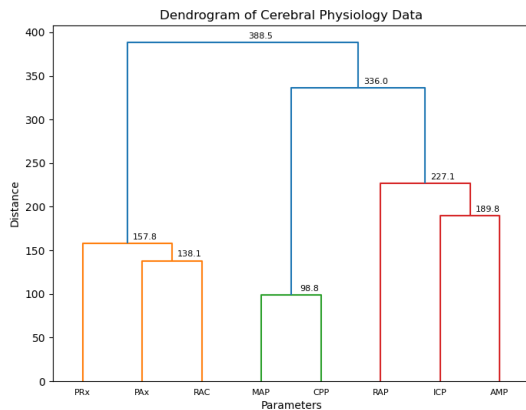


(b) ICP-ABP-derived and NIRS-derived parameters

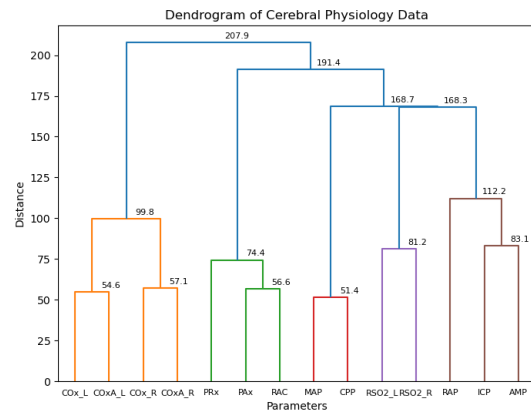


(c) ICP-ABP-derived parameters and PbtO₂

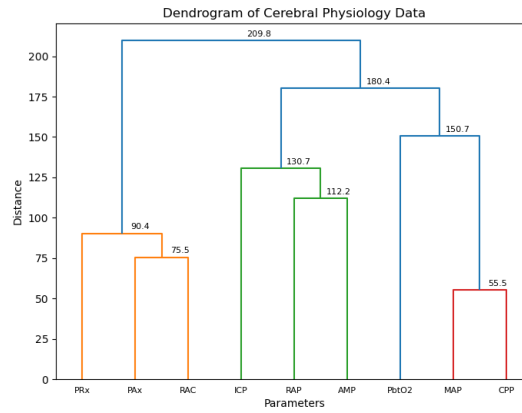
Figure 5.5 Dendrograms at hour-by-hour resolution across whole population



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

Figures 5.2-5.5 demonstrate the dendrograms obtained by AHC applications at lower resolutions to (a) ICP-ABP-derived parameters, (b) ICP-ABP-derived and NIRS-derived parameters, and (c) ICP-ABP-derived parameters with PbtO₂. The dendrograms showed similar clusterings as shown at the minute-by-minute resolution.

ABP, arterial blood pressure; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve

For both the ICP-ABP-derived parameter analysis and the combined ICP-ABP and NIRS-derived parameter analysis, the dendrograms consistently showed the same clustering patterns as observed in the minute-by-minute resolution (Figure 5.1). However, in the analysis involving ICP-ABP-derived parameters and PbtO₂, RAP did not cluster directly with PbtO₂. Instead, it initially grouped with ICP and AMP, and this cluster later merged with the MAP-CPP-PbtO₂ group. This pattern was consistently observed across all other lower resolutions. The difference observed at the minute-by-minute resolution compared to the lower resolutions was likely caused by the higher temporal granularity of the data. The cophenetic correlation values for the dendrograms are illustrated below:

Table 5.3 The cophenetic correlations for the dendrograms across all the resolutions

Data groups	Minute-by-minute	5-minute-by-5-minute	10-minute-by-10-minute	30-minute-by-30-minute	Hour-by-hour
ICP-ABP-derived parameters	0.89	0.89	0.89	0.89	0.89
ICP-ABP-derived and NIRS-derived parameters	0.9	0.89	0.89	0.89	0.88

ICP-ABP-derived parameters and PbtO ₂	0.9	0.86	0.85	0.84	0.84
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ABP, arterial blood pressure; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; PbtO₂, brain tissue oxygenation

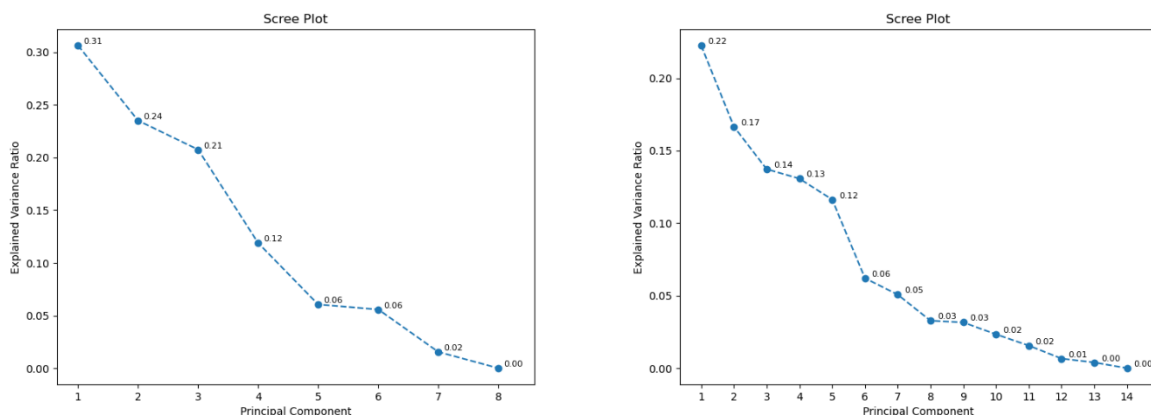
Across all groups and resolutions, the cophenetic correlation coefficients were consistently high, with most cases nearing 0.9, indicating that the agglomerative hierarchical clustering provided a strong and reliable representation of the data structure.

Furthermore, AHC analysis was performed across different RAP states at all the discussed resolutions. The resulting dendrograms of RAP > 0.4 state are presented in Figures H.1–H.5. The dendrograms of the other two RAP states can be found in the submitted manuscript. Across all dendrograms, most of the larger clusters were consistent with the findings from the analysis on the entire population. However, noticeable variations appeared within the smaller clusters. For instance, in several dendrograms, particularly for the RAP < 0 and $0 \leq \text{RAP} \leq 0.4$ states, RAP did not cluster directly with ICP-AMP. Another interesting observation was the frequent direct clustering of PbtO₂ with RAP, suggesting a potentially strong association between these two. Table H.1 presents the cophenetic correlation values from the subgroup analysis, with most values exceeding 0.85, suggesting that the AHC models demonstrated a strong overall fit.

5.3.4.2 Principal component analysis (PCA)

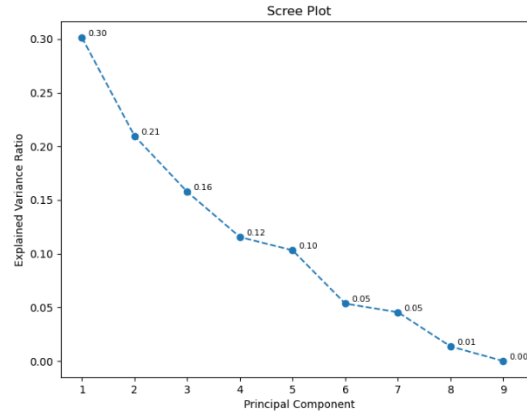
At first, PCA was conducted on minute-by-minute resolution data. To assess the contribution and effectiveness of the principal components, scree plots of the explained variance ratio and cumulative explained variance were analyzed, as depicted in Figures 5.6 and 5.7.

Figure 5.6 Scree plots of explained variance ratio at minute-by-minute resolution across whole population



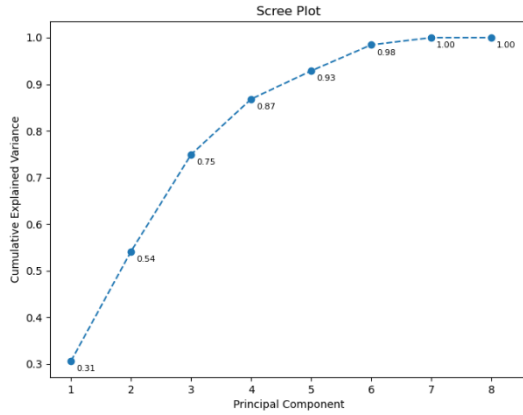
(a) ICP-ABP-derived parameters

(b) ICP-ABP-derived and NIRS-derived parameters

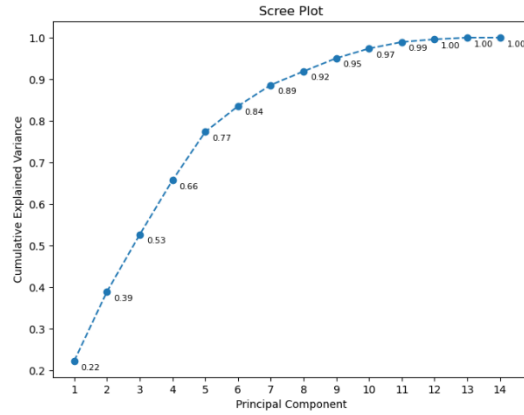


(c) ICP-ABP-derived parameters and PbtO₂

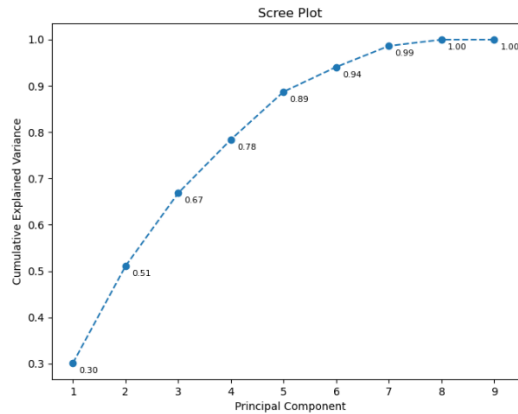
Figure 5.7 Scree plots of cumulative explained variance at minute-by-minute resolution across whole population



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



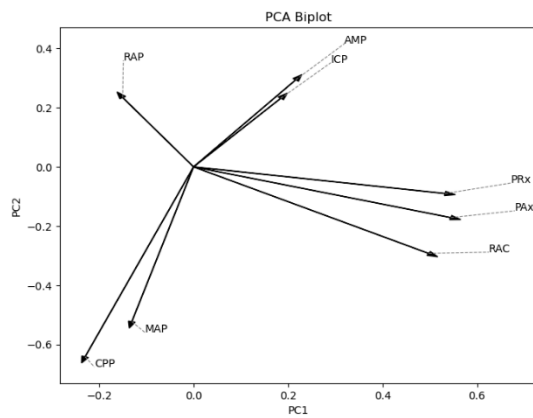
(c) ICP-ABP-derived parameters and PbtO₂

Figures 5.6 and 5.7 illustrate the scree plots of the explained variance ratio and cumulative explained variance of (a) ICP-ABP-derived parameters, (b) ICP-ABP-derived and NIRS-derived parameters, and (c) ICP-ABP-derived parameters with PbtO₂ at minute-by-minute resolution.

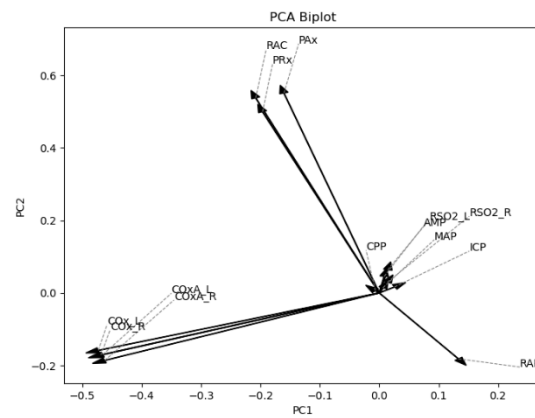
ABP, arterial blood pressure; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; PbtO₂, brain tissue oxygenation

As illustrated in the figures, the first two principal components accounted for 54%, 39%, and 51% of the variance in the data for the respective predefined analysis groups. Notably, the ICP-ABP-derived and NIRS-derived parameter group explained less than 50% of the variance (39%), likely due to the higher number of parameters included in that group. The corresponding biplots for these data groups are shown in Figure 5.8.

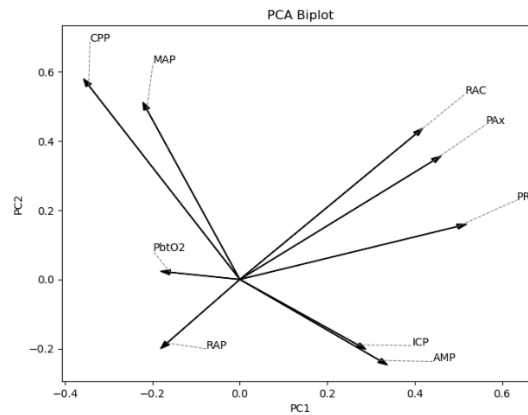
Figure 5.8 PCA biplots at minute-by-minute resolution across whole population



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

The figure documents the PCA biplots of (a) ICP-ABP-derived parameters, (b) ICP-ABP-derived and NIRS-derived parameters, and (c) ICP-ABP-derived parameters with PbtO₂. Among all the parameters, ICP, AMP and PbtO₂ (in (c) biplot) aligned in the same direction as RAP within the PC1–PC2 axis system.. rSO₂_L and rSO₂_R were the next closest to RAP in direction (in (b) biplot). Similar to findings from dendrograms.

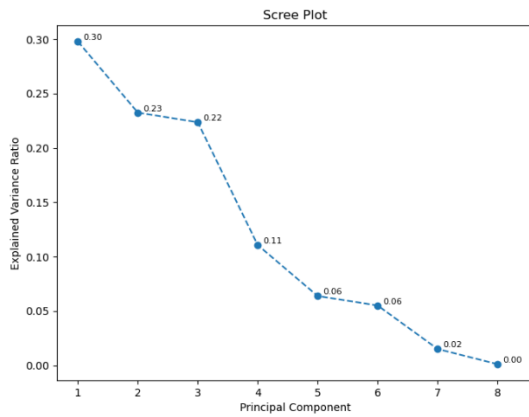
ABP, arterial blood pressure; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere

As depicted in Figure 5.8, for the ICP-ABP-derived parameters, ICP-AMP-RAP, MAP-CPP and PAX-RAC-PRx formed groups aligning in a similar direction (Figure 5.1(a)). Incorporating NIRS-derived parameters to this group resulted in forming the ICP-AMP-RAP-rSO₂_L-rSO₂_R group, whereas COx and COx-a parameters formed another group in a different direction, as depicted in Figure 5.1(b). Notably, in both cases, RAP appeared slightly offset from the core direction of its group. Lastly, for the ICP-ABP-derived parameters and PbtO₂, Figure 5.1(c) illustrates the formation of a MAP-CPP-RAP-PbtO₂ group, while ICP-AMP-PAX-RAC-PRx aligned along a different axis. These patterns were consistent with the cluster structures observed in the AHC dendrograms presented in Figure 5.1.

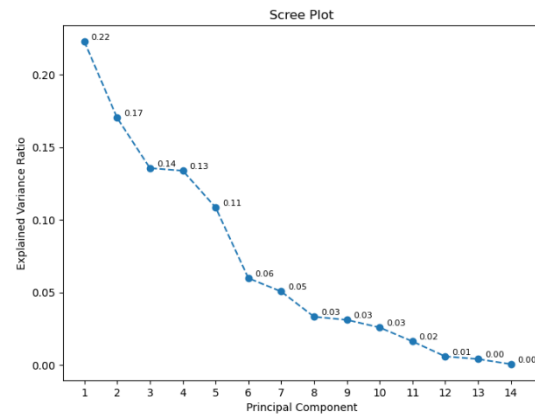
To be noted, although COx and COx-a are derived from rSO₂, they did not align with it but instead showed closer directional alignment with PRx, PAX, and RAC. This is because, similar to PRx, PAX, and RAC, both COx and COx-a are CA indices, which explains their closer clustering. A similar pattern was also observed in the AHC dendrograms.

Subsequently, this analysis was extended to the lower-resolution data. The scree plots corresponding to these resolutions are presented in Figures 5.9 to 5.16.

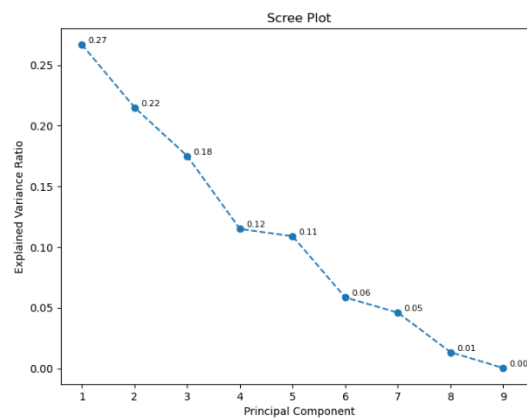
Figure 5.9 Scree plots of explained variance ratio at 5-minute-by-5-minute resolution across whole population



(a) ICP-ABP-derived parameters

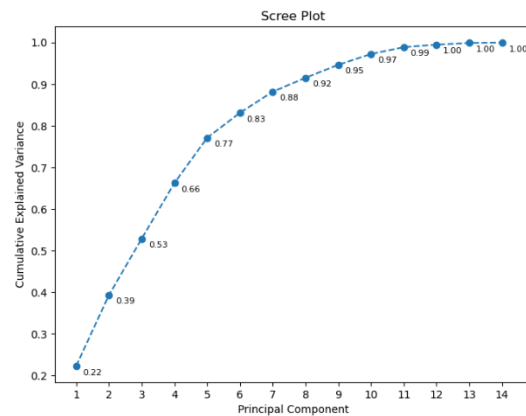
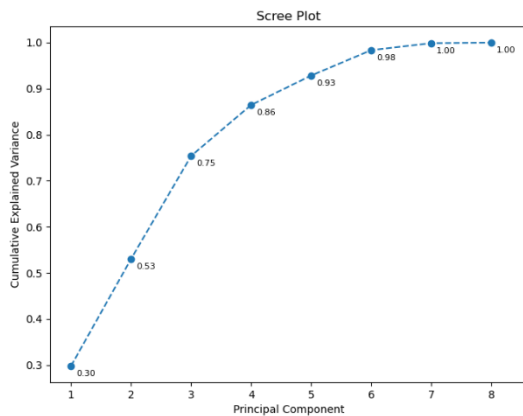


(b) ICP-ABP-derived and NIRS-derived parameters



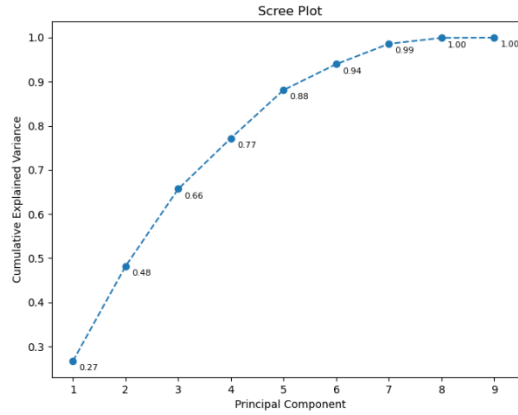
(c) ICP-ABP-derived parameters and PbtO₂

Figure 5.10 Scree plots of cumulative explained variance at 5-minute-by-5-minute resolution across whole population



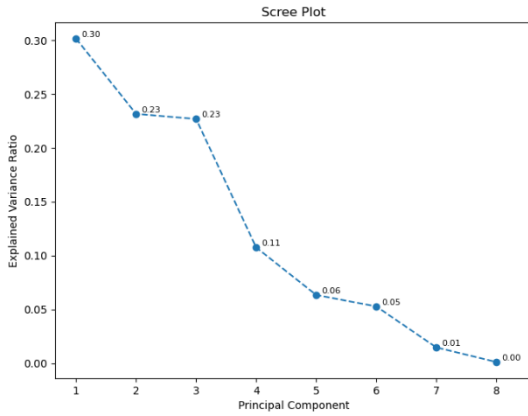
(a) ICP-ABP-derived parameters

(b) ICP-ABP-derived and NIRS-derived parameters

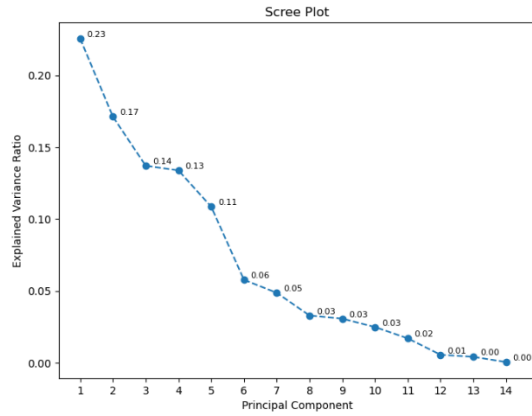


(c) ICP-ABP-derived parameters and PbtO₂

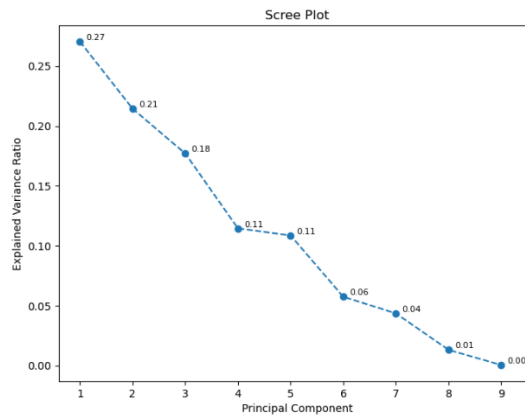
Figure 5.11 Scree plots of explained variance ratio at 10-minute-by-10-minute resolution across whole population



(a) ICP-ABP-derived parameters

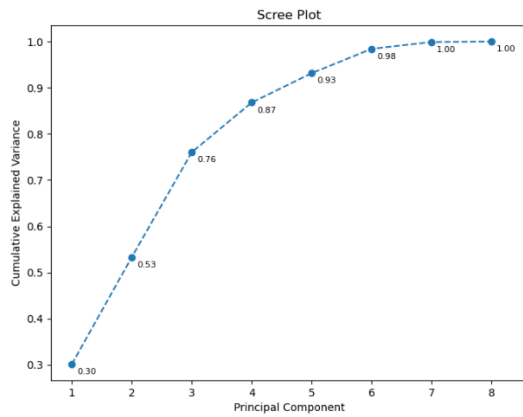


(b) ICP-ABP-derived and NIRS-derived parameters

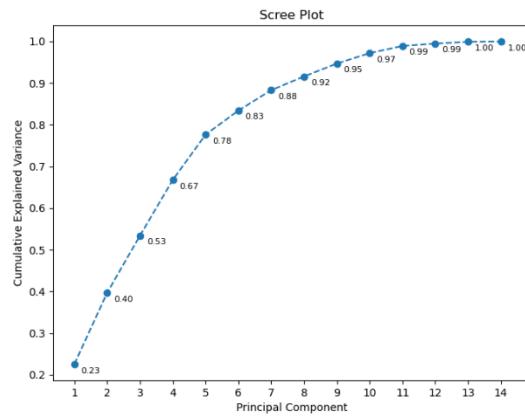


(c) ICP-ABP-derived parameters and PbtO₂

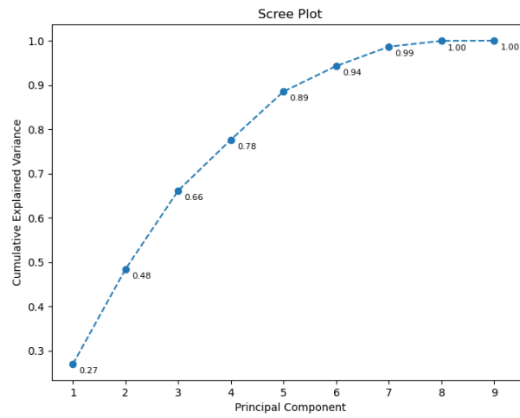
Figure 5.12 Scree plots of cumulative explained variance at 10-minute-by-10-minute resolution across the whole population



(a) ICP-ABP-derived parameters

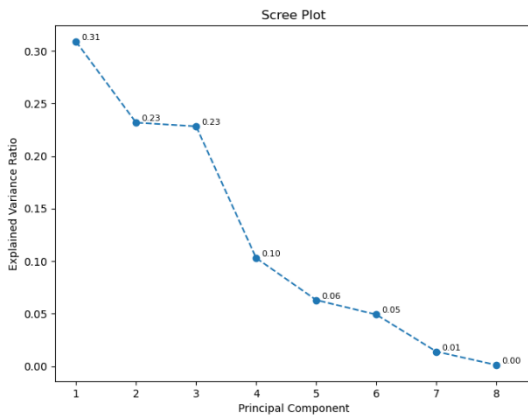


(b) ICP-ABP-derived and NIRS-derived parameters

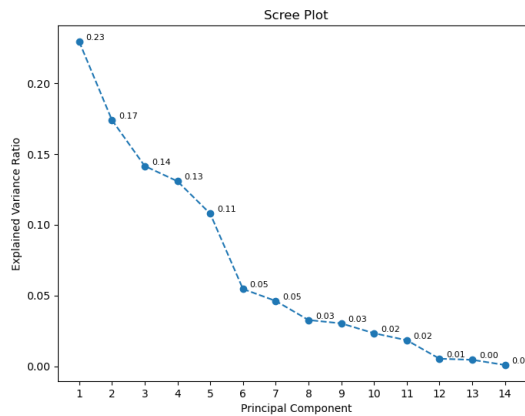


(c) ICP-ABP-derived parameters and PbtO₂

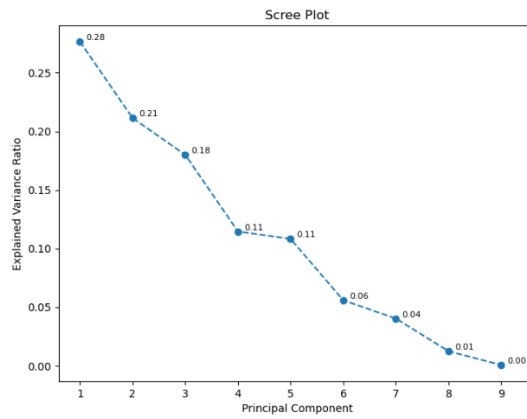
Figure 5.13 Scree plots of explained variance ratio at 30-minute-by-30-minute resolution across whole population



(a) ICP-ABP-derived parameters

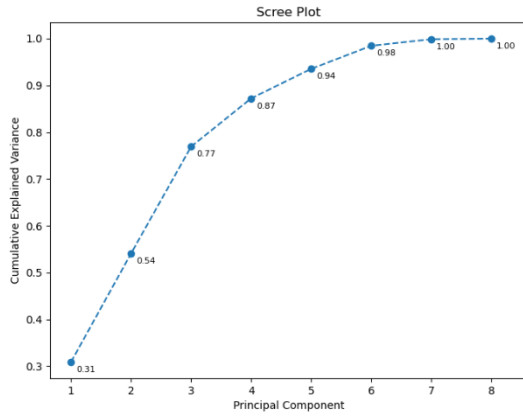


(b) ICP-ABP-derived and NIRS-derived parameters

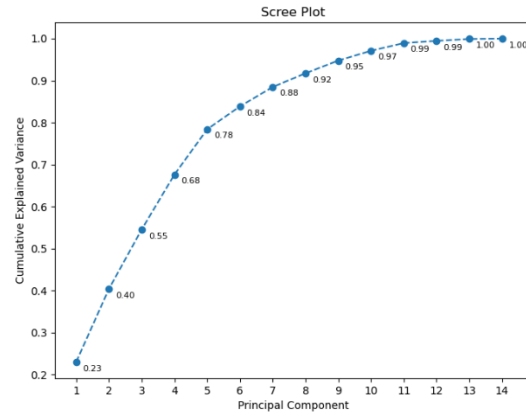


(c) ICP-ABP-derived parameters and PbtO₂

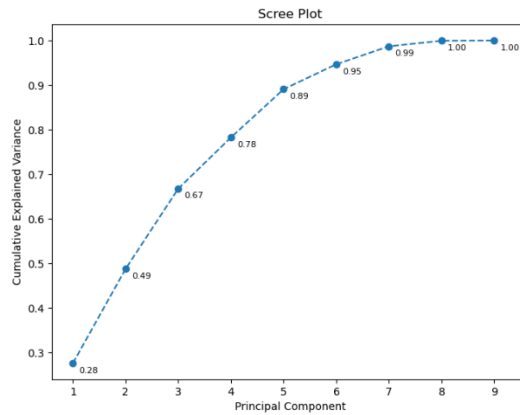
Figure 5.14 Scree plots of cumulative explained variance at 30-minute-by-30-minute resolution across whole population



(a) ICP-ABP-derived parameters

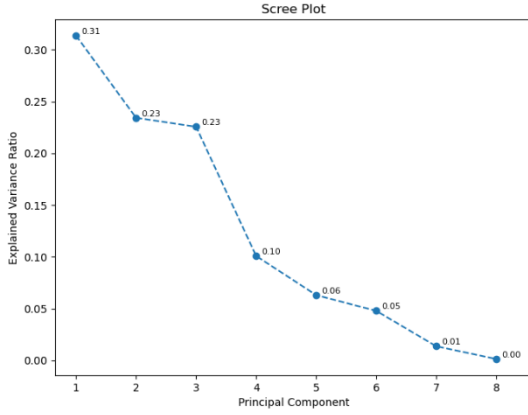


(b) ICP-ABP-derived and NIRS-derived parameters

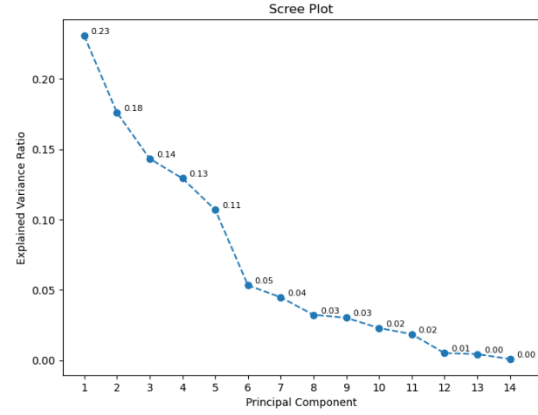


(c) ICP-ABP-derived parameters and PbtO₂

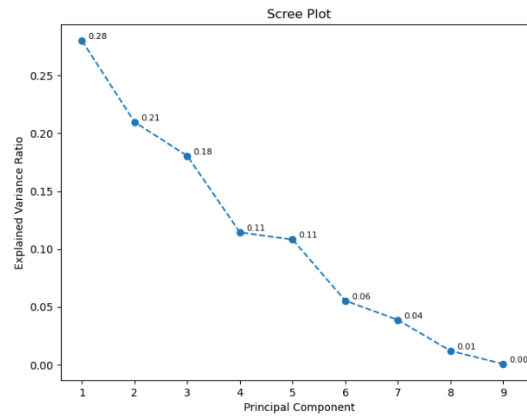
Figure 5.15 Scree plots of explained variance ratio at hour-by-hour resolution across whole population



(a) ICP-ABP-derived parameters

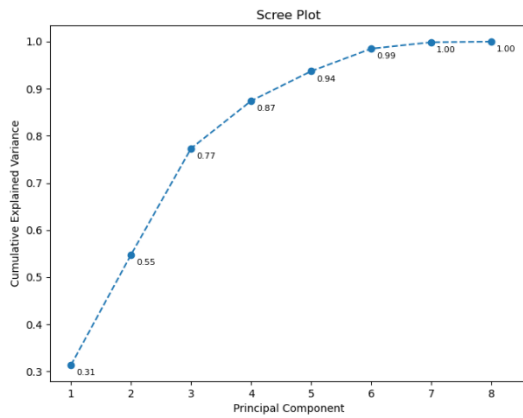


(b) ICP-ABP-derived and NIRS-derived parameters

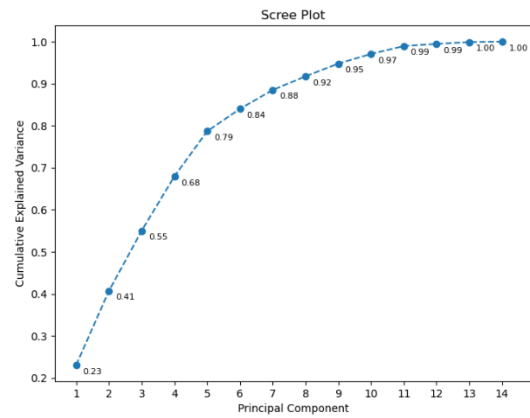


(c) ICP-ABP-derived parameters and PbtO₂

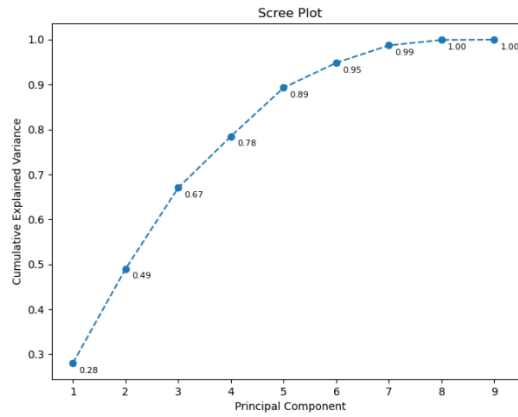
Figure 5.16 Scree plots of cumulative explained variance at hour-by-hour resolution across whole population



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



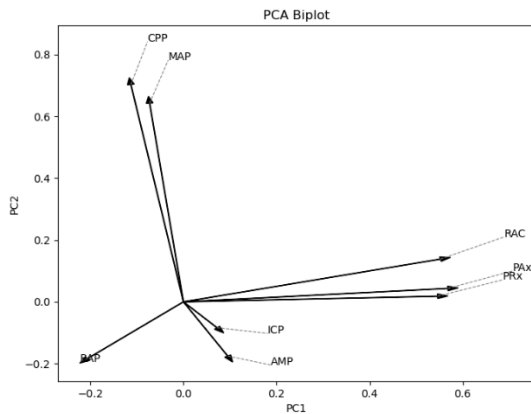
(c) ICP-ABP-derived parameters and PbtO₂

Figures 5.9 and 5.16 illustrate the scree plots of the explained variance ratio and cumulative explained variance of (a) ICP-ABP-derived parameters, (b) ICP-ABP-derived and NIRS-derived parameters, and (c) ICP-ABP-derived parameters with PbtO₂ at lower resolution.

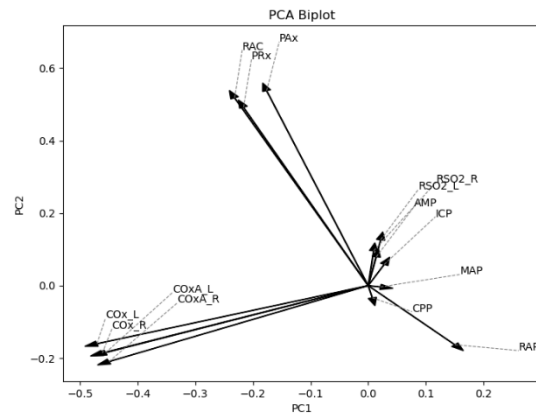
ABP, arterial blood pressure; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; PbtO₂, brain tissue oxygenation

The proportion of variance explained by the first two principal components remained comparable to that observed in the minute-by-minute resolution data. The PCA biplots for lower-resolution data are presented in Figures 5.17 through 5.20.

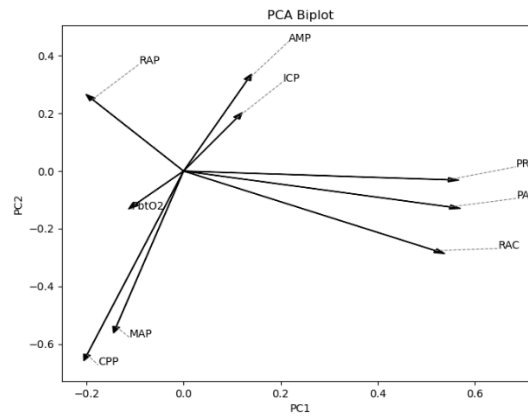
Figure 5.17 PCA biplots at 5-minute-by-5-minute resolution across whole population



(a) ICP-ABP-derived parameters

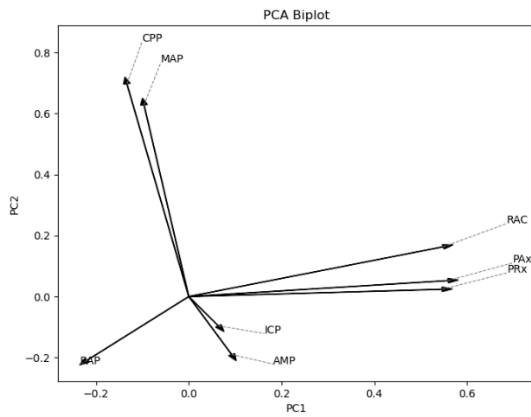


(b) ICP-ABP-derived and NIRS-derived parameters

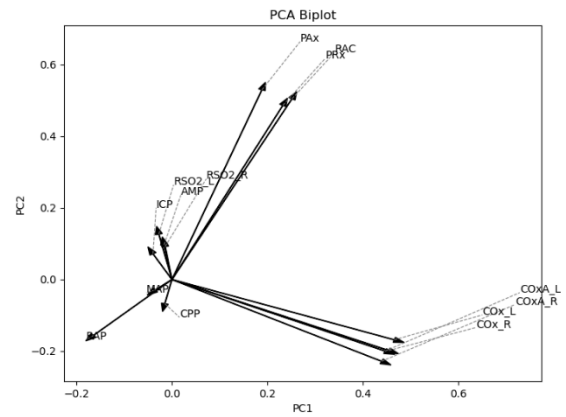


(c) ICP-ABP-derived parameters and PbtO₂

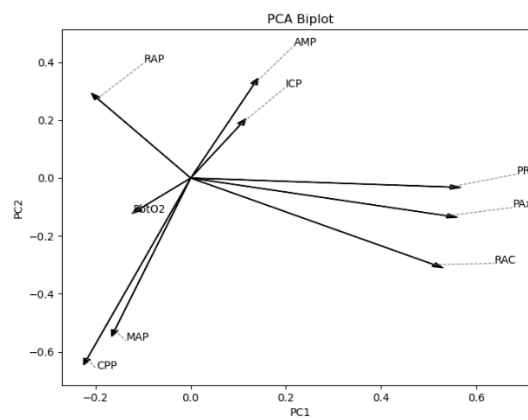
Figure 5.18 PCA biplots at 10-minute-by-10-minute resolution across whole population



(a) ICP-ABP-derived parameters

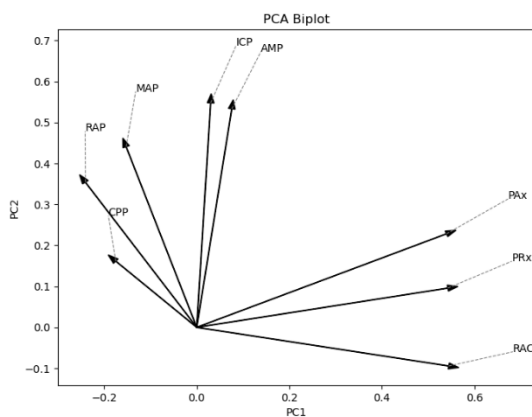


(b) ICP-ABP-derived and NIRS-derived parameters

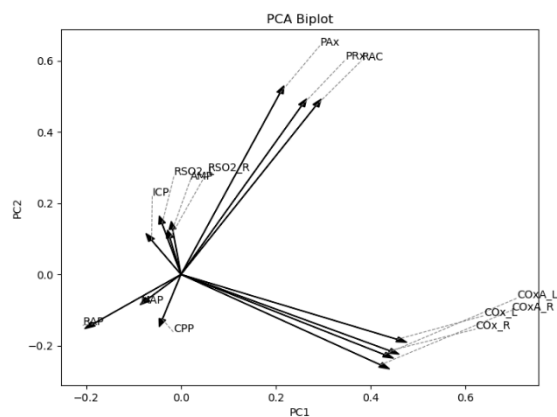


(c) ICP-ABP-derived parameters and PbtO₂

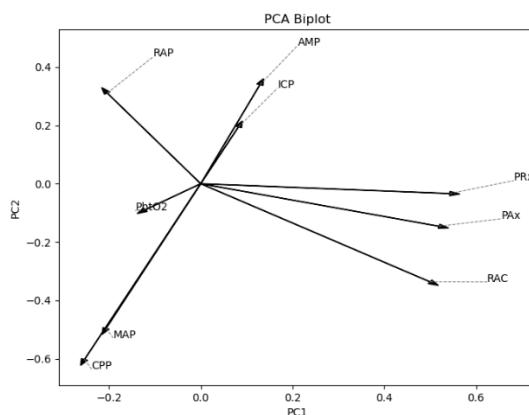
Figure 5.19 PCA biplots at 30-minute-by-30-minute resolution across whole population



(a) ICP-ABP-derived parameters

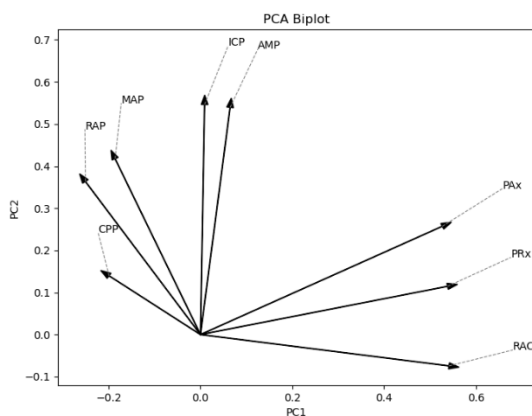


(b) ICP-ABP-derived and NIRS-derived parameters

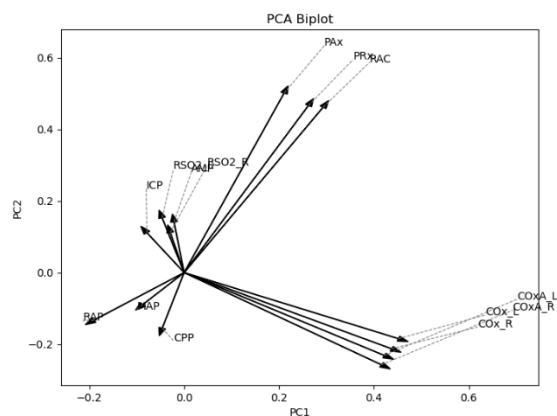


(c) ICP-ABP-derived parameters and PbtO₂

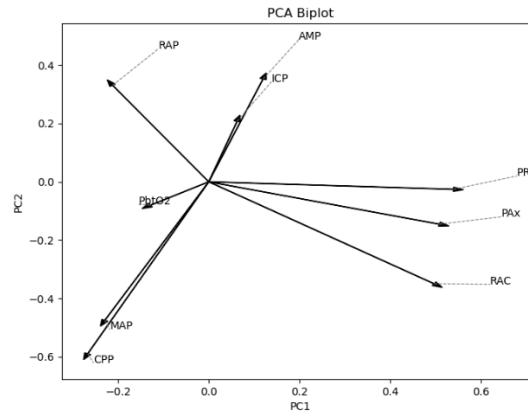
Figure 5.20 PCA biplots at hour-by-hour resolution across whole population



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

Figures 5.17-5.20 document the PCA biplots of (a) ICP-ABP-derived parameters, (b) ICP-ABP-derived and NIRS-derived parameters, and (c) ICP-ABP-derived parameters with PbtO₂ at lower resolutions. The directional alignments were similar as observed at minute-by-minute resolution

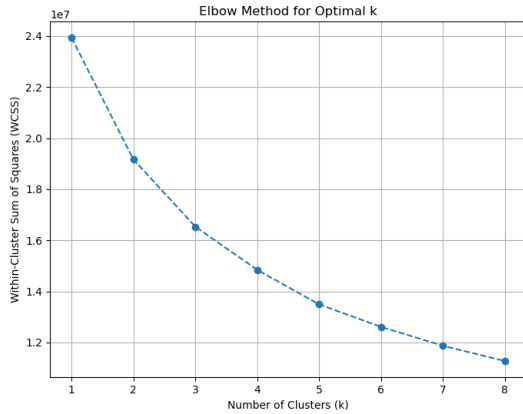
ABP, arterial blood pressure; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere

Across these resolutions, the majority of biplots demonstrated grouping patterns consistent with those observed at the minute-by-minute resolution. While some minor deviations were present, for instance, RAP was positioned between MAP and CPP in Figures 5.19(a) and 5.20(a), the larger clusters remained largely unchanged. The biplots of sub-group analysis of RAP > 0.4 state are illustrated in Figures I.1 through I.6. The rest of the PCA biplots of the sub-group analysis can be observed in the submitted manuscript. This analysis showed certain deviations in the smaller groups from the results observed in the whole population, especially within the RAP < 0 and 0 ≤ RAP ≤ 0.4 states.

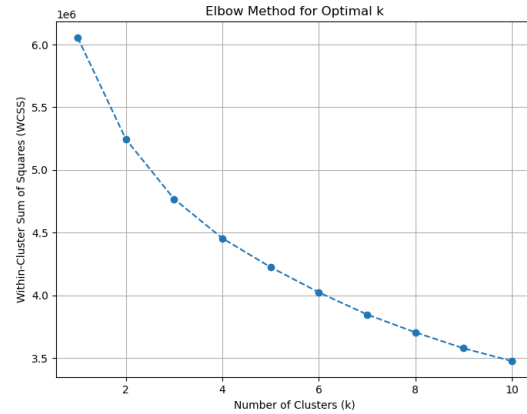
5.3.4.3 K-means clustering analysis (KMCA)

As outlined in Section 5.2.4, the elbow method was employed to identify the optimal value of k, with its visual representation provided in Figure 5.21.

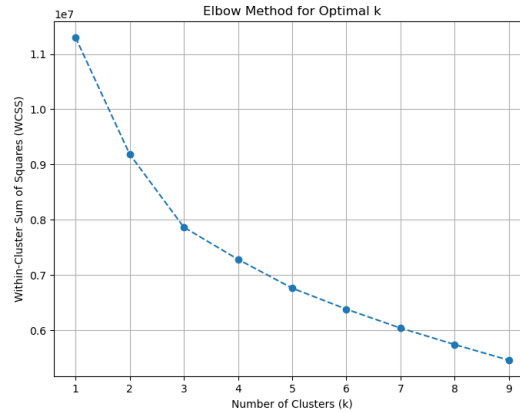
Figure 5.21 Application of the elbow method at minute-by-minute resolution across whole population



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

The figure presents the number of clusters vs WCSS plots of (a) ICP-ABP-derived parameters, (b) ICP-ABP-derived and NIRS-derived parameters, and (c) ICP-ABP-derived parameters with PbtO₂ at minute-by-minute resolution. All the plots showed, after $k = 3$, the rate of decrease in WCSS (Within-Cluster Sum of Squares) diminished considerably.

ABP, arterial blood pressure; *ICP*, intracranial pressure; *k*, number of clusters; *NIRS*, near-infrared spectroscopy; *PbtO₂*, brain tissue oxygenation; *WCSS*, within-cluster sum of squared errors

As illustrated in the figures, at $k=1$ and $k=2$, there were sharp drops in WCSS. Beyond $k=3$, the reduction in WCSS became more gradual and consistent, indicating diminishing returns with increasing k . This was noticeable across all the groups. This pattern suggests that $k=3$ is the optimal choice for KMCA and can be applied across all data groups. Putting optimal $k=3$, KMCA was applied across the groups at the minute-by-minute resolution data, and the three clusters that were found are illustrated in Table 5.4.

Table 5.4 Clusters generated from KMCA across all resolutions

Minute-by-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
5-minute-by-5-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
10-minute-by-10-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
30-minute-by-30-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP

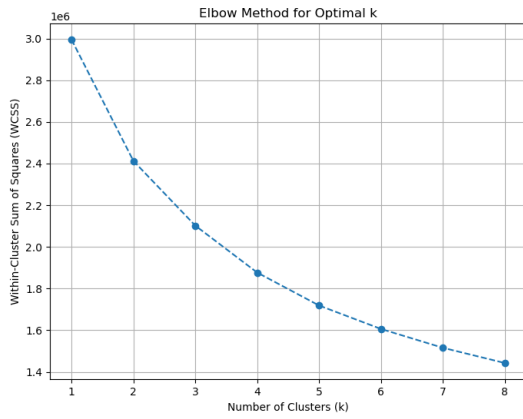
ICP-ABP-derived parameters and PbtO₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAX, RAC
Hour-by-hour			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAX, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAX, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAX, RAC

ABP, arterial blood pressure; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

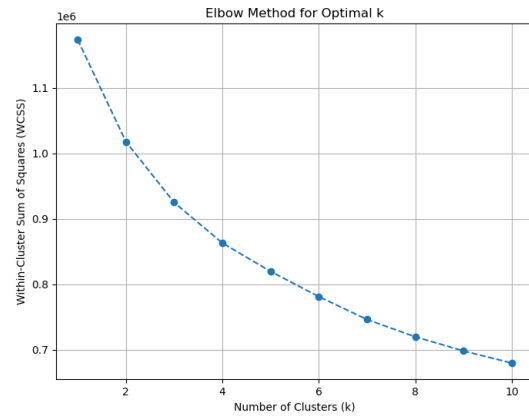
The first row of the table presents the clustering results at the minute-by-minute resolution. The three clusters identified through KMCA showed some differences compared to those observed in the AHC dendrograms and PCA biplots. Notably, in both the ICP-ABP-derived parameters group and the ICP-ABP-derived parameters with PbtO₂ group, RAP was not clustered with its source signal, ICP. Additionally, across all data groups, RAP consistently clustered with the ICP-ABP-derived CA indices (i.e., PRx, PAX, and RAC).

Additionally, this analysis was extended to lower-resolution data. Using the elbow method in the same manner, the optimal k was determined, with graphical illustrations provided in Figures 5.22 to 5.25.

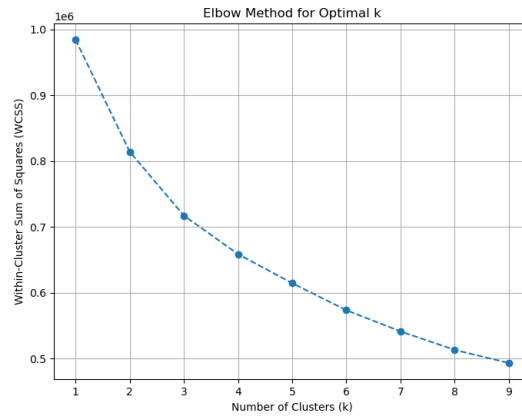
Figure 5.22 Application of the elbow method at 5-minute-by-5-minute resolution across whole population



(a) ICP-ABP-derived parameters

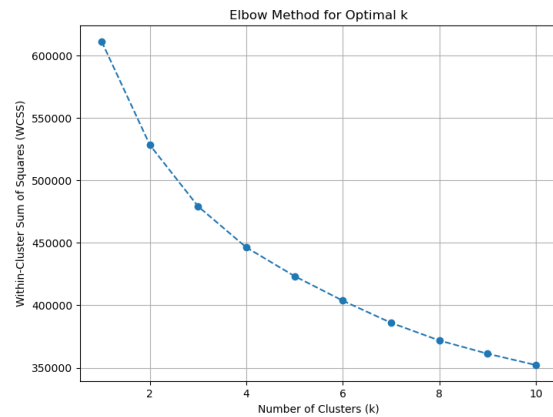
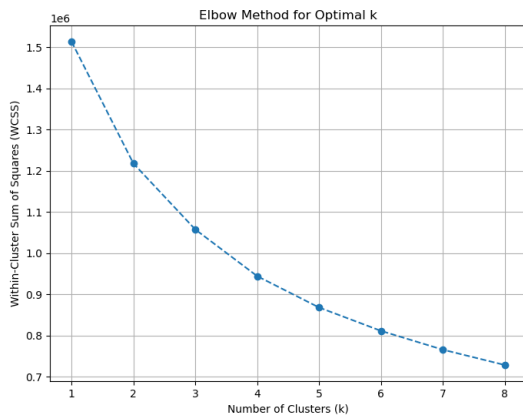


(b) ICP-ABP-derived and NIRS-derived parameters



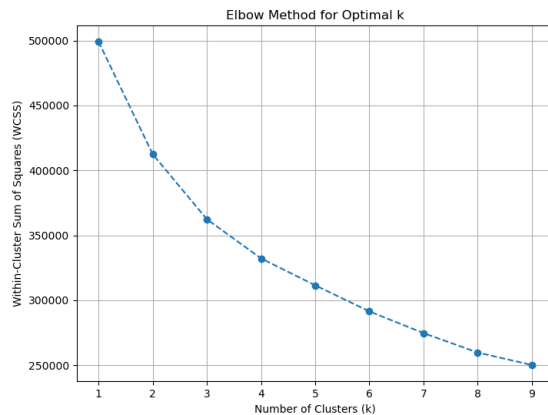
(c) ICP-ABP-derived parameters and PbtO₂

Figure 5.23 Application of the elbow method at 10-minute-by-10-minute resolution across whole population



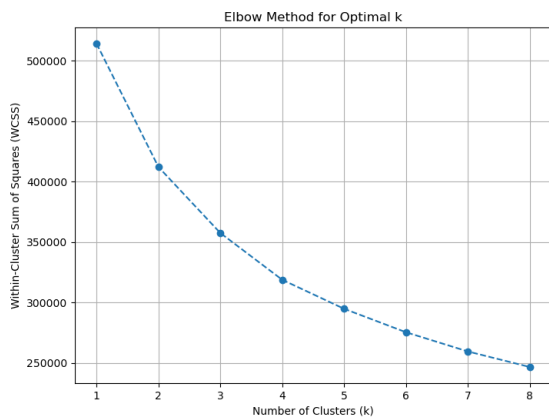
(a) ICP-ABP-derived parameters

(b) ICP-ABP-derived and NIRS-derived parameters

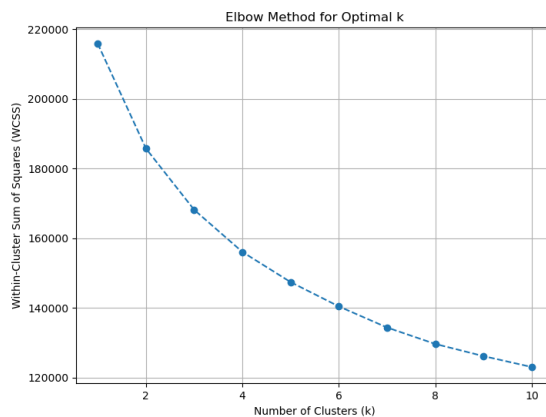


(c) ICP-ABP-derived parameters and PbtO₂

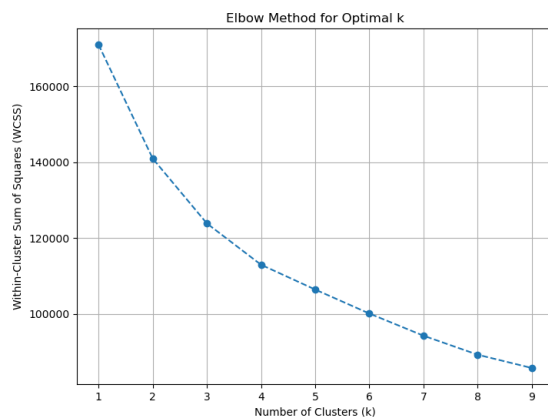
Figure 5.24 Application of the elbow method at 30-minute-by-30-minute resolution across whole population



(a) ICP-ABP-derived parameters

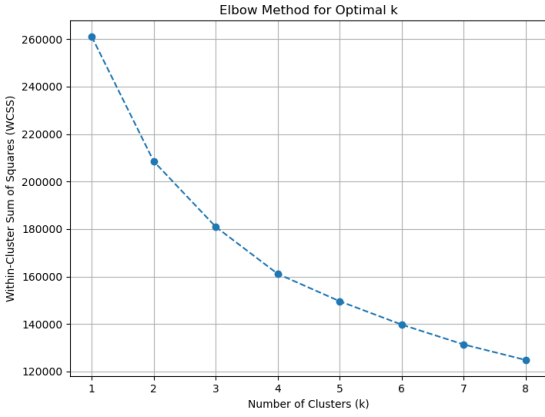


(b) ICP-ABP-derived and NIRS-derived parameters

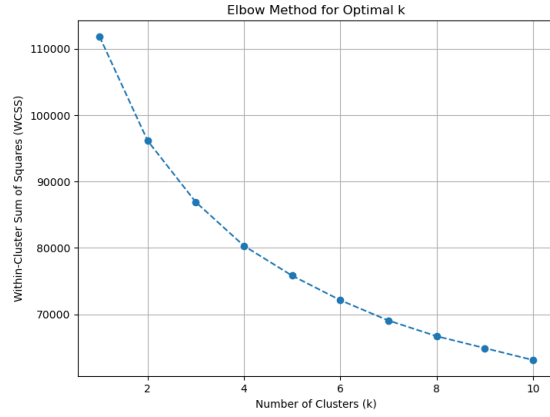


(c) ICP-ABP-derived parameters and PbtO₂

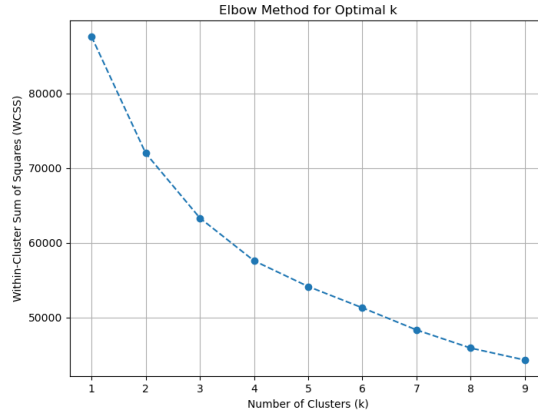
Figure 5.25 Application of the elbow method at hour-by-hour resolution across whole population



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

Figures 5.22-5.25 present the number of clusters vs WCSS plots of (a) ICP-ABP-derived parameters, (b) ICP-ABP-derived and NIRS-derived parameters, and (c) ICP-ABP-derived parameters with PbtO₂ at lower resolutions. All the plots showed, after $k = 3$, the rate of decrease in WCSS (Within-Cluster Sum of Squares) diminished considerably.

ABP, arterial blood pressure; *ICP*, intracranial pressure; *k*, number of clusters; *NIRS*, near-infrared spectroscopy; *PbtO₂*, brain tissue oxygenation; *WCSS*, within-cluster sum of squared errors

Based on these visualizations, an optimal k of 3 was consistently selected for all data groups and resolutions. The KMCA clustering results for each resolution were summarized in Table 5.3, which clearly demonstrates that the cluster structures remained consistent across all resolutions. Next, sub-group analysis was conducted. The remaining figures in Appendix J display the elbow method plots for the $RAP > 0.4$ sub-

group. The rest are available in the submitted manuscript. In this context, the optimal number of clusters was also determined to be 3 for all RAP states. The KMCA clustering outcomes were summarized in Tables J.1 to J.3, indicating that the cluster structures remained consistent across all RAP states and resolution levels.

5.3.5 High-frequency temporal response patterns of RAP to MMM Changes

5.3.5.1 VARIMA impulse response function (IRF) analysis

The optimal VARIMA model was determined for each patient and each RAP-X pair across all analyzed resolutions. From these, the median values of the model orders were computed, yielding the median optimal VARIMA models summarized in Table K.1 of Appendix K. Following model fitting, impulse response function (IRF) coefficients were extracted and plotted over time. Figures K.1 to K.3 present sample IRF plots for a representative patient across all the discussed RAP-X pairs and resolutions. In most instances, the responses remained within the 95% confidence interval, suggesting statistical reliability. Given the observed variability in responses, a thresholding approach was applied to the normalized IRF data, as outlined in Section 5.2.5.1, to classify responses as either “more responsive” or “less responsive.” The outcome for the “more responsiveness” group was summarized in Table 5.5. In some cases, insufficient data points prevented the test from yielding results; these instances were marked as not applicable (NA) in the table.

Table 5.5 Responsiveness of RAP to the orthogonal impulse of cerebral physiological parameters

Direction	Minute-by-minute		5-minute-by-5-minute		10-minute-by-10-minute	
	>0.1%	NA	>0.1%	NA	>0.1%	NA
$\Delta\text{ICP} \rightarrow \Delta\text{RAP}$	77.84%(295)	0	63.73%(239)	4	65.50%(243)	8
$\Delta\text{AMP} \rightarrow \Delta\text{RAP}$	75.60%(285)	2	62.30%(233)	5	59.84%(222)	8
$\Delta\text{MAP} \rightarrow \Delta\text{RAP}$	73.74%(278)	2	68.36%(255)	6	59.14%(220)	7
$\Delta\text{CPP} \rightarrow \Delta\text{RAP}$	71.43%(270)	1	67.56%(252)	6	57.99%(214)	10
$\Delta\text{PRx} \rightarrow \Delta\text{RAP}$	78.99%(297)	3	53.60%(201)	4	44.09%(164)	7
$\Delta\text{Pax} \rightarrow \Delta\text{RAP}$	78.72%(296)	3	52.13%(196)	3	40.32%(150)	7
$\Delta\text{RAC} \rightarrow \Delta\text{RAP}$	80.32%(302)	3	56.60%(210)	8	42.32%(157)	8
$\Delta\text{rSO}_2\text{_L} \rightarrow \Delta\text{RAP}$	72.79%(107)	9	67.65%(92)	20	65.91%(87)	24
$\Delta\text{rSO}_2\text{_R} \rightarrow \Delta\text{RAP}$	74.31%(107)	11	72.39%(97)	21	61.36%(81)	23
$\Delta\text{COx_L} \rightarrow \Delta\text{RAP}$	71.33%(102)	9	42.11%(56)	19	34.59%(46)	19
$\Delta\text{COx_R} \rightarrow \Delta\text{RAP}$	74.47%(105)	11	47.37%(63)	19	33.59%(44)	21
$\Delta\text{COx-a_L} \rightarrow \Delta\text{RAP}$	77.86%(109)	0	47.69%(62)	10	34.62%(45)	10
$\Delta\text{COx-a_R} \rightarrow \Delta\text{RAP}$	77.54%(107)	2	47.29%(61)	11	32.56%(42)	11
$\Delta\text{PbtO}_2 \rightarrow \Delta\text{RAP}$	64.60%(73)	3	69.37%(77)	5	67.59%(73)	8

To calculate the percentage values in this table, the NA cases were excluded from the total number of patients.

Δ , first-order differenced; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NA, not applicable; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

The table presents the percentage and count of cases classified as belonging to the “more responsive” group for each parameter pair across resolutions. At the minute-by-minute resolution, ICP-ABP-derived parameters consistently exhibited higher responsiveness percentages compared to NIRS-derived parameters and PbtO₂. While a general decline in responsiveness percentages was observed at lower resolutions, the trend of ICP-ABP-derived parameters showing higher responsiveness largely persisted. The only notable exception was rSO₂_L and rSO₂_R, which demonstrated comparatively higher responsiveness percentages at the lower resolutions.

As outlined in Section 5.2.5, subgroup analysis was also performed based on patients' median RAP values. The corresponding results are presented in Table K.2. As indicated, the number of patients within the RAP < 0 category was limited—only six for ICP-ABP-derived parameters, one for NIRS-derived parameters, and four for PbtO₂. Similarly, the $0 \leq \text{RAP} \leq 0.4$ category included relatively few patients. Due to these small sample sizes, the findings from these two RAP states may lack sufficient reliability. In contrast, the RAP > 0.4 group included a larger number of patients and produced results largely consistent with those observed in the full cohort analysis.

5.3.5.2 Granger causality testing

By comparing the F-statistic values of $\Delta X \rightarrow \Delta \text{RAP}$ and $\Delta \text{RAP} \rightarrow \Delta X$ for each patient example, the direction of the causality was determined. Since the focus of the research is to check how RAP responds to the change of another variable, the percentage of $\Delta X \rightarrow \Delta \text{RAP}$ was calculated and summarized in Table 5.6.

Table 5.6 Granger causality testing of ΔX and ΔRAP pairs across the resolutions for whole population

Parameters	Direction	Minute-by-minute	5-minute-by-5-minute	10-minute-by-10-minute
$\Delta \text{ICP} \ \& \ \Delta \text{RAP}$	$\Delta \text{ICP} \rightarrow \Delta \text{RAP}$	8.97%(34)	40.63%(154)	28.31%(107)
	$\Delta \text{RAP} \rightarrow \Delta \text{ICP}$	54.62%(207)	20.05%(76)	15.87%(60)
	NS	36.41%(138)	39.31%(149)	55.82%(211)
	NA	0	0	1
$\Delta \text{AMP} \ \& \ \Delta \text{RAP}$	$\Delta \text{AMP} \rightarrow \Delta \text{RAP}$	12.4%(47)	54.09%(205)	32.54%(123)
	$\Delta \text{RAP} \rightarrow \Delta \text{AMP}$	44.33%(168)	16.36%(62)	22.22%(84)
	NS	43.27%(164)	29.55%(112)	45.24%(171)

	NA	0	0	1
$\Delta\text{MAP} \& \Delta\text{RAP}$	$\Delta\text{MAP} \rightarrow \Delta\text{RAP}$	14.78%(56)	47.23%(179)	28.57%(108)
	$\Delta\text{RAP} \rightarrow \Delta\text{MAP}$	42.22%(160)	13.46%(51)	14.02%(53)
	NS	43.01%(163)	39.31%(149)	57.41%(217)
	NA	0	0	1
$\Delta\text{CPP} \& \Delta\text{RAP}$	$\Delta\text{CPP} \rightarrow \Delta\text{RAP}$	16.09%(61)	46.17%(175)	29.1%(110)
	$\Delta\text{RAP} \rightarrow \Delta\text{CPP}$	37.47%(142)	13.72%(52)	17.72%(67)
	NS	46.44%(176)	40.11%(152)	53.17%(201)
	NA	0	0	1
$\Delta\text{PRx} \& \Delta\text{RAP}$	$\Delta\text{PRx} \rightarrow \Delta\text{RAP}$	30.87%(117)	14.78%(56)	12.17%(46)
	$\Delta\text{RAP} \rightarrow \Delta\text{PRx}$	27.44%(104)	19.26%(73)	15.34%(58)
	NS	41.69%(158)	65.96%(250)	72.49%(274)
	NA	0	0	1
$\Delta\text{PAx} \& \Delta\text{RAP}$	$\Delta\text{PAx} \rightarrow \Delta\text{RAP}$	33.51%(127)	11.35%(43)	8.99%(34)
	$\Delta\text{RAP} \rightarrow \Delta\text{PAx}$	22.69%(86)	24.54%(93)	17.2%(65)
	NS	43.8%(166)	64.12%(243)	73.81%(279)
	NA	0	0	1
$\Delta\text{RAC} \& \Delta\text{RAP}$	$\Delta\text{RAC} \rightarrow \Delta\text{RAP}$	38.52%(146)	12.66%(48)	9.26%(35)
	$\Delta\text{RAP} \rightarrow \Delta\text{RAC}$	24.01%(91)	24.27%(92)	22.49%(85)
	NS	37.47%(142)	63.06%(239)	68.25%(258)
	NA	0	0	1
$\Delta\text{rSO}_2_L \& \Delta\text{RAP}$	$\Delta\text{rSO}_2_L \rightarrow \Delta\text{RAP}$	11.35%(16)	23.74%(33)	14.6%(20)
	$\Delta\text{RAP} \rightarrow \Delta\text{rSO}_2_L$	45.39%(64)	21.58%(30)	16.06%(22)
	NS	43.26%(61)	54.68%(76)	69.34%(95)
	NA	15	17	19
$\Delta\text{rSO}_2_R \& \Delta\text{RAP}$	$\Delta\text{rSO}_2_R \rightarrow \Delta\text{RAP}$	13.67%(19)	19.57%(27)	11.76%(16)
	$\Delta\text{RAP} \rightarrow \Delta\text{rSO}_2_R$	40.29%(56)	20.29%(28)	16.91%(23)
	NS	46.04%(64)	60.14%(83)	71.32%(97)
	NA	16	17	19
$\Delta\text{COx}_L \& \Delta\text{RAP}$	$\Delta\text{COx}_L \rightarrow \Delta\text{RAP}$	10.71%(15)	7.97%(11)	11.03%(15)
	$\Delta\text{RAP} \rightarrow \Delta\text{COx}_L$	28.57%(40)	25.36%(35)	13.97%(19)
	NS	60.71%(85)	66.67%(92)	75.0%(102)
	NA	12	14	16
$\Delta\text{COx}_R \& \Delta\text{RAP}$	$\Delta\text{COx}_R \rightarrow \Delta\text{RAP}$	15.11%(21)	5.07%(7)	6.62%(9)
	$\Delta\text{RAP} \rightarrow \Delta\text{COx}_R$	20.14%(28)	26.09%(36)	17.65%(24)
	NS	64.75%(90)	68.84%(95)	75.74%(103)
	NA	13	14	16
$\Delta\text{COx-a}_L \& \Delta\text{RAP}$	$\Delta\text{COx-a}_L \rightarrow \Delta\text{RAP}$	11.03%(15)	6.72%(9)	9.85%(13)
	$\Delta\text{RAP} \rightarrow \Delta\text{COx-a}_L$	34.56%(47)	20.9%(28)	16.67%(22)
	NS	54.41%(74)	72.39%(97)	73.48%(97)
	NA	4	6	8
$\Delta\text{COx-a}_R \& \Delta\text{RAP}$	$\Delta\text{COx-a}_R \rightarrow \Delta\text{RAP}$	19.26%(26)	8.96%(12)	5.3%(7)
	$\Delta\text{RAP} \rightarrow \Delta\text{COx-a}_R$	27.41%(37)	23.13%(31)	17.42%(23)

	NS	53.33%(72)	67.91%(91)	77.27%(102)
	NA	5	6	8
Δ PbtO ₂ & Δ RAP	Δ PbtO ₂ → Δ RAP	8.7%(10)	15.93%(18)	16.07%(18)
	Δ RAP→ Δ PbtO ₂	16.52%(19)	16.81%(19)	14.29%(16)
	NS	74.78%(86)	67.26%(76)	69.64%(78)
	NA	1	3	4

To calculate the percentage values in this table, the NA cases were excluded from the total number of patients.

Δ , first-order differenced; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NA, not applicable, NS, not significant; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation ; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

As shown in the table, most parameter pairs had a large proportion of non-significant (NS) cases, indicating that, in many instances, there was no statistically significant Granger causality in either direction. Among the significant results, Δ PRx, Δ PAX, and Δ RAC were the only parameters for which Δ X→ Δ RAP was more frequently significant than the reverse direction (Δ RAP→ Δ X) at the minute-by-minute resolution. However, at lower resolutions, Δ ICP, Δ AMP, Δ MAP, and Δ CPP more often showed significant influence on RAP, suggesting resolution-dependent patterns of directional association. A similar pattern was observed at the sub-group level, as shown in Tables L.1 to L.3. However, given that the majority of patient cases yielded non-significant results, the directional findings from the remaining data should not be interpreted as broadly generalizable.

5.3.5.3 Cross-correlation analysis

Initially, cross-correlation analysis was performed at the patient level across the entire population, with the results presented in Table 5.7.

Table 5.7 Δ RAP- Δ X cross-correlation analysis across the resolutions for whole population

Parameter pair	Minute-by-minute			5-minute-by-5-minute			10-minute-by-10-minute		
	Maximum correlation	Maximum lag	NA	Maximum correlation	Maximum lag	NA	Maximum correlation	Maximum lag	NA
Δ RAP- Δ ICP	0.086(0.062—0.122)	1.0(0.0—5.0)	0	0.128(0.095—0.179)	1.0(0.0—4.0)	0	0.165(0.118—0.237)	1.0(0.0—4.0)	0
Δ RAP- Δ AMP	0.115(0.081—0.166)	0.0(0.0—4.0)	0	0.165(0.109—0.222)	0.0(0.0—1.0)	0	0.205(0.14—0.289)	0.0(0.0—3.0)	0

Δ RAP- Δ MAP	0.062(0.044—0.1)	2.0(0.0—6.0)	0	0.157(0.1—0.238)	0.0(0.0—3.0)	0	0.199(0.139—0.315)	0.0(0.0—6.0)	0
Δ RAP- Δ CPP	0.064(0.044—0.1)	2.0(0.0—6.0)	0	0.142(0.095—0.227)	1.0(0.0—4.0)	0	0.18(0.124—0.289)	0.0(0.0—6.5)	0
Δ RAP- Δ PRx	0.143(0.075—0.236)	0.0(0.0—0.0)	0	0.191(0.116—0.3)	0.0(0.0—3.0)	0	0.218(0.148—0.334)	0.0(0.0—6.0)	0
Δ RAP- Δ Pax	0.152(0.084—0.244)	0.0(0.0—0.0)	0	0.167(0.1—0.264)	0.0(0.0—4.0)	0	0.198(0.128—0.288)	0.0(0.0—6.5)	0
Δ RAP- Δ RAC	0.194(0.11—0.306)	0.0(0.0—0.0)	0	0.264(0.158—0.376)	0.0(0.0—0.0)	0	0.301(0.188—0.432)	0.0(0.0—1.0)	0
Δ RAP- Δ rSO ₂ _L	0.079(0.053—0.121)	3.0(1.0—8.0)	9	0.15(0.105—0.22)	2.0(0.0—12.0)	9	0.179(0.124—0.253)	3.0(0.5—10.0)	9
Δ RAP- Δ rSO ₂ _R	0.075(0.05—0.132)	3.0(1.0—7.0)	10	0.132(0.104—0.208)	4.0(0.0—14.0)	10	0.185(0.126—0.264)	4.0(0.0—11.0)	10
Δ RAP- Δ COx_L	0.073(0.052—0.108)	4.0(1.0—11.75)	6	0.126(0.095—0.179)	4.0(1.0—12.0)	6	0.178(0.131—0.267)	5.0(0.0—12.0)	6
Δ RAP- Δ COx_R	0.064(0.043—0.098)	4.0(1.0—10.0)	7	0.127(0.093—0.193)	6.0(1.0—15.0)	7	0.175(0.123—0.268)	5.0(1.0—12.0)	7
Δ RAP- Δ COx-a_L	0.074(0.052—0.114)	2.0(0.0—9.0)	4	0.135(0.103—0.181)	3.0(0.0—8.0)	4	0.175(0.128—0.265)	4.0(0.0—12.0)	4
Δ RAP- Δ COx-a_R	0.065(0.044—0.122)	3.0(1.0—8.0)	5	0.129(0.09—0.21)	5.0(0.0—12.0)	5	0.169(0.128—0.269)	6.0(1.0—12.0)	5
Δ RAP- Δ PbtO ₂	0.086(0.062—0.122)	6.0(2.0—12.0)	1	0.107(0.076—0.149)	5.0(1.0—12.0)	1	0.137(0.099—0.201)	4.0(1.0—12.0)	2

To calculate the percentage values in this table, the NA cases were excluded from the total number of patients.

Δ , first-order differenced; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NA, not applicable; Pax, pulse amplitude index; PbtO₂, brain tissue oxygenation; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

Among the variables, Δ ICP, Δ AMP, and the ICP-ABP-derived CA indices— Δ PRx, Δ Pax, and Δ RAC—exhibited relatively higher median correlation values with Δ RAP, particularly when compared to NIRS-derived CA indices. These parameters also showed median maximum lags of 0 or 1 (i.e., the lag values at which peak correlation occurred), suggesting they fluctuated synchronously with Δ RAP. The findings were largely consistent across all resolutions. Notably, in the lower-resolution data, Δ MAP and Δ CPP showed correlation values comparable to or greater than those of Δ ICP and Δ AMP, with similarly low median maximum lags, indicating synchronous behaviour with Δ RAP.

Tables M.1 to M.3 of Appendix M present the results from the subgroup analysis. The $RAP > 0.4$ subgroup largely resembled the trends observed in the full dataset. In contrast, the $RAP < 0$ and $0 \leq RAP \leq 0.4$ subgroups displayed notable differences. These groups showed generally higher median maximum lags across most parameter pairs, although ΔPRx , ΔPAX , and ΔRAC showed the lowest lag values. Interestingly, in these states, the NIRS-derived parameters demonstrated stronger correlation magnitudes than the ICP-ABP-derived indices. Additionally, a higher frequency of NA cases was observed, especially at lower resolutions, highlighting the impact of insufficient data on the analysis.

5.4 Discussion

Our objective was to investigate the burden of impaired cerebral compliance (i.e., RAP) in moderate-to-severe TBI patients and how it relates to other key components of MMM cerebral physiology in this population. First, we performed a detailed descriptive analysis to assess statistical associations across different sub-groups and threshold ranges. Next, we applied semi-supervised ML techniques to examine parameter clustering, with a particular focus on how RAP grouped with other variables. Finally, we analyzed high-frequency temporal response patterns to evaluate how RAP dynamically responds to changes in other MMM parameters. Several key aspects deserve highlighting.

5.4.1 General descriptive relationships

Firstly, the analysis of general descriptive relationships showed that higher ICP and AMP were associated with impaired RAP, whereas with exhausted RAP, though ICP was high, AMP was comparatively lower. This explains the negative RAP value in the exhausted cerebral compliance period. Furthermore, CPP was observed to be lower during impaired and exhausted RAP states, consistent with the concept of diminished perfusion resulting from compromised CA.

In the context of CA indices, theoretical expectations indicate that worsening compliance is associated with positive CA indices. As such, both impaired and exhausted compliance states should exhibit positive CA indices, with the exhausted state showing the most elevated values. The conducted analyses aligned with these expectations in the exhausted RAP state but not in the $RAP > 0.4$ and $0 \leq RAP \leq 0.4$ ranges. This discrepancy can be explained by the typical progression of TBI patients into an exhausted compliance state. Initially, in an impaired compliance phase, patients may experience further deterioration, leading to arteriolar dilation failure and discontinuity in CBF. This reduces the transmission of arterial pulse pressure to the intracranial compartment, resulting in decreased AMP. Consequently, RAP begins to decline and may pass through the $0 \leq RAP \leq 0.4$ range, which is normally indicative of intact compliance, but in this context, it represents a transitional phase toward negative RAP values, indicating exhausted compliance. Therefore,

the analyses showed that CA indices were higher when RAP was near zero or negative, compared to when RAP was greater than 0.4.

Changes in PbtO₂ can similarly be explained by this theoretical framework. As RAP transitioned from the impaired to the exhausted state, CBF decreased, resulting in reduced brain tissue oxygenation; thus, PbtO₂ levels were also lower compared to the RAP > 0.4 state. These findings were mostly consistent across the graphical representation, analysis of MMM physiology compared to RAP thresholds and the reverse analysis of RAP against different parameter thresholds. Both the median values and the percentage time spent across different thresholds align with the findings from the graphical illustrations.

Secondly, the analysis of the percentage of time spent in different RAP threshold ranges revealed that, across all cases, the majority of the population remained in the RAP > 0.4 state for most of the recording period, as illustrated in Table G.2 of Appendix G, suggesting that most TBI patients experienced a high positive RAP, indicating a potential association between TBI and impaired cerebral compliance. Another interesting observation in the analysis of MMM physiology compared to RAP thresholds is that TBI patients spent a significant amount of time with impaired CVR, as a substantial percentage of the time was associated with positive values of the CA indices. For example, PRx ≥ 0 was observed in 74.17%, 72.73%, and 57.89% of the time within the RAP < 0, 0 ≤ RAP ≤ 0.4, and RAP > 0.4 ranges, respectively, from A.1. This indicates that, alongside impaired cerebral compliance, TBI is also potentially associated with impaired CVR.

Lastly, regarding the formal comparison tests, ICP, AMP, MAP, PRx and RAC were significantly different across the RAP states. In the reverse analysis, notably, RAP was significantly different across the thresholds of PRx and RAC. The consistent involvement of these two ICP-derived CA indices in both analyses suggests a potential bidirectional relationship between CA and CC/CCR. This mutual association supports the concept that cerebral compliance and autoregulation are interlinked physiological processes, and disturbances in one may reflect or contribute to dysfunction in the other. This also explains why impaired compliance was often associated with impaired autoregulation in the majority of TBI patients in this study.

5.4.2 Comparative clustering patterns of the parameters

The consistency in clustering across both AHC and PCA suggests stable underlying relationships among physiological signals. ICP and AMP, which are the constituent signals of RAP, were found to be the closest to RAP. When comparing ICP-ABP-derived parameters with NIRS-derived parameters, rSO₂ was the closest to RAP, after ICP and AMP, which may reflect RAP's sensitivity to cerebral perfusion and oxygenation changes. Furthermore, when PbtO₂ was considered alongside ICP-ABP-derived parameters, it

emerged as the closest to RAP, surpassing even ICP and AMP, suggesting a potentially stronger physiological coupling between brain tissue oxygenation and intracranial compliance. None of the CA indices were closer to RAP than ICP, AMP, rSO₂, or PbtO₂, except in sub-group analyses, where PRx was found to be the closest to RAP under the $RAP < 0$ and $0 \leq RAP \leq 0.4$ conditions, indicating that CVR becomes more functionally linked to compliance in compromised autoregulatory states. In this context, the $0 \leq RAP \leq 0.4$ range is referred to as a “compromised” autoregulatory state, instead of an intact condition. As previously discussed, this range may reflect a transitional phase in which RAP decreases from high positive values, marking the shift from impaired to exhausted cerebral compliance.

Additionally, in the majority of the PCA biplots, RAP appeared slightly offset from the core direction of its groups in the majority of the plots, suggesting that although it was statistically associated with parameters like ICP and AMP, it also captured additional variance not fully explained by these constituent signals alone, aligning with the finding of one of the previous research from our group.

Although AHC and PCA produced highly similar outcomes, KMCA revealed a slightly different clustering pattern. The result of KMCA was the most consistent across all the resolutions and sub-groups. In this analysis, all CA indices clustered with RAP, along with AMP. This contrasts with the findings from AHC and PCA, which indicated that CA indices were not closely associated with RAP. This may be because of the fundamental differences in the underlying methodologies of these three models. While PCA and AHC primarily capture linear associations and are sensitive to Euclidean distance or linear variance, therefore, they may miss nonlinear or more subtle functional relationships, KMCA, being kernel-based, is designed to capture nonlinear patterns and higher-dimensional associations, which allows it to detect nonlinear coupling or shared variance structures that linear methods overlook. Additionally, KMCA indicated that RAP was more closely associated with AMP than with ICP.

5.4.3 High-frequency temporal response patterns

The VARIMA IRF analysis revealed that RAP was consistently more responsive to changes in ICP-ABP-derived parameters across all resolutions, particularly at the minute-by-minute scale, compared to NIRS-derived parameters and PbtO₂, suggesting a strong physiological coupling between RAP and ICP-ABP-derived measures, likely reflecting their direct mathematical and physiological interdependence. Interestingly, rSO₂_L and rSO₂_R showed comparatively increased responsiveness at lower resolutions, potentially reflecting delayed or cumulative oxygenation dynamics that become more apparent when fine temporal fluctuations are minimized. Sub-group analysis confirmed similar trends in the $RAP > 0.4$ group, though limited patient numbers in the $RAP < 0$ and $0 \leq RAP \leq 0.4$ groups reduced confidence in these two RAP states' results.

In the context of Granger causality testing, while the analysis revealed limited overall directionality due to the predominance of non-significant cases, some resolution- and parameter-specific patterns did emerge. The finding that $\Delta X \rightarrow \Delta \text{RAP}$ was more frequently significant for ΔPRx , ΔPAx , and ΔRAC at the minute-by-minute resolution suggests that ICP-derived autoregulatory indices might exert predictive influence on RAP during periods of finer temporal granularity, potentially reflecting faster physiological responses. In contrast, the shift at lower resolutions, where parameters like ICP, AMP, MAP, and CPP more often Granger-caused RAP, might point to broader systemic influences becoming more apparent over longer time windows. However, due to the high prevalence of non-significant results, these associations should be interpreted cautiously and might not reflect consistent causal dynamics across all patient cases.

The cross-correlation analysis demonstrated that ΔRAP fluctuates synchronously with its constituent signals (ΔICP , ΔAMP) and ICP-derived CA indices, supporting RAP's physiological relevance in real-time cerebrovascular monitoring. However, at lower resolutions, ΔMAP and ΔCPP showed stronger associations, suggesting a greater influence of systemic hemodynamics over longer timescales. Analysis at sub-group level revealed that in impaired states ($\text{RAP} < 0$ and $0 \leq \text{RAP} \leq 0.4$), NIRS-derived parameters (and also CA indices) showed stronger correlations than ICP-derived CA indices, indicating their potential role in compromised autoregulatory conditions.

5.4.4 Bilateral consistency of cerebral physiology

Across all analyses, parameters recorded from both the left and right hemispheres (rSO_2 , COx , and COx-a) exhibited similar behaviour, and in the clustering results, each pair of corresponding hemispheric parameters consistently grouped together. This suggests that the physiological processes they represent, such as cerebral oxygenation (rSO_2) and CVR (COx and COx-a), are similarly regulated or influenced in both hemispheres, and are likely to exert a comparable influence on RAP and vice versa.

5.4.5 Impact of temporal resolution and RAP sub-groups on analytical consistency

In both the clustering and high-frequency temporal analyses, lower temporal resolutions were applied in addition to the original minute-by-minute data. Across all models, the clustering results remained largely consistent across resolutions, with only minor variations observed in the AHC and PCA analyses. Similarly, high-frequency response patterns were generally stable across resolutions, with the exception of some differences noted in the Granger causality tests. Overall, these findings suggest that co-variance structures and high-frequency temporal dynamics are largely preserved regardless of the resolution, indicating that these patterns are not strongly influenced by the sampling frequency.

Moreover, the sub-group analysis revealed that deviations from the overall population results were more frequent in the $RAP < 0$ and $0 \leq RAP \leq 0.4$ states, whereas the $RAP > 0.4$ state largely mirrored the full cohort findings. This is likely because $RAP < 0$ reflects a state of exhausted compliance, and $0 \leq RAP \leq 0.4$ represents a transitional phase toward this exhaustion. These conditions mark the late stages of cerebrovascular dysfunction. Consequently, physiological relationships in these states may become more unstable and variable across individuals, resulting in greater inconsistency in how cerebral parameters relate to RAP.

5.5 Limitations

Even though this study yielded several important findings, it was not without limitations. Firstly, although the ICP-ABP-derived parameters included 379 data points, the NIRS-derived parameters collectively had only 133, and PbtO₂ had 116, which are relatively small sample sizes for drawing reliable conclusions from this analysis. Secondly, in the sub-group analysis, the $RAP < 0$ and $0 \leq RAP \leq 0.4$ categories often yielded results that differed from those observed in the $RAP > 0.4$ group and the overall population. These discrepancies may be caused by the fact that the former two states ($RAP < 0$ and $0 \leq RAP \leq 0.4$) reflect a condition of exhausted cerebral compliance, where cerebrovascular dysfunction is present, potentially leading to altered physiological relationships. However, these differences could also be attributed to the limited data available for these states. Acquiring more data in these ranges would help resolve this uncertainty.

5.6 Conclusion

In this analysis, we set out to describe the multivariate relationship between RAP and other cerebral physiology. There were consistent patterns of the cerebral physiology parameters across the three predefined RAP states for the majority of the cases, which was also observed in the reverse analysis (i.e., consistent pattern of RAP values across the sub-groups of other parameter thresholds). Findings suggest that worsening RAP was associated with decreased MAP, CPP rSO₂, and PbtO₂ values. Impaired RAP was also associated with impaired CA indices, which was also evident in the transition state of RAP.

Furthermore, both the clustering and high-frequency temporal response analyses revealed physiologically coherent and largely stable patterns across all examined temporal resolutions. These findings collectively suggest that RAP maintains a consistent and meaningful relationship with other cerebral physiological parameters. Additionally, the observed differences between the impaired and exhausted compliance states highlight the potential of these relationships to inform bedside monitoring, patient trajectory modeling, and

future interventional studies. While further research is needed to translate these findings into clinical practice, this analysis demonstrates RAP's potential as a valuable physiological marker.

6 Summary and Conclusions

The studies presented in the preceding chapters have thoroughly explored the statistical and temporal features of RAP in moderate-to-severe TBI. Although these findings are preliminary, they offer meaningful insights into the two hypotheses introduced in Chapter 1. This chapter summarizes the key results in relation to each hypothesis.

6.1 Summary of Findings

Hypothesis #1: Viable RAP data streams will display a reproducible time-domain structure, highlighting the distinct information RAP conveys relative to its components, ICP and AMP. This will also facilitate the identification of artifacts and the development of semi-automated/automated methods of management.

As highlighted in Section 2.6, there is currently no clear understanding of RAP's temporal characteristics. However, as previously discussed, gaining insight into any underlying temporal patterns of RAP is crucial for its clinical application, as this knowledge could increase the accuracy of models for personalized treatment strategies.

As presented in section 4.3.3, indeed, RAP data streams displayed inherent autoregressive features, as reflected by optimal ARIMA models with non-zero autoregressive and moving average components. Of note, this was applicable at lower resolutions as well. Furthermore, the temporal characteristics of RAP derived by the ARIMA model varied from those of ICP and AMP, indicating RAP contains different information beyond its constituent signals, further supporting its distinctiveness.

In the context of management of artifactual RAP data, several promising features were identified leveraging the temporal properties derived from ARIMA models. As detailed in Section 4.3.4, at the minute-by-minute resolution, useful features for artifact detection included: (a) the ICP q-order, AMP p-order, and both p- and q-orders of RAP, (b) the residuals of ICP, AMP, and RAP, and (c) the cross-correlation between RAP and AMP residuals. In contrast, for the 10-minute resolution data, only the q-orders of the optimal ARIMA models for ICP and AMP proved to be informative. A basic sliding window algorithm was implemented to test these features, yielding a promising artifact detection rate. However, a significant number of false positives were associated with it.

Hypothesis #2: Total insult burden of impaired RAP will vary based on the selected RAP threshold. Consistent patterns of cerebral physiologies with relation to RAP will be evident across all the resolutions for different RAP thresholds.

Through the comprehensive review of the literature as presented in sections 2.6 and 2.7, several physiological parameters, outcomes, and neuroimaging features were consistently associated with RAP across previous studies. Consistent patterns were evident in these observations. However, none of the observations emphasized RAP's relationship. Their primary objectives were different.

Chapter 5 addresses this gap, conducting a thorough investigation of RAP's relationships with other parameters. Three RAP states were determined based on the overall physiological condition as defined in section 2.7. Findings revealed that most TBI patients spent the majority of their monitoring time in RAP state 2, reflecting impaired compensatory reserve and autoregulation. Therefore, as the patient's condition worsened, RAP values began to decline and eventually became negative. This observation introduced a new RAP state – a transitional state of RAP, when a large positive RAP value starts to decrease. This helped to avoid confusion with the intact RAP state, since both RAP states have similar values (i.e., low positive value). They can be differentiated using other parameters, for instance, ICP and CA indices are significantly higher in the transitional RAP state.

Other key findings are as follows: descriptive analysis in sections 5.3.2 and 5.3.3 revealed that the impaired RAP state was associated with elevated ICP and AMP, while the exhausted RAP state was associated with high ICP but reduced AMP. These two RAP states were also associated with compromised autoregulation and diminished perfusion. Next, clustering analyses as presented in section 5.3.4, consistently grouped RAP with its constituent signals (ICP and AMP), followed by PbtO₂ and rSO₂. Notably, CA indices clustered more closely with RAP under impaired autoregulatory states, hinting that cerebrovascular reactivity becomes more functionally linked to compliance in compromised autoregulatory states. This could be a valuable insight for the clinical use of RAP. Lastly, high-frequency temporal analyses in 5.3.5 revealed that RAP showed comparatively stronger responsiveness to ICP-ABP-derived parameters at minute-by-minute resolution. Moreover, RAP demonstrated greater sensitivity to changes in these ICP-derived CA indices in high-frequency temporal analyses. These trends remained consistent at lower temporal resolutions as well.

These relations were consistent with the theoretical concepts of physiology and also aligned with previous findings, while providing additional insights regarding RAP ranges. Interestingly, in some cases, transitional and exhausted RAP states exhibited anomalies in patterns, likely due to the late stages of cerebrovascular dysfunction. These anomalies may hold clinical value in predicting patient deterioration and guiding early intervention.

6.2 Conclusion

In conclusion, the work presented in this thesis represents a significant step forward in the comprehensive understanding of the RAP index and its role in assessing CC/CCR in moderate-to-severe TBI patients. The thesis confirmed that RAP signals carry reproducible and distinct temporal characteristics, including autoregressive and trend-like behaviours. These features not only enhance RAP's physiological reliability but also offer a promising avenue for detecting artifactual data segments through time-series modeling. Furthermore, clear, consistent patterns were found between RAP and various physiological markers across predefined states of RAP. These associations were further supported through clustering and high-resolution temporal response analysis, reinforcing RAP's meaningful relationship with broader cerebral physiology.

Overall, this thesis offers strong preliminary evidence for RAP as a robust, physiologically meaningful marker. While further validation in larger, multicenter cohorts is necessary, this thesis lays the groundwork for the future clinical integration of RAP in real-time bedside monitoring, modeling of patient outcomes, and targeted therapeutic interventions.

7 Future Directions

This thesis conducted comprehensive analyses on statistical behaviours of RAP and its relationships with other physiologies. However, as highlighted throughout this work, there were significant limitations in different aspects. Building upon the findings of this thesis, several key future directions are necessary to address these limitations, therefore further refining and validating the role of RAP in clinical practice.

7.1 Validation Using Larger Multi-Center Datasets

Future investigations should aim to utilize larger, multi-center, high-frequency physiological datasets, particularly those that include PbtO₂, ICP-ABP-, and NIRS-derived cerebrovascular reactivity indices. As discussed earlier, the CAHR-TBI dataset employed in this thesis contained relatively limited patient recordings for these parameters, resulting in smaller sample sizes that may hinder the reliability of the conclusions drawn. Additionally, within the subgroup analyses, the $RAP < 0$ and $0 \leq RAP \leq 0.4$ states were underrepresented relative to the full dataset. The inconsistent patterns observed in these exhausted and transitional RAP categories may reflect physiological states of exhausted cerebral compliance but could also be caused by insufficient data. Expanding the dataset in these specific RAP ranges would help clarify these findings and enhance the robustness of future analyses. Insufficient recording data also impacted the results obtained at lower temporal resolutions. In many cases, patient data segments were too short to yield valid outputs from ARIMA modeling and VARIMA IRF analyses.

7.2 Advanced Artifact Detection Techniques

While the thesis explored temporal features for identifying artifactual RAP data, the validation of these features remained limited. A basic sliding window algorithm was employed, resulting in a high rate of false positives. Future work should integrate more advanced techniques such as signal morphological assessments, wavelet decomposition, and machine learning-based classification. These layered approaches could reduce false positives and improve detection reliability, particularly in real-time clinical monitoring settings.

7.3 Incorporation of Treatment-Based Subgroup Analyses

This thesis did not account for the effects of specific treatments such as decompressive craniectomy, variations in arterial pCO₂, or hyperosmolar therapies like mannitol infusion. As described earlier, these treatments may exert immediate physiological impacts in the minutes following treatment. Therefore, when modeling RAP signals at high temporal resolutions (e.g., minute-by-minute), the influence of these

interventions should not be overlooked. Including treatment metadata in future models could enable more precise interpretations of RAP dynamics, particularly when analyzing acute transitions in patient state.

7.4 Missing Data Handling

Both datasets used in this thesis had some missing data due to sensor failures, manual artifact removal, or inconsistent signal recordings. In both studies, these missing segments were excluded from the analyses. For instance, in the clustering analysis, the absence of parameters such as PbtO₂ and NIRS-derived CA indices in many patients necessitated separate analyses for these parameters. To date, there has been no dedicated effort to define optimal strategies for handling missing data in this field. Improper handling or outright exclusion of missing data can introduce significant bias and lead to conclusions that may not reflect true physiological relationships. Therefore, future research should explore imputation methods, probabilistic modeling approaches, or data fusion techniques to better address missing data challenges and enhance the robustness and generalizability of findings.

7.5 Different Clustering Approaches

In chapter 5, a bottom-up (i.e., agglomerative) clustering approach was selected for MMM relationships. While this method allowed for the stepwise identification of similarity patterns among physiological signals, it is essential to acknowledge that alternative approaches, such as top-down (divisive) clustering, may potentially provide new insights into the multimodal relationships. As such, future work should evaluate these relationships using top-down or other clustering methodologies to validate and confirm the robustness of the observed MMM associations.

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Appendix A. Section 4.3.2: Summary measurements, time spent within thresholds, and analysis of ICP/AMP/RAP

The following appendix demonstrates the tables for summary measurements, percentage time spent within certain thresholds, across the whole population.

AMP, pulse amplitude of ICP; CPP, cerebral perfusion pressure; CT, computed tomography; GOSE, Glasgow outcome scale-extended; ICP, intracranial pressure; MAP, mean arterial blood pressure; PRx, pressure reactivity index; RAP, compensatory reserve index; std, standard deviation

Table A.1 Summary measurements

Metrics	ICP	MAP	CPP	AMP	RAP
mean	10.818	85.374	74.555	2.244	0.632
std	7.564	13.881	14.049	1.855	0.483
min	-15	0.035	-34.26	0	-1
25%	6.138	76.69	66.5005	0.9977	0.49635
50%	10.17	83.94	73.03	1.711	0.8578
75%	14.74	92.65	81.69	2.91	0.9646
max	80.06	200	197.362	22.41	1

Table A.2 Time spent within threshold

Ranges	Time spent (unit)	% time spent	Total Time (unit)
[0.4, 1]	267.578	78.091	342.646
(0, 0.4)	30.889	9.014	
[0, -1]	43.166	12.597	

Table A.3 Sub-group analysis—age (first comparison)

Condition	ICP	MAP	CPP	AMP	RAP
Below 40 years (n = 46)	10.56481 ± 6.85241	84.44187 ± 7.36121	73.68225 ± 7.94464	1.71982 ± 1.21450	0.60043 ± 0.18153
Above 40 years (n = 63)	8.51253 ± 6.63832	84.07349 ± 7.70570	76.12142 ± 8.49570	2.40335 ± 1.82718	0.53754 ± 0.20982
p-value	0.047852	0.710493	0.136793	0.065227	0.119867

Table A.4 Sub-group analysis—age (second comparison)

Condition	ICP	MAP	CPP	AMP	RAP
Below 40 years (n = 46)	10.56481 ± 6.85241	84.44187 ± 7.36121	73.68225 ± 7.94464	1.71982 ± 1.21450	0.60043 ± 0.18153
Between 40 and 60 years (n = 39)	8.71919 ± 7.12835	86.03822 ± 8.03764	77.66581 ± 9.36177	2.21371 ± 1.61825	0.59274 ± 0.19015
Above 60 years (n = 24)	8.17672 ± 5.88620	80.88080 ± 6.01193	73.61179 ± 6.25669	2.71151 ± 2.12438	0.44784 ± 0.21301
p-value	0.28399	0.02818	0.05323	0.04624	0.00459

Table A.5 Sub-group analysis—M/F Sex

Condition	ICP	MAP	CPP	AMP	RAP
Male (n = 89)	8.90705 ± 6.30729	84.74958 ± 7.90121	76.15799 ± 8.24657	2.02947 ± 1.54173	0.55111 ± 0.20298
Female (n = 20)	11.47718 ± 8.42448	81.91215 ± 5.12074	70.34861 ± 7.02543	2.49502 ± 1.96119	0.62181 ± 0.17918
p-value	0.333628	0.192417	0.00805	0.483515	0.164657

Table A.6 Sub-group analysis—Pupillary response

Condition	ICP	MAP	CPP	AMP	RAP
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Bilat Reactive (n = 65)	9.68200 ± 6.32553	84.11428 ± 7.34526	74.95088 ± 7.44597	2.25631 ± 1.76652	0.59983 ± 0.19003
Bilat Unreactive (n = 19)	7.21860 ± 6.62510	85.25445 ± 10.43550	77.67136 ± 10.39840	1.84440 ± 1.38851	0.51583 ± 0.19264
Unilateral Unreactive (n = 25)	10.23149 ± 7.88851	83.74773 ± 5.33723	73.49879 ± 8.63051	1.95276 ± 1.41453	0.50780 ± 0.21717
p-value	0.29519	0.79378	0.25327	0.53557	0.07446

Table A.7 Sub-group analysis—Marshall CT grade

Condition	ICP	MAP	CPP	AMP	RAP
Grade II (n=3)	8.41885 ± 1.46502	88.19054 ± 2.95348	79.67350 ± 4.20626	1.10567 ± 0.32360	0.53874 ± 0.23926
Grade III (n=31)	10.10747 ± 5.75164	85.77724 ± 7.99221	75.28605 ± 6.88824	2.34405 ± 1.30344	0.65335 ± 0.16089
Grade IV (n=20)	13.85727 ± 7.61941	86.37602 ± 7.24507	73.34250 ± 8.89201	3.30238 ± 2.28233	0.67305 ± 0.16134
Grade V (n=55)	7.39158 ± 6.41152	82.35945 ± 7.18358	75.36899 ± 9.00899	1.60895 ± 1.28146	0.47552 ± 0.19312
p-value	0.00227	0.06480	0.60516	0.00028	0.00001

Table A.8 Sub-group analysis—Alive/Dead (1-month GOSE)

Condition	ICP	MAP	CPP	AMP	RAP
Alive (n = 71)	8.08183 ± 5.20270	84.54202 ± 7.87658	76.48282 ± 8.44677	1.65068 ± 1.01478	0.57072 ± 0.19835
Dead (n = 38)	11.98871 ± 8.45046	83.68252 ± 7.01954	72.27488 ± 7.38769	2.96776 ± 2.15609	0.55279 ± 0.20754
p-value	0.033485	0.668784	0.031911	0.002865	0.604539

Table A.9 Sub-group analysis—Favourable/Unfavourable (1-month GOSE)

Condition	ICP	MAP	CPP	AMP	RAP
Favourable(n=52)	7.29237 ± 5.30263	84.20479 ± 7.90128	77.03737 ± 8.74621	1.44024 ± 0.79148	0.54361 ± 0.20245
Unfavorable(n=57)	11.46599 ± 7.36347	84.27194 ± 7.30886	73.11250 ± 7.46122	2.73982 ± 1.94607	0.58373 ± 0.19920
p-value	0.001883	1.0	0.016348	0.000358	0.294478

Table A.10 Sub-group analysis—Alive/Dead (6-month GOSE)

Condition	ICP	MAP	CPP	AMP	RAP
Alive (n = 68)	8.42374 ± 5.18191	84.72952 ± 7.98240	76.32846 ± 8.45665	1.66250 ± 1.02750	0.58264 ± 0.19200
Dead (n = 41)	11.37039 ± 8.47379	83.53319 ± 7.27248	72.68237 ± 7.72236	2.83479 ± 2.12879	0.53877 ± 0.21121
p-value	0.169741	0.562849	0.065448	0.010051	0.258864

Table A.11 Sub-group analysis—Favourable/Unfavourable (6-month GOSE)

Condition	ICP	MAP	CPP	AMP	RAP
Favourable(n=25)	8.12572 ± 5.14666	84.64676 ± 8.09823	76.55841 ± 8.59283	1.67795 ± 1.04272	0.57845 ± 0.19602
Unfavorable(n=64)	11.61034 ± 8.23577	83.83620 ± 6.72062	72.72268 ± 7.47357	2.77978 ± 2.10187	0.54720 ± 0.20960
p-value	0.048501	0.738688	0.041701	0.01456	0.4034

Table A.12 ICP thresholds

Condition	ICP	MAP	CPP	AMP	RAP
ICP > 22	28.34662 ± 7.12649	91.16469 ± 17.08712	62.81109 ± 17.58897	4.99916 ± 3.26314	0.72418 ± 0.43710

ICP < 20	9.34625 ± 5.61682	84.79938 ± 13.48051	75.54584 ± 13.34231	2.06319 ± 1.57050	0.62705 ± 0.48596
p-value	Close to 0	Close to 0	Close to 0	Close to 0	Close to 0

Table A.13 AMP thresholds

Condition	ICP	MAP	CPP	AMP	RAP
AMP < 1	6.99299 ± 5.69411	84.26304 ± 14.03507	77.38008 ± 13.74575	0.58311 ± 0.26164	0.43376 ± 0.55036
1 < AMP < 3	10.94096 ± 7.58453	85.39152 ± 13.89387	74.56503 ± 14.06739	2.31228 ± 1.93635	0.63582 ± 0.48283
AMP > 3	15.60541 ± 8.33541	86.79509 ± 14.63808	71.22871 ± 14.81692	5.01951 ± 1.90360	0.78769 ± 0.36104
p-value	Close to 0	Close to 0	Close to 0	Close to 0	Close to 0

Table A.14 PRx thresholds (first comparison)

Condition	ICP	MAP	CPP	AMP	RAP	PRx
PRx < 0	10.44394 ± 6.53201	85.41019 ± 12.90041	74.88617 ± 12.82014	2.22166 ± 1.73685	0.68340 ± 0.44809	-0.42581 ± 0.26188
PRx > 0	11.25437 ± 8.56936	85.55157 ± 14.99946	74.20460 ± 15.28773	2.27123 ± 1.98214	0.57066 ± 0.51977	0.42869 ± 0.27811
p-value	Close to 0	Close to 0	Close to 0	Close to 0	Close to 0	Close to 0

Table A.15 PRx thresholds (second comparison)

Condition	ICP	MAP	CPP	AMP	RAP	PRx
PRx < 0.25	10.82641 ± 7.57303	85.47692 ± 13.93089	74.56473 ± 14.04217	2.24505 ± 1.85682	0.63016 ± 0.48653	-0.02201 ± 0.50469
PRx > 0.25	11.77002 ± 9.13674	85.55960 ± 15.74818	73.67751 ± 16.11601	2.34873 ± 2.09150	0.55701 ± 0.52997	0.57686 ± 0.21250
p-value	Close to 0	Close to 0	Close to 0	0.002642	Close to 0	Close to 0

Appendix B. Section 4.3.3: Summary of stationarity analysis tests – ADF/ KPSS tests for original and differenced data

This appendix highlights that after first ordered differencing was applied, the overall the data became stationary at each resolution.

ADF, Augmented Dickey-Fuller; AMP, pulse amplitude of ICP; ICP, intracranial pressure; KPSS, Kwiatkowski-Phillips-Schmidt-Shin; RAP, compensatory reserve index.

Table B.1 Stationarity check of the original data based on ADF

Parameter	Minute by minute			10 min by 10 min			30 min by 30 min			Hour by hour		
	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A
ICP	86	23	0	66	43	0	60	49	0	51	55	3
AMP	80	29	0	58	51	0	52	57	0	48	58	3
RAP	109	0	0	93	16	0	76	33	0	69	37	3

Table B.2 Stationarity check of the original data based on KPSS

Parameter	Minute by minute			10 min by 10 min			30 min by 30 min			Hour by hour		
	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A
ICP	8	101	0	33	76	0	49	60	0	59	49	1
AMP	13	96	0	34	75	0	48	61	0	54	54	1
RAP	33	76	0	46	63	0	56	53	0	57	52	0

Table B.3 Stationarity check of the first difference data based on ADF

c	Minute by minute			10 min by 10 min			30 min by 30 min			Hour by hour		
	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A
ICP	108	1	0	106	3	0	104	4	1	91	14	4
AMP	109	0	0	108	1	0	101	7	1	89	16	4
RAP	109	0	0	107	2	0	100	8	1	92	13	4

Table B.4 Stationarity check of the first difference data based on KPSS

Parameter	Minute by minute			10 min by 10 min			30 min by 30 min			Hour by hour		
	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A	Stationary	Non-stationary	N/A
ICP	109	0	0	108	1	0	106	3	0	98	8	3

AMP	108	1	0	105	4	0	105	4	0	99	7	3
RAP	108	1	0	103	6	0	100	9	0	93	13	3

Appendix C. Section 4.3.3: Optimal ARIMA models for each signal and each patient

The following is the most significant ARIMA models (as informed through AIC) at individual patient level for each resolution and each signal. Each cell has four values corresponding to p, d, q orders and associated AIC value for the model. m refers to minute and h refers to hour.

AIC, Akaike information criterion; AMP, pulse amplitude of ICP; ARIMA, autoregressive integrated moving average; ICP, intracranial pressure; RAP, compensatory reserve index.

Table C.1 Optimal ARIMA models

Patient	ICP m by m	ICP 10 by 10m	ICP 30m by 30m	ICP h by h	AMP m by m	AMP 10m by 10m	AMP 30m by 30m	AMP h by h	RAP m by m	RAP 10m by 10m	RAP 30m by 30m	RAP h by h
TBI_001	[10, 1, 3, '1531.771']	[6, 1, 1, '4255.733']	[4, 1, 3, '1522.509']	[2, 1, 4, '788.013']	[1, 1, 9, '35487.221']	[6, 1, 1, '1332.552']	[3, 1, 1, '498.284']	[6, 1, 7, '265.408']	[2, 1, 5, '14862.477']	[6, 1, 5, '192.534']	[6, 1, 5, '243.988']	[1, 1, 1, '186.431']
TBI_002	[4, 1, 1, '301.383']	[3, 1, 1, '798.246']	[2, 1, 4, '312.842']	[2, 1, 3, '165.722']	[9, 1, 4, '7043.873']	[1, 1, 2, '390.750']	[8, 1, 1, '22.000']	[5, 1, 1, '99.766']	[9, 1, 3, '2469.440']	[2, 1, 1, '52.852']	[1, 1, 1, '55.084']	[1, 1, 1, '29.913']
TBI_003	[6, 1, 1, '1091.937']	[4, 1, 3, '609.108']	[1, 1, 2, '221.819']	[1, 1, 5, '123.989']	[1, 1, 5, '3681.918']	[2, 1, 2, '613.493']	[2, 1, 1, '213.387']	[4, 1, 1, '86.515']	[3, 1, 1, '5762.879']	[3, 1, 4, '102.301']	[1, 1, 1, '10.314']	[1, 1, 2, '5.858']
TBI_004	[1, 1, 1, '33.269']	[8, 1, 5, '19.483']	[2, 1, 1, '15.142']	[1, 1, 1, '5.331']	[1, 1, 1, '339.517']	[10, 1, 1, '8.337']	[3, 1, 1, '24.703']	[1, 1, 1, '12.050']	[1, 1, 1, '68.348']	[1, 1, 1, '7.550']	[3, 1, 1, '4.856']	[1, 1, 1, '10.030']
TBI_007	[2, 1, 1, '337.225']	[1, 1, 1, '341.530']	[1, 1, 1, '121.113']	[1, 1, 1, '58.863']	[1, 1, 1, '2403.149']	[1, 1, 1, '42.308']	[1, 1, 1, '21.910']	[10, 1, 2, '29.149']	[1, 1, 1, '66.362']	[1, 1, 1, '29.447']	[1, 1, 2, '1.014']	[9, 1, 5, '2.568']
TBI_008	[7, 1, 2, '1230.670']	[6, 1, 7, '640.823']	[1, 1, 1, '292.706']	[1, 1, 1, '170.699']	[8, 1, 1, '3091.271']	[1, 1, 5, '234.704']	[1, 1, 3, '51.200']	[1, 1, 1, '6.116']	[6, 1, 1, '3794.499']	[1, 1, 1, '133.499']	[2, 1, 3, '19.027']	[1, 1, 2, '0.816']
TBI_009	[3, 1, 1, '5942.191']	[3, 1, 1, '2728.697']	[2, 1, 5, '1043.663']	[7, 1, 2, '567.291']	[5, 1, 8, '17479.477']	[2, 1, 5, '198.338']	[2, 1, 3, '37.041']	[4, 1, 4, '77.012']	[3, 1, 5, '4518.618']	[2, 1, 3, '405.306']	[6, 1, 8, '28.212']	[3, 1, 5, '54.206']
TBI_010	[2, 1, 1, '609.152']	[2, 1, 8, '829.657']	[2, 1, 4, '339.936']	[1, 1, 1, '174.663']	[4, 1, 10, '4585.005']	[8, 1, 2, '421.414']	[1, 1, 3, '208.454']	[1, 1, 1, '111.955']	[2, 1, 8, '1342.374']	[2, 1, 4, '123.974']	[1, 1, 1, '106.847']	[2, 1, 3, '67.124']
TBI_011	[9, 1, 2, '2021.678']	[4, 1, 1, '3969.556']	[8, 1, 7, '34.000']	[2, 1, 3, '616.790']	[3, 1, 10, '34337.153']	[5, 1, 5, '1322.034']	[10, 1, 10, '472.085']	[2, 1, 3, '262.872']	[2, 1, 7, '10386.355']	[9, 1, 1, '66.064']	[4, 1, 5, '104.843']	[3, 1, 5, '120.804']
TBI_012	[3, 1, 1, '120.069']	[3, 1, 3, '932.354']	[2, 1, 1, '350.342']	[2, 1, 4, '190.127']	[10, 1, 10, '6289.455']	[3, 1, 4, '170.531']	[1, 1, 3, '99.561']	[1, 1, 1, '57.176']	[3, 1, 4, '615.635']	[1, 1, 1, '34.510']	[6, 1, 3, '57.594']	[2, 1, 3, '41.261']
TBI_013	[3, 1, 1, '704.728']	[1, 1, 1, '285.451']	[2, 1, 1, '129.206']	[10, 1, 4, '61.929']	[2, 1, 4, '1008.086']	[1, 1, 1, '116.816']	[5, 1, 2, '59.733']	[10, 1, 6, '11.389']	[2, 1, 4, '430.580']	[1, 1, 1, '111.659']	[1, 1, 1, '49.679']	[1, 1, 1, '30.654']
TBI_014	[5, 1, 2, '913.826']	[6, 1, 2, '705.939']	[1, 1, 1, '341.638']	[1, 1, 4, '200.105']	[8, 1, 7, '3008.562']	[4, 1, 1, '170.705']	[7, 1, 3, '80.471']	[3, 1, 2, '53.547']	[7, 1, 8, '803.703']	[1, 1, 1, '149.620']	[1, 1, 4, '25.501']	[1, 1, 1, '6.100']
TBI_015	[9, 1, 1, '3613.128']	[4, 1, 10, '3273.361']	[10, 1, 8, '1261.074']	[7, 1, 2, '711.312']	[10, 1, 9, '15518.215']	[6, 1, 7, '887.067']	[10, 1, 9, '464.622']	[2, 1, 8, '316.652']	[9, 1, 9, '2847.042']	[4, 1, 1, '325.832']	[2, 1, 1, '53.187']	[1, 1, 1, '24.501']
TBI_016	[2, 1, 1, '701.730']	[4, 1, 5, '577.298']	[2, 1, 2, '190.466']	[1, 1, 1, '108.708']	[7, 1, 7, '32.000']	[2, 1, 6, '92.695']	[1, 1, 1, '30.722']	[1, 1, 1, '12.994']	[9, 1, 10, '1331.935']	[3, 1, 5, '35.309']	[1, 1, 1, '1.111']	[1, 1, 1, '2.441']

TBI_017	[1, 1, 1, '889.808']	[1, 1, 2, '841.047']	[2, 1, 3, '274.709']	[1, 1, 1, '142.480']	[8, 1, 8, '2882.115']	[5, 1, 6, '-46.309']	[3, 1, 2, '-9.950']	[6, 1, 1, '-11.021']	[9, 1, 10, '-116.108']	[5, 1, 5, '144.457']	[1, 1, 1, '12.939']	[2, 1, 3, '7.099']
TBI_018	[1, 1, 5, '752.011']	[1, 1, 3, '433.669']	[2, 1, 2, '178.075']	[6, 1, 1, '91.705']	[9, 1, 9, '2441.415']	[1, 1, 2, '-13.491']	[1, 1, 1, '8.642']	[1, 1, 1, '7.812']	[3, 1, 4, '-629.140']	[3, 1, 3, '89.550']	[3, 1, 1, '26.384']	[1, 1, 4, '11.223']
TBI_019	[1, 1, 4, '498.112']	[2, 1, 6, '408.893']	[1, 1, 1, '148.683']	[1, 1, 1, '82.831']	[6, 1, 9, '3812.284']	[4, 1, 3, '13.428']	[1, 1, 3, '8.181']	[1, 1, 1, '8.756']	[5, 1, 7, '-287.769']	[8, 1, 7, '18.908']	[2, 1, 2, '-3.921']	[2, 1, 3, '-5.043']
TBI_020	[8, 1, 1, '1784.103']	[8, 1, 3, '4486.602']	[2, 1, 9, '1865.086']	[1, 1, 2, '1012.086']	[8, 1, 3, '28969.156']	[1, 1, 3, '5.157']	[2, 1, 4, '357.707']	[1, 1, 1, '256.960']	[8, 1, 10, '-17023.134']	[3, 1, 1, '-23.169']	[9, 1, 2, '194.386']	[2, 1, 2, '182.112']
TBI_021	[6, 1, 1, '1098.804']	[1, 1, 2, '2075.738']	[3, 1, 4, '862.914']	[1, 1, 3, '477.400']	[9, 1, 10, '9002.559']	[1, 1, 3, '-1094.246']	[1, 1, 2, '-174.995']	[1, 1, 1, '-30.954']	[3, 1, 10, '-13874.873']	[1, 1, 2, '105.751']	[1, 1, 2, '195.491']	[1, 1, 1, '112.378']
TBI_022	[10, 1, 2, '4169.616']	[3, 1, 4, '2732.960']	[6, 1, 8, '1014.211']	[4, 1, 3, '570.046']	[5, 1, 8, '17558.366']	[6, 1, 3, '-1294.473']	[1, 1, 2, '-303.740']	[2, 1, 4, '-117.154']	[8, 1, 8, '-14891.883']	[1, 1, 2, '339.065']	[1, 1, 1, '4.223']	[1, 1, 1, '-54.605']
TBI_023	[2, 1, 1, '1588.588']	[5, 1, 8, '2102.452']	[3, 1, 1, '722.915']	[2, 1, 5, '342.677']	[4, 1, 1, '10881.139']	[2, 1, 2, '286.001']	[3, 1, 8, '109.017']	[7, 1, 10, '51.368']	[3, 1, 5, '-5418.788']	[1, 1, 1, '140.425']	[4, 1, 4, '-45.122']	[4, 1, 3, '-65.264']
TBI_024	[4, 1, 2, '772.025']	[2, 1, 2, '1977.338']	[2, 1, 7, '759.301']	[2, 1, 4, '405.739']	[1, 1, 5, '9235.961']	[3, 1, 7, '213.528']	[4, 1, 8, '193.197']	[2, 1, 4, '94.872']	[6, 1, 8, '-3654.987']	[5, 1, 1, '46.978']	[3, 1, 2, '101.452']	[1, 1, 1, '-52.779']
TBI_025	[5, 1, 4, '813.208']	[5, 1, 7, '673.930']	[1, 1, 1, '246.431']	[1, 1, 1, '128.190']	[7, 1, 1, '536.739']	[2, 1, 1, '-187.712']	[1, 1, 1, '-67.705']	[1, 1, 1, '-45.265']	[2, 1, 3, '-3299.656']	[1, 1, 1, '182.025']	[4, 1, 5, '-2.759']	[1, 1, 1, '-20.589']
TBI_026	[7, 1, 1, '5398.748']	[3, 1, 1, '3079.708']	[4, 1, 10, '1065.744']	[1, 1, 1, '561.883']	[5, 1, 6, '27609.011']	[4, 1, 7, '884.406']	[3, 1, 9, '277.779']	[3, 1, 3, '109.451']	[1, 1, 2, '12092.375']	[2, 1, 1, '282.125']	[2, 1, 3, '-83.756']	[1, 1, 1, '-79.607']
TBI_027	[5, 1, 1, '122.719']	[6, 1, 6, '3432.804']	[6, 1, 9, '1294.061']	[3, 1, 8, '688.991']	[1, 1, 1, '1913.341']	[8, 1, 9, '1810.299']	[5, 1, 5, '757.074']	[1, 1, 1, '417.487']	[5, 1, 5, '24.000']	[3, 1, 2, '46.304']	[1, 1, 1, '-5.930']	[4, 1, 1, '-57.306']
TBI_028	[10, 1, 1, '3115.825']	[6, 1, 5, '2481.023']	[2, 1, 8, '789.797']	[5, 1, 3, '388.397']	[7, 1, 8, '17153.619']	[1, 1, 1, '558.722']	[3, 1, 1, '152.829']	[2, 1, 1, '70.552']	[1, 1, 6, '872.965']	[1, 1, 1, '228.778']	[2, 1, 1, '-3.613']	[2, 1, 4, '-26.064']
TBI_029	[5, 1, 1, '3549.700']	[9, 1, 9, '3676.162']	[7, 1, 5, '1466.528']	[2, 1, 2, '810.891']	[3, 1, 2, '16689.107']	[4, 1, 6, '1817.830']	[7, 1, 4, '763.579']	[2, 1, 4, '467.189']	[2, 1, 10, '11026.043']	[3, 1, 1, '323.412']	[1, 1, 1, '-38.610']	[3, 1, 1, '-57.485']
TBI_030	[1, 1, 1, '689.969']	[2, 1, 5, '1440.883']	[3, 1, 3, '521.747']	[2, 1, 5, '265.548']	[1, 1, 4, '10910.172']	[2, 1, 1, '424.745']	[6, 1, 1, '178.014']	[6, 1, 1, '95.864']	[2, 1, 3, '1378.543']	[1, 1, 1, '125.002']	[1, 1, 1, '-38.493']	[1, 1, 1, '-42.582']
TBI_031	[2, 1, 1, '110.431']	[1, 1, 1, '116.934']	[8, 1, 9, '38.000']	[1, 1, 1, '0.909']	[1, 1, 1, '633.083']	[9, 1, 1, '65.009']	[4, 1, 1, '24.710']	[1, 1, 1, '-5.600']	[1, 1, 3, '133.559']	[10, 1, 1, '12.878']	[1, 1, 1, '4.687']	[1, 1, 1, '-12.100']
TBI_032	[3, 1, 1, '1373.186']	[4, 1, 6, '1243.360']	[10, 1, 5, '448.944']	[1, 1, 5, '229.956']	[10, 1, 9, '8316.565']	[8, 1, 6, '414.222']	[3, 1, 3, '179.034']	[2, 1, 2, '88.697']	[1, 1, 8, '1870.893']	[1, 1, 1, '90.492']	[2, 1, 3, '11.638']	[1, 1, 1, '-14.844']
TBI_033	[1, 1, 3, '1446.406']	[1, 1, 2, '556.279']	[1, 1, 2, '185.070']	[1, 1, 1, '85.864']	[1, 1, 4, '4367.810']	[1, 1, 1, '-196.827']	[1, 1, 6, '-67.299']	[1, 1, 1, '-27.247']	[2, 1, 4, '-1988.852']	[1, 1, 1, '134.205']	[1, 1, 1, '19.728']	[1, 1, 3, '0.756']
TBI_034	[3, 1, 1, '1534.139']	[2, 1, 5, '608.336']	[1, 1, 1, '246.840']	[1, 1, 1, '136.863']	[6, 1, 9, '2876.342']	[2, 1, 1, '-560.840']	[9, 1, 1, '-168.536']	[1, 1, 1, '-77.134']	[6, 1, 6, '-6995.116']	[1, 1, 1, '118.680']	[1, 1, 1, '14.645']	[1, 1, 1, '13.331']
TBI_036	[8, 1, 1, '1070.938']	[5, 1, 7, '6284.400']	[1, 1, 1, '2438.594']	[1, 1, 1, '1340.666']	[10, 1, 10, '29070.777']	[10, 1, 8, '2447.168']	[1, 1, 1, '1382.036']	[1, 1, 4, '838.793']	[10, 1, 10, '-5956.178']	[1, 1, 1, '-40.093']	[1, 1, 1, '233.931']	[1, 1, 1, '128.070']
TBI_037	[6, 1, 1, '2029.214']	[1, 1, 1, '3174.555']	[6, 1, 9, '1047.098']	[4, 1, 6, '548.494']	[1, 1, 9, '26139.197']	[1, 1, 2, '692.762']	[1, 1, 9, '231.005']	[7, 1, 1, '122.810']	[7, 1, 1, '3980.163']	[6, 1, 7, '186.534']	[2, 1, 3, '-50.336']	[1, 1, 1, '-22.760']

TBI_038	[1, 1, 3, '1137.245']	[3, 1, 10, '3651.071']	[2, 1, 5, '1274.656']	[6, 1, 5, '642.687']	[4, 1, 7, '24104.256']	[2, 1, 8, '1418.069']	[1, 1, 1, '563.827']	[6, 1, 5, '272.605']	[1, 1, 10, '6255.177']	[1, 1, 1, '163.865']	[1, 1, 1, '-51.497']	[1, 1, 1, '-89.936']
TBI_039	[8, 1, 1, '1246.661']	[1, 1, 1, '1373.530']	[3, 1, 3, '441.113']	[1, 1, 5, '210.307']	[1, 1, 9, '9913.909']	[1, 1, 2, '461.798']	[3, 1, 3, '117.948']	[1, 1, 1, '45.445']	[1, 1, 4, '2137.736']	[1, 1, 1, '147.763']	[1, 1, 5, '26.651']	[6, 1, 1, '2.691']
TBI_040	[6, 1, 1, '1058.681']	[1, 1, 3, '2388.786']	[1, 1, 1, '928.918']	[4, 1, 2, '447.237']	[1, 1, 5, '17070.922']	[3, 1, 4, '507.213']	[1, 1, 1, '284.378']	[8, 1, 2, '117.861']	[2, 1, 1, '-475.122']	[1, 1, 2, '98.532']	[1, 1, 1, '-51.851']	[1, 1, 1, '-46.974']
TBI_041	[6, 1, 1, '1725.814']	[1, 1, 1, '2322.222']	[1, 1, 1, '887.819']	[2, 1, 2, '490.180']	[6, 1, 8, '15273.113']	[1, 1, 3, '218.837']	[1, 1, 1, '131.967']	[1, 1, 1, '103.582']	[6, 1, 9, '-4903.485']	[3, 1, 1, '215.685']	[1, 1, 4, '-37.146']	[3, 1, 1, '-31.963']
TBI_042	[3, 1, 3, '2374.186']	[1, 1, 1, '1491.790']	[1, 1, 2, '497.446']	[1, 1, 4, '256.675']	[4, 1, 5, '12487.824']	[4, 1, 1, '275.034']	[3, 1, 3, '64.228']	[1, 1, 1, '40.204']	[5, 1, 5, '3175.527']	[2, 1, 3, '229.795']	[2, 1, 7, '7.164']	[1, 1, 1, '-5.512']
TBI_043	[9, 1, 1, '2253.945']	[1, 1, 1, '583.359']	[1, 1, 1, '232.064']	[1, 1, 1, '124.113']	[3, 1, 3, '4389.474']	[1, 1, 1, '-742.371']	[1, 1, 1, '-232.103']	[1, 1, 3, '-113.272']	[3, 1, 4, '-7498.478']	[1, 1, 2, '159.959']	[1, 1, 1, '22.316']	[1, 1, 1, '4.356']
TBI_044	[5, 1, 1, '863.795']	[3, 1, 4, '712.394']	[2, 1, 1, '274.918']	[1, 1, 1, '159.557']	[7, 1, 1, '5306.273']	[2, 1, 1, '165.178']	[2, 1, 1, '116.624']	[1, 1, 1, '72.517']	[5, 1, 2, '-377.611']	[6, 1, 1, '70.514']	[2, 1, 1, '-4.925']	[1, 1, 1, '-1.222']
TBI_045	[3, 1, 1, '1084.027']	[4, 1, 3, '1595.632']	[7, 1, 9, '603.971']	[3, 1, 2, '303.459']	[9, 1, 1, '11149.290']	[2, 1, 1, '125.979']	[3, 1, 7, '126.147']	[1, 1, 1, '65.471']	[10, 1, 3, '-2520.470']	[2, 1, 5, '13.006']	[3, 1, 1, '-52.951']	[1, 1, 1, '-34.911']
TBI_046	[2, 1, 1, '-376.596']	[2, 1, 8, '745.024']	[1, 1, 2, '291.109']	[1, 1, 1, '153.518']	[6, 1, 8, '3834.026']	[2, 1, 10, '340.444']	[1, 1, 4, '161.518']	[1, 1, 2, '85.585']	[4, 1, 1, '-513.709']	[2, 1, 2, '-91.210']	[1, 1, 1, '-80.802']	[4, 1, 1, '-42.388']
TBI_047	[1, 1, 1, '2007.200']	[3, 1, 1, '1124.876']	[1, 1, 1, '414.130']	[1, 1, 3, '209.099']	[3, 1, 7, '8677.843']	[7, 1, 10, '1.010']	[1, 1, 7, '42.471']	[1, 1, 3, '30.669']	[4, 1, 7, '-144.422']	[1, 1, 1, '179.101']	[1, 1, 1, '25.246']	[1, 1, 1, '8.012']
TBI_048	[3, 1, 7, '422.350']	[1, 1, 1, '233.857']	[2, 1, 3, '75.631']	[1, 1, 1, '35.737']	[1, 1, 1, '1613.809']	[1, 1, 2, '-20.787']	[3, 1, 1, '7.269']	[7, 1, 1, '-1.320']	[4, 1, 4, '-316.729']	[3, 1, 2, '43.998']	[8, 1, 2, '5.953']	[5, 1, 6, '-11.224']
TBI_049	[8, 1, 2, '5376.289']	[1, 1, 3, '1656.563']	[5, 1, 1, '590.479']	[4, 1, 2, '326.338']	[9, 1, 1, '12735.921']	[2, 1, 1, '-669.049']	[1, 1, 9, '-206.879']	[1, 1, 8, '-69.388']	[2, 1, 8, '-7883.849']	[1, 1, 2, '436.151']	[3, 1, 3, '55.406']	[1, 1, 1, '22.745']
TBI_050	[5, 1, 1, '944.591']	[2, 1, 4, '543.931']	[5, 1, 2, '177.022']	[10, 1, 1, '74.081']	[1, 1, 6, '4487.034']	[6, 1, 9, '7.473']	[1, 1, 1, '-7.671']	[1, 1, 1, '2.830']	[4, 1, 1, '-258.752']	[2, 1, 4, '75.450']	[2, 1, 1, '-19.339']	[1, 1, 1, '-12.623']
TBI_051	[10, 1, 1, '1667.820']	[2, 1, 2, '779.306']	[1, 1, 1, '325.370']	[2, 1, 1, '186.721']	[1, 1, 1, '4609.700']	[2, 1, 1, '-239.027']	[1, 1, 1, '-43.043']	[1, 1, 1, '-4.290']	[1, 1, 1, '-3481.606']	[1, 1, 2, '129.049']	[1, 1, 1, '40.426']	[1, 1, 2, '15.658']
TBI_052	[5, 1, 1, '1006.793']	[1, 1, 1, '420.971']	[3, 1, 1, '163.236']	[2, 1, 4, '90.520']	[4, 1, 1, '3439.819']	[2, 1, 10, '-111.112']	[2, 1, 6, '-6.848']	[1, 1, 2, '-0.973']	[1, 1, 2, '-412.020']	[1, 1, 1, '120.369']	[1, 1, 1, '33.371']	[1, 1, 1, '16.747']
TBI_053	[10, 1, 1, '1936.359']	[4, 1, 8, '1055.686']	[2, 1, 4, '413.145']	[2, 1, 3, '213.149']	[1, 1, 5, '6752.862']	[8, 1, 10, '-414.364']	[3, 1, 1, '-69.436']	[1, 1, 1, '-35.399']	[9, 1, 5, '-8195.877']	[3, 1, 7, '171.868']	[6, 1, 1, '35.312']	[3, 1, 3, '9.527']
TBI_054	[1, 1, 2, '97.217']	[4, 1, 3, '248.705']	[2, 1, 2, '98.762']	[8, 1, 1, '47.618']	[3, 1, 4, '2007.982']	[2, 1, 2, '-69.739']	[1, 1, 1, '2.627']	[1, 1, 2, '9.658']	[3, 1, 1, '-1096.791']	[2, 1, 3, '-34.805']	[9, 1, 2, '-27.100']	[8, 1, 1, '-17.537']
TBI_055	[3, 1, 6, '3047.808']	[1, 1, 1, '1387.897']	[2, 1, 8, '532.821']	[5, 1, 2, '289.671']	[5, 1, 10, '11484.450']	[1, 1, 4, '-662.759']	[1, 1, 2, '-150.499']	[4, 1, 1, '-56.964']	[1, 1, 10, '-8744.441']	[2, 1, 1, '240.594']	[1, 1, 1, '28.482']	[4, 1, 1, '14.028']
TBI_056	[3, 1, 10, '149.263']	[8, 1, 1, '26.408']	[2, 1, 2, '7.467']	[None, 1, None, 'inf']	[1, 1, 2, '160.266']	[6, 1, 1, '-13.890']	[3, 1, 1, '-7.409']	[None, 1, None, 'inf']	[2, 1, 1, '-138.260']	[9, 1, 1, '17.316']	[2, 1, 1, '-5.010']	[None, 1, None, 'inf']
TBI_057	[1, 1, 4, '226.678']	[9, 1, 9, '7011.416']	[5, 1, 2, '2492.357']	[1, 1, 5, '1296.788']	[1, 1, 10, '47415.546']	[7, 1, 1, '2779.937']	[1, 1, 10, '1061.677']	[2, 1, 6, '588.615']	[3, 1, 10, '14844.050']	[5, 1, 1, '443.905']	[1, 1, 1, '340.513']	[3, 1, 10, '260.502']
TBI_058	[5, 1, 2, '2732.924']	[1, 1, 1, '1432.209']	[5, 1, 5, '570.988']	[2, 1, 4, '308.583']	[3, 1, 3, '10142.468']	[2, 1, 2, '-44.341']	[3, 1, 3, '100.081']	[1, 1, 2, '70.793']	[7, 1, 7, '-2675.763']	[1, 1, 1, '146.171']	[1, 1, 1, '-31.155']	[2, 1, 3, '-28.780']

TBI_059	[1, 1, 2, '901.127']	[2, 1, 2, '383.868']	[9, 1, 2, '173.476']	[8, 1, 1, '101.238']	[3, 1, 2, '2550.066']	[1, 1, 1, '-221.804']	[1, 1, 3, '-80.575']	[1, 1, 2, '-32.740']	[1, 1, 1, '-741.986']	[1, 1, 1, '73.161']	[2, 1, 3, '0.247']	[1, 1, 1, '-6.916']
TBI_060	[5, 1, 1, '1531.158']	[1, 1, 2, '1363.277']	[1, 1, 1, '485.037']	[1, 1, 1, '218.728']	[1, 1, 7, '9299.601']	[1, 1, 5, '471.852']	[1, 1, 1, '188.544']	[1, 1, 1, '84.654']	[6, 1, 1, '1608.989']	[2, 1, 4, '35.108']	[2, 1, 3, '-40.964']	[1, 1, 1, '-37.416']
TBI_061	[1, 1, 4, '924.972']	[3, 1, 2, '258.540']	[1, 1, 1, '90.891']	[2, 1, 3, '50.873']	[2, 1, 1, '2468.625']	[1, 1, 7, '-451.396']	[1, 1, 3, '-131.510']	[1, 1, 1, '-58.715']	[2, 1, 1, '-3542.816']	[2, 1, 1, '84.490']	[1, 1, 1, '22.054']	[6, 1, 1, '16.638']
TBI_062	[3, 1, 4, '840.774']	[1, 1, 1, '401.476']	[1, 1, 1, '144.057']	[10, 1, 5, '59.231']	[3, 1, 6, '2105.820']	[3, 1, 7, '19.553']	[1, 1, 5, '2.998']	[3, 1, 1, '5.310']	[9, 1, 7, '-1379.051']	[3, 1, 3, '88.883']	[1, 1, 3, '16.904']	[6, 1, 1, '13.276']
TBI_063	[6, 1, 1, '1464.237']	[1, 1, 1, '1489.315']	[3, 1, 4, '475.502']	[2, 1, 3, '249.235']	[6, 1, 1, '8515.205']	[1, 1, 2, '35.883']	[8, 1, 1, '21.126']	[1, 1, 2, '20.784']	[5, 1, 1, '-1578.509']	[2, 1, 2, '40.785']	[5, 1, 6, '-59.043']	[4, 1, 10, '-64.118']
TBI_064	[9, 1, 1, '813.256']	[1, 1, 1, '274.303']	[1, 1, 1, '101.098']	[9, 1, 4, '45.068']	[5, 1, 1, '2593.017']	[2, 1, 2, '-79.875']	[2, 1, 2, '-15.617']	[6, 1, 2, '-1.653']	[1, 1, 1, '-724.017']	[1, 1, 1, '76.839']	[1, 1, 1, '30.018']	[1, 1, 1, '13.842']
TBI_065	[6, 1, 1, '439.493']	[1, 1, 2, '465.404']	[2, 1, 2, '170.347']	[1, 1, 2, '83.113']	[6, 1, 3, '3353.609']	[1, 1, 1, '120.083']	[1, 1, 2, '57.380']	[9, 1, 1, '24.896']	[10, 1, 7, '-13.545']	[1, 1, 1, '10.605']	[5, 1, 4, '-22.987']	[2, 1, 2, '-22.768']
TBI_066	[8, 1, 1, '2979.779']	[4, 1, 3, '1368.894']	[3, 1, 3, '531.940']	[10, 1, 2, '28.000']	[5, 1, 2, '9401.210']	[2, 1, 1, '-896.379']	[2, 1, 3, '-243.850']	[3, 1, 2, '-102.689']	[7, 1, 2, '-11537.109']	[1, 1, 1, '150.551']	[1, 1, 1, '-66.236']	[1, 1, 1, '-63.698']
TBI_067	[4, 1, 4, '384.851']	[7, 1, 1, '385.927']	[3, 1, 2, '133.193']	[2, 1, 2, '78.913']	[8, 1, 10, '3470.167']	[2, 1, 10, '158.461']	[1, 1, 3, '82.468']	[6, 1, 1, '51.740']	[2, 1, 5, '340.122']	[1, 1, 1, '33.999']	[2, 1, 1, '0.999']	[1, 1, 2, '-4.503']
TBI_068	[4, 1, 6, '3658.594']	[1, 1, 1, '1229.778']	[1, 1, 2, '436.566']	[2, 1, 1, '263.000']	[3, 1, 1, '11219.746']	[1, 1, 3, '-217.419']	[4, 1, 4, '-0.259']	[3, 1, 2, '13.244']	[5, 1, 1, '-6317.538']	[3, 1, 3, '296.879']	[1, 1, 1, '-1.660']	[2, 1, 1, '-32.790']
TBI_069	[9, 1, 1, '1746.409']	[3, 1, 4, '4544.290']	[9, 1, 8, '38.000']	[1, 1, 1, '753.053']	[1, 1, 3, '36583.517']	[1, 1, 2, '1296.419']	[4, 1, 7, '514.515']	[7, 1, 7, '305.057']	[5, 1, 1, '4522.254']	[10, 1, 1, '15.428']	[2, 1, 9, '139.607']	[1, 1, 4, '129.456']
TBI_070	[5, 1, 1, '371.028']	[1, 1, 4, '126.313']	[9, 1, 4, '55.252']	[5, 1, 2, '25.958']	[5, 1, 5, '866.349']	[1, 1, 1, '-26.652']	[1, 1, 1, '-4.945']	[5, 1, 1, '4.785']	[1, 1, 3, '-282.991']	[2, 1, 1, '49.412']	[1, 1, 1, '19.752']	[7, 1, 2, '12.056']
TBI_071	[9, 1, 2, '38.752']	[7, 1, 4, '6316.318']	[3, 1, 4, '2280.672']	[1, 1, 1, '1201.920']	[1, 1, 8, '44941.599']	[2, 1, 2, '2622.449']	[2, 1, 5, '1233.442']	[3, 1, 3, '717.558']	[8, 1, 3, '2079.592']	[1, 1, 1, '-38.552']	[1, 1, 10, '347.219']	[1, 1, 1, '249.390']
TBI_072	[2, 1, 1, '701.818']	[7, 1, 9, '36.000']	[1, 1, 1, '233.732']	[1, 1, 1, '119.949']	[1, 1, 2, '3653.861']	[6, 1, 9, '288.003']	[2, 1, 3, '128.512']	[1, 1, 1, '75.537']	[8, 1, 10, '1476.957']	[3, 1, 1, '75.470']	[2, 1, 1, '-7.223']	[3, 1, 1, '-2.434']
TBI_073	[8, 1, 3, '6044.737']	[2, 1, 3, '5265.377']	[8, 1, 9, '1972.521']	[1, 1, 1, '1102.534']	[1, 1, 9, '31152.953']	[3, 1, 5, '-1026.621']	[7, 1, 1, '163.573']	[5, 1, 1, '226.264']	[1, 1, 1, '-19788.132']	[1, 1, 1, '602.585']	[4, 1, 3, '-41.957']	[5, 1, 3, '-96.271']
TBI_074	[5, 1, 3, '2033.327']	[1, 1, 2, '2353.766']	[1, 1, 1, '658.238']	[1, 1, 1, '365.060']	[3, 1, 2, '9292.142']	[6, 1, 10, '-38.469']	[2, 1, 2, '-1.884']	[1, 1, 1, '7.819']	[9, 1, 1, '1484.169']	[1, 1, 1, '72.476']	[4, 1, 7, '-44.283']	[1, 1, 3, '-41.262']
TBI_075	[10, 1, 9, '1006.698']	[8, 1, 10, '40.000']	[1, 1, 1, '447.754']	[1, 1, 1, '254.442']	[2, 1, 8, '7379.604']	[3, 1, 6, '244.269']	[2, 1, 1, '110.424']	[1, 1, 1, '63.610']	[1, 1, 2, '1187.449']	[3, 1, 3, '93.193']	[1, 1, 1, '19.821']	[2, 1, 4, '16.645']
TBI_076	[6, 1, 1, '2015.329']	[1, 1, 2, '3795.065']	[5, 1, 5, '1281.480']	[3, 1, 6, '657.078']	[2, 1, 9, '32735.636']	[6, 1, 5, '668.983']	[6, 1, 3, '223.408']	[1, 1, 3, '113.712']	[4, 1, 1, '7345.278']	[3, 1, 1, '37.733']	[2, 1, 1, '171.251']	[1, 1, 1, '154.354']
TBI_077	[2, 1, 1, '2091.058']	[1, 1, 1, '2098.357']	[4, 1, 6, '694.607']	[2, 1, 1, '347.893']	[1, 1, 8, '16326.011']	[3, 1, 3, '643.225']	[1, 1, 2, '193.850']	[2, 1, 4, '88.605']	[9, 1, 1, '3221.436']	[3, 1, 1, '119.313']	[4, 1, 2, '-75.504']	[1, 1, 10, '-38.655']
TBI_078	[3, 1, 1, '1499.557']	[1, 1, 1, '561.375']	[2, 1, 4, '208.265']	[1, 1, 2, '113.232']	[4, 1, 1, '3817.208']	[3, 1, 9, '-312.053']	[2, 1, 6, '-56.841']	[2, 1, 2, '-9.575']	[2, 1, 1, '-4448.552']	[1, 1, 1, '131.781']	[1, 1, 3, '-3.660']	[2, 1, 2, '-12.584']

TBI_079	[9, 1, 3, '499.800']	[1, 1, 1, '989.121']	[2, 1, 3, '313.918']	[2, 1, 2, '149.683']	[4, 1, 5, '8679.081']	[1, 1, 1, '140.132']	[1, 1, 1, '78.511']	[2, 1, 1, '56.192']	[2, 1, 1, '-36.576']	[4, 1, 1, '37.465']	[3, 1, 4, '-45.035']	[2, 1, 2, '-54.737']
TBI_080	[8, 1, 1, '8519.552']	[3, 1, 1, '2914.104']	[8, 1, 2, '1121.896']	[3, 1, 4, '621.151']	[1, 1, 9, '23574.334']	[1, 1, 1, '-1450.861']	[1, 1, 1, '-513.780']	[1, 1, 1, '-215.740']	[8, 1, 2, '-9852.278']	[1, 1, 2, '532.785']	[1, 1, 1, '-6.488']	[3, 1, 1, '-65.627']
TBI_081	[6, 1, 2, '-192.512']	[8, 1, 8, '5232.541']	[5, 1, 6, '1827.975']	[3, 1, 1, '900.265']	[8, 1, 9, '41173.806']	[3, 1, 4, '1931.642']	[3, 1, 3, '771.634']	[1, 1, 1, '385.392']	[7, 1, 8, '3577.089']	[1, 1, 1, '49.576']	[1, 1, 1, '249.189']	[2, 1, 3, '201.320']
TBI_082	[6, 1, 7, '30.000']	[2, 1, 2, '324.380']	[1, 1, 1, '121.923']	[9, 1, 1, '72.337']	[2, 1, 1, '2085.297']	[1, 1, 3, '-106.536']	[1, 1, 1, '-21.566']	[10, 1, 5, '-15.568']	[1, 1, 1, '-902.423']	[1, 1, 1, '76.542']	[1, 1, 3, '-0.877']	[2, 1, 1, '-2.428']
TBI_083	[8, 1, 3, '1950.808']	[4, 1, 4, '615.931']	[6, 1, 3, '22.000']	[1, 1, 1, '94.761']	[1, 1, 3, '4618.665']	[1, 1, 1, '-480.234']	[1, 1, 1, '-177.361']	[1, 1, 1, '-83.381']	[3, 1, 1, '-3100.572']	[1, 1, 6, '182.994']	[2, 1, 1, '45.060']	[1, 1, 1, '5.575']
TBI_084	[9, 1, 3, '2452.702']	[1, 1, 1, '254.656']	[3, 1, 3, '160.261']	[7, 1, 4, '26.000']	[1, 1, 3, '992.612']	[1, 1, 1, '-724.082']	[7, 1, 1, '-277.703']	[2, 1, 1, '-150.735']	[2, 1, 1, '-5710.491']	[1, 1, 1, '227.432']	[1, 1, 1, '38.168']	[1, 1, 7, '-13.910']
TBI_085	[2, 1, 1, '1617.882']	[9, 1, 8, '3805.534']	[8, 1, 3, '1284.198']	[2, 1, 1, '639.988']	[1, 1, 6, '32483.590']	[8, 1, 7, '282.638']	[1, 1, 5, '273.116']	[1, 1, 3, '156.721']	[8, 1, 9, '-1157.248']	[1, 1, 1, '-56.330']	[1, 1, 2, '220.808']	[1, 1, 1, '154.243']
TBI_086	[8, 1, 1, '3759.659']	[4, 1, 9, '4333.346']	[3, 1, 4, '1525.961']	[3, 1, 2, '733.449']	[7, 1, 3, '30851.610']	[4, 1, 1, '43.771']	[2, 1, 3, '84.952']	[4, 1, 2, '-2.803']	[10, 1, 1, '-7510.855']	[1, 1, 2, '148.433']	[3, 1, 1, '142.687']	[3, 1, 2, '154.657']
TBI_087	[8, 1, 1, '3330.323']	[1, 1, 2, '2362.099']	[2, 1, 1, '1097.819']	[1, 1, 2, '649.338']	[3, 1, 7, '15117.197']	[4, 1, 2, '-1591.208']	[2, 1, 1, '-348.556']	[1, 1, 6, '-92.731']	[3, 1, 3, '-16709.147']	[1, 1, 1, '99.391']	[1, 1, 1, '141.305']	[1, 1, 3, '131.817']
TBI_088	[8, 1, 2, '-3676.644']	[3, 1, 4, '5733.186']	[3, 1, 3, '1977.226']	[2, 1, 1, '964.577']	[1, 1, 8, '47020.336']	[7, 1, 1, '1185.601']	[3, 1, 5, '477.970']	[1, 1, 1, '233.392']	[10, 1, 2, '1892.864']	[1, 1, 1, '-719.332']	[5, 1, 1, '385.957']	[2, 1, 1, '386.385']
TBI_089	[3, 1, 1, '5410.816']	[1, 1, 2, '2767.672']	[3, 1, 3, '830.000']	[4, 1, 4, '499.134']	[1, 1, 2, '26948.639']	[1, 1, 1, '-898.413']	[3, 1, 3, '-143.604']	[1, 1, 2, '-26.113']	[6, 1, 1, '-7917.505']	[1, 1, 1, '361.620']	[1, 1, 2, '-24.255']	[2, 1, 10, '-63.433']
TBI_090	[1, 1, 2, '1496.104']	[2, 1, 7, '2391.440']	[5, 1, 2, '876.949']	[1, 1, 1, '473.946']	[4, 1, 8, '20812.777']	[7, 1, 3, '605.383']	[3, 1, 2, '270.077']	[2, 1, 2, '171.229']	[7, 1, 3, '1453.419']	[1, 1, 1, '212.776']	[2, 1, 3, '-36.092']	[3, 1, 8, '-52.744']
TBI_091	[8, 1, 2, '-4326.074']	[7, 1, 2, '6128.983']	[1, 1, 6, '2341.587']	[6, 1, 2, '1206.340']	[8, 1, 5, '45969.072']	[5, 1, 7, '2342.235']	[7, 1, 2, '1126.075']	[1, 1, 1, '621.492']	[4, 1, 8, '9385.585']	[6, 1, 8, '-668.544']	[3, 1, 3, '487.607']	[2, 1, 2, '315.631']
TBI_092	[10, 1, 1, '2866.928']	[1, 1, 5, '3760.560']	[5, 1, 4, '1400.699']	[3, 1, 3, '733.603']	[7, 1, 4, '32217.740']	[3, 1, 4, '1543.450']	[1, 1, 3, '685.049']	[2, 1, 4, '393.198']	[3, 1, 5, '5891.441']	[7, 1, 2, '261.090']	[3, 1, 2, '17.611']	[1, 1, 1, '-56.554']
TBI_093	[10, 1, 1, '3214.846']	[1, 1, 2, '5118.541']	[1, 1, 1, '1505.439']	[1, 1, 1, '757.552']	[2, 1, 6, '46132.657']	[3, 1, 1, '1003.610']	[5, 1, 5, '24.000']	[1, 1, 4, '180.726']	[3, 1, 10, '10307.165']	[1, 1, 2, '279.230']	[2, 1, 2, '-66.665']	[3, 1, 3, '-68.089']
TBI_094	[5, 1, 1, '1137.523']	[6, 1, 6, '394.269']	[4, 1, 2, '123.858']	[2, 1, 1, '65.781']	[7, 1, 3, '3598.210']	[1, 1, 1, '54.721']	[3, 1, 2, '-7.700']	[1, 1, 1, '-1.032']	[1, 1, 3, '1028.863']	[1, 1, 1, '127.756']	[2, 1, 3, '7.444']	[1, 1, 1, '-6.719']
TBI_095	[1, 1, 2, '772.852']	[1, 1, 1, '2364.346']	[3, 1, 1, '910.020']	[1, 1, 2, '520.535']	[10, 1, 4, '20958.908']	[1, 1, 3, '126.146']	[9, 1, 6, '34.000']	[2, 1, 10, '91.484']	[10, 1, 2, '-1725.344']	[4, 1, 9, '9.800']	[1, 1, 1, '138.419']	[1, 1, 1, '117.862']
TBI_096	[1, 1, 8, '176.761']	[1, 1, 1, '96.413']	[5, 1, 1, '16.524']	[2, 1, 2, '6.240']	[4, 1, 4, '714.264']	[1, 1, 2, '34.204']	[5, 1, 1, '-11.838']	[5, 1, 1, '-5.110']	[1, 1, 1, '119.360']	[1, 1, 4, '4.547']	[6, 1, 2, '-21.070']	[2, 1, 1, '-4.530']

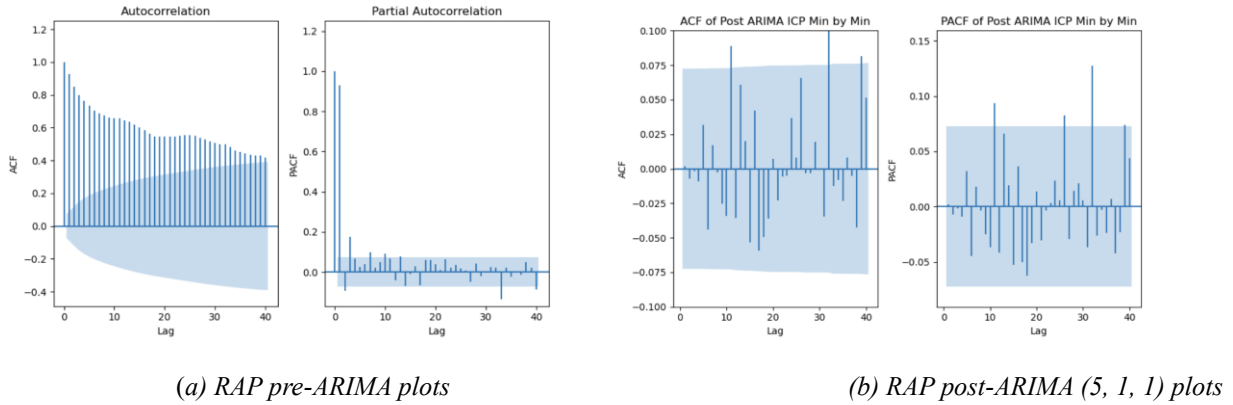
TBI_097	[1, 1, 3, '1772.148']	[2, 1, 7, '539.291']	[2, 1, 3, '254.764']	[5, 1, 7, '155.859']	[1, 1, 7, '2955.267']	[3, 1, 3, '-861.808']	[1, 1, 1, '-208.121']	[1, 1, 1, '-77.235']	[1, 1, 1, '-8073.485']	[2, 1, 1, '164.963']	[1, 1, 1, '-8.749']	[1, 1, 4, '-11.313']
TBI_098	[8, 1, 2, '3516.109']	[1, 1, 2, '1453.918']	[2, 1, 2, '495.557']	[3, 1, 3, '271.226']	[2, 1, 9, '7701.261']	[9, 1, 6, '-722.735']	[2, 1, 6, '-292.401']	[1, 1, 6, '-156.646']	[6, 1, 4, '-7365.467']	[3, 1, 1, '291.945']	[2, 1, 2, '7.306']	[5, 1, 5, '-6.385']
TBI_099	[10, 1, 1, '4428.079']	[4, 1, 6, '1044.266']	[2, 1, 4, '381.526']	[1, 1, 1, '201.112']	[2, 1, 3, '7677.228']	[5, 1, 5, '-1355.549']	[7, 1, 5, '-465.568']	[2, 1, 2, '-207.105']	[9, 1, 3, '-13088.411']	[4, 1, 4, '28.276']	[2, 1, 1, '-31.254']	[1, 1, 1, '-30.302']
TBI_100	[5, 1, 1, '-888.900']	[5, 1, 1, '5978.417']	[2, 1, 10, '2357.758']	[6, 1, 9, '1231.232']	[3, 1, 10, '35412.892']	[2, 1, 9, '2860.168']	[4, 1, 10, '1285.253']	[6, 1, 9, '671.428']	[3, 1, 9, '4643.162']	[4, 1, 6, '-204.319']	[3, 1, 1, '229.001']	[1, 1, 2, '229.658']
TBI_101	[3, 1, 1, '887.794']	[8, 1, 6, '32.000']	[2, 1, 2, '257.635']	[1, 1, 1, '146.425']	[1, 1, 2, '3901.882']	[1, 1, 3, '135.282']	[1, 1, 6, '60.055']	[1, 1, 3, '51.528']	[7, 1, 10, '731.290']	[1, 1, 2, '55.751']	[1, 1, 1, '3.045']	[1, 1, 1, '-9.219']
TBI_102	[4, 1, 2, '2788.047']	[1, 1, 1, '1168.088']	[1, 1, 1, '390.724']	[1, 1, 2, '219.561']	[1, 1, 6, '10221.411']	[6, 1, 2, '409.388']	[1, 1, 1, '211.116']	[2, 1, 1, '124.576']	[3, 1, 5, '4170.125']	[7, 1, 1, '166.367']	[1, 1, 3, '1.027']	[1, 1, 1, '-14.126']
TBI_103	[8, 1, 2, '2542.697']	[8, 1, 8, '8422.112']	[9, 1, 3, '2832.935']	[4, 1, 2, '1384.877']	[10, 1, 1, '59606.024']	[1, 1, 9, '4707.190']	[7, 1, 5, '1614.544']	[3, 1, 1, '791.598']	[10, 1, 1, '27946.372']	[6, 1, 2, '55.531']	[2, 1, 1, '193.827']	[1, 1, 1, '193.076']
TBI_104	[4, 1, 2, '3715.331']	[7, 1, 10, '1789.902']	[3, 1, 3, '601.941']	[1, 1, 1, '337.912']	[1, 1, 4, '16471.188']	[1, 1, 1, '486.303']	[1, 1, 2, '80.663']	[2, 1, 2, '22.752']	[9, 1, 1, '7244.001']	[1, 1, 2, '242.016']	[1, 1, 2, '1.158']	[1, 1, 1, '-14.056']
TBI_105	[6, 1, 1, '2386.668']	[1, 1, 2, '1976.162']	[3, 1, 3, '770.934']	[1, 1, 1, '374.930']	[1, 1, 8, '13743.443']	[1, 1, 2, '737.405']	[1, 1, 2, '359.042']	[2, 1, 3, '184.929']	[3, 1, 2, '14.000']	[1, 1, 1, '204.868']	[1, 1, 1, '-3.069']	[5, 1, 2, '-31.658']
TBI_106	[7, 1, 1, '5618.687']	[3, 1, 5, '1840.146']	[9, 1, 2, '696.184']	[3, 1, 5, '330.181']	[1, 1, 9, '16364.647']	[8, 1, 9, '-964.441']	[2, 1, 1, '-407.916']	[3, 1, 1, '-209.424']	[4, 1, 1, '-2092.997']	[1, 1, 1, '458.617']	[2, 1, 1, '30.024']	[1, 1, 5, '-16.150']
TBI_107	[10, 1, 1, '6173.907']	[5, 1, 6, '1661.255']	[2, 1, 4, '574.528']	[1, 1, 1, '318.744']	[1, 1, 6, '14679.800']	[5, 1, 1, '-602.737']	[2, 1, 1, '-215.790']	[1, 1, 1, '-105.277']	[8, 1, 1, '-466.665']	[1, 1, 1, '545.032']	[1, 1, 1, '86.081']	[1, 1, 1, '11.488']
TBI_108	[1, 1, 3, '2004.242']	[1, 1, 1, '648.972']	[1, 1, 1, '266.534']	[1, 1, 3, '140.861']	[2, 1, 8, '5369.098']	[1, 1, 1, '-625.873']	[3, 1, 3, '-153.625']	[1, 1, 1, '-72.004']	[1, 1, 1, '-5104.216']	[2, 1, 1, '96.404']	[1, 1, 1, '-25.264']	[1, 1, 1, '-32.791']
TBI_109	[6, 1, 3, '276.721']	[1, 1, 1, '335.184']	[10, 1, 2, '107.985']	[8, 1, 4, '45.989']	[1, 1, 8, '771.134']	[3, 1, 3, '14.186']	[1, 1, 1, '22.349']	[1, 1, 1, '13.994']	[3, 1, 3, '-79.196']	[1, 1, 6, '55.569']	[1, 1, 1, '7.995']	[6, 1, 1, '-5.137']
TBI_110	[6, 1, 6, '4470.392']	[4, 1, 8, '2406.468']	[8, 1, 9, '812.468']	[5, 1, 5, '440.770']	[1, 1, 7, '18946.739']	[6, 1, 5, '369.640']	[2, 1, 10, '94.481']	[3, 1, 1, '59.186']	[8, 1, 1, '917.587']	[1, 1, 2, '367.743']	[1, 1, 5, '-35.338']	[3, 1, 4, '-65.701']
TBI_111	[5, 1, 1, '-884.091']	[5, 1, 1, '3183.328']	[1, 1, 1, '1111.862']	[1, 1, 1, '574.672']	[8, 1, 2, '16406.020']	[5, 1, 1, '1905.199']	[1, 1, 1, '702.719']	[5, 1, 5, '359.829']	[3, 1, 9, '6931.459']	[1, 1, 1, '-224.253']	[1, 1, 1, '191.500']	[1, 1, 1, '121.690']
TBI_112	[5, 1, 1, '1860.804']	[2, 1, 7, '1897.303']	[5, 1, 3, '838.261']	[2, 1, 6, '485.937']	[9, 1, 6, '8815.433']	[9, 1, 10, '-324.208']	[4, 1, 1, '81.606']	[1, 1, 2, '77.601']	[5, 1, 7, '-9640.931']	[3, 1, 1, '58.025']	[1, 1, 2, '-87.276']	[1, 1, 3, '-78.763']

Appendix D. Section 4.3.3: Residuals, ACF, and PACF plots of residuals and analysis

This appendix contains the figures and tables for the evaluation of the median optimal ARIMA models. Included are comparative ACF/PACF plots of the residuals (original vs. post-ARIMA) for a single patient's ICP and AMP data at both minute-by-minute and hour-by-hour resolutions. Additionally, the variance of the overall data, the residual variance, and the count of significant spikes are provided both an individual patient and a summary of the entire population to demonstrate effective data modeling.

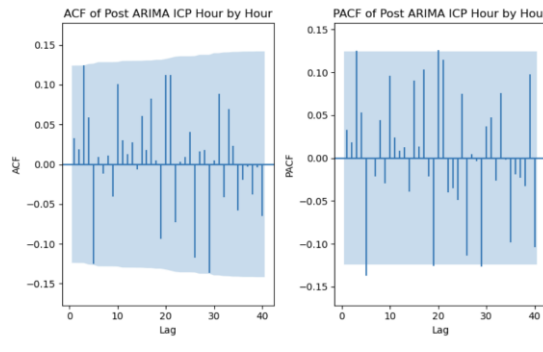
ACF, autocorrelative function; AMP, pulse amplitude of ICP; ARIMA, auto-regressive integrated moving average; ICP, intracranial pressure; PACF, partial ACF; RAP, compensatory reserve index.

Figure D.1 ACF and PACF plots for ICP at minute-by-minute resolution for Individual



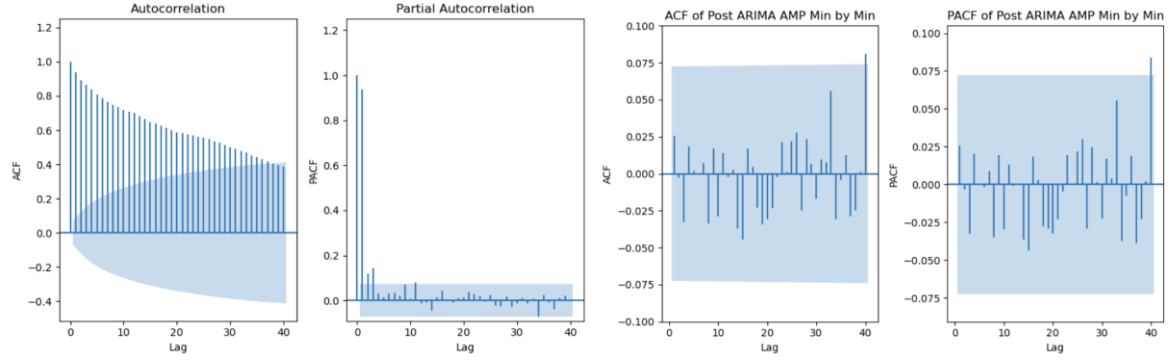
The figure corresponds to the ACF and PACF plots of residuals of the ICP signal (a) before and (b) after ARIMA (5, 1, 1), demonstrating that the model moderately accounts for the ICP structure.

Figure D.2 ACF and PACF plots for ICP at hour-by-hour resolution for individual



The figure documents the ACF and PACF of the residuals of ICP-mapped ARIMA (2, 1, 2) structure in the hour-by-hour relationship

Figure D.3 ACF and PACF plots for AMP at minute-by-minute resolution for whole population

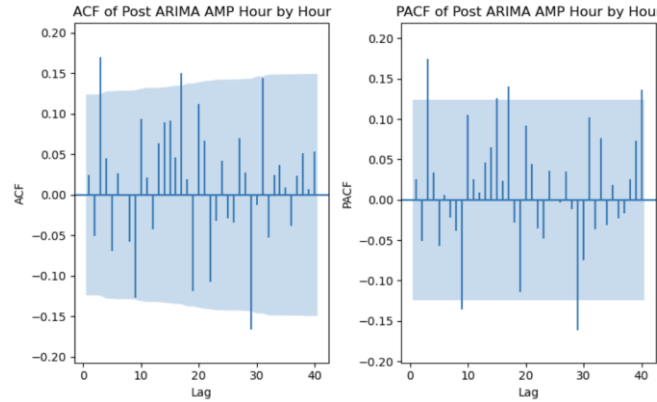


a) AMP pre-ARIMA plots

(b) AMP post-ARIMA (3, 1, 5) plots

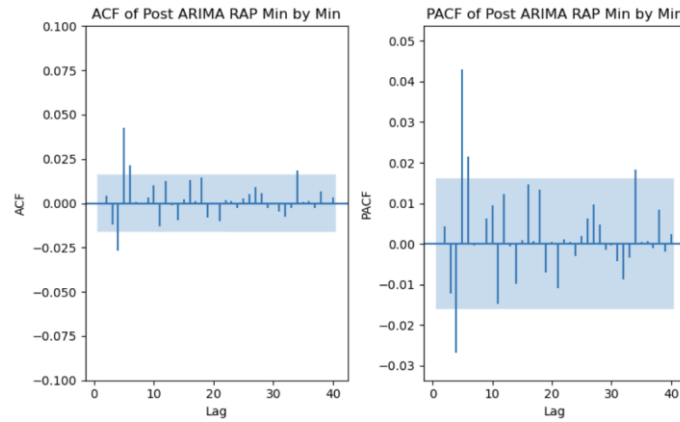
The figure corresponds to the ACF and PACF plots of residuals of the AMP signal (a) before and (b) after ARIMA (3, 1, 5), demonstrating that the model moderately accounts for the AMP structure.

Figure D.4 ACF and PACF plots for AMP at hour-by-hour resolution for whole population



The figure documents the ACF and PACF of the residuals of AMP-mapped ARIMA (1, 1, 1) structure in the hour-by-hour relationship

Figure D.5 ACF/PACF plots for TBI_071 patient at minute-by-minute resolution



The figure documents the ACF and PACF of the residuals of RAP-mapped AMIRA structure at the minute-by-minute resolution for a particular patient.

Table D.1 Summary of Data Variance, Residual Variance, and Significant Spike Counts (single patient at minute-by-minute resolution)

Var data	Var model res	ACF org spikes	PACF org spikes	ACF model spikes	PACF model spikes
0.094394	0.067213	7	2	1	1

Table D.2 Summary of Data Variance, Residual Variance, and Significant Spike Counts (single patient at hour-by-hour resolution)

Var data	Var model res	ACF org spikes	PACF org spikes	ACF model spikes	PACF model spikes
0.022591	0.026622	5	4	0	0

Table D.3 Summary of Data Variance, Residual Variance, and Significant Spike Counts (all patients at minute-by-minute resolution for ICP)

Patient	Var data	Var model res	ACF org spikes	PACF org spikes	ACF model spikes	PACF model spikes
TBI 001	25.48364436	3.63261979	40	10	6	6
TBI 002	25.99239918	3.778211379	40	10	3	4
TBI 003	5.832911742	0.356290631	40	6	3	3
TBI 004	1.54749846	2.001749317	6	7	0	1
TBI 007	22.17284736	3.71386495	40	2	0	0
TBI 008	22.45823401	0.697897216	40	3	2	2
TBI 009	23.04243095	0.596444037	40	12	7	7
TBI 010	29.64771327	0.891392079	40	11	8	7
TBI 011	22.05212994	4.220736902	40	25	4	4
TBI 012	8.013360239	1.38645657	40	9	5	5
TBI 013	11.92649002	1.011265432	40	5	0	0
TBI 014	206.3275595	0.610974052	40	3	1	1
TBI 015	29.38595765	1.487679455	40	8	3	6
TBI 016	28.67873462	3.962485758	40	11	2	3
TBI 017	4.884287991	1.247570184	40	9	5	5
TBI 018	30.26943771	0.710362582	40	9	2	2
TBI 019	64.84611485	3.392462708	40	13	4	7
TBI 020	34.66444142	0.812315036	40	10	8	7
TBI 021	12.99958649	0.304253507	40	8	8	10
TBI 022	41.26722995	0.78598675	40	16	4	4
TBI 023	8.39310931	0.96030019	40	6	0	0
TBI 024	9.937736888	0.737050098	40	6	0	0
TBI 025	5.6131576	0.131189605	40	5	1	1
TBI 026	13.6038047	3.197814484	40	16	3	3
TBI 027	218.8180735	11.78564682	33	2	0	0
TBI 028	44.69377387	3.839957714	40	9	8	13
TBI 029	153.6065005	2.604778911	40	11	5	5
TBI 030	17.70042196	1.864784494	40	5	1	1
TBI 031	147.8990394	3.600599954	19	14	0	1
TBI 032	123.15142	4.647488278	40	11	4	5
TBI 033	6.812439381	1.480322155	40	4	0	0
TBI 034	5.133167901	0.410004545	40	6	5	4
TBI 036	23.65478526	1.112019449	40	21	16	18
TBI 037	26.11314189	4.098089686	40	15	3	3
TBI 038	30.29076485	2.577853074	40	13	7	12
TBI 039	13.49696824	2.099302804	40	7	1	1
TBI 040	18.745057	1.784692725	40	17	0	0
TBI 041	11.31047671	1.123032534	40	14	7	7
TBI 042	24.22023835	4.499294917	40	9	4	4
TBI 043	2.586822103	0.35153109	40	11	2	2
TBI 044	35.55668495	1.533421164	40	4	1	1
TBI 045	18.5711965	1.337769803	40	8	5	5
TBI 046	47.47698993	1.477596291	40	6	0	0
TBI 047	25.41274556	2.654093577	40	9	3	4
TBI 048	41.20398957	2.262642035	40	6	1	3

TBI 049	6.126654845	0.713296488	40	13	4	3
TBI 050	7.785341194	2.311403027	37	5	4	4
TBI 051	139.8629741	1.426159636	40	3	1	1
TBI 052	33.71746377	1.110466773	40	9	0	0
TBI 053	10.76379679	0.356262064	40	11	3	3
TBI 054	7.084499918	0.976554498	40	8	3	4
TBI 055	10.90634253	1.650016163	40	13	4	5
TBI 056	0.804043501	0.891392712	3	3	0	0
TBI 057	48.87681393	2.8263661	40	16	2	2
TBI 058	16.03008498	0.809140693	40	9	3	3
TBI 059	10.0463926	0.446258303	40	5	0	0
TBI 060	21.93151746	2.3508094	39	4	0	0
TBI 061	1.574957371	0.460113272	40	7	0	0
TBI 062	21.71215414	0.904106032	40	9	4	5
TBI 063	7.333539552	1.204839187	40	10	3	3
TBI 064	8.221775923	2.506947257	40	10	2	3
TBI 065	14.54504238	1.197050539	40	11	3	4
TBI 066	8.034627278	0.383159191	40	13	5	6
TBI 067	5.070425724	1.817565311	40	6	2	2
TBI 068	6.864396674	0.848308599	40	14	0	0
TBI 069	35.0070712	5.026144838	40	22	0	0
TBI 070	48.96745992	1.081846427	40	2	0	0
TBI 071	15.38350768	1.259515207	40	12	4	3
TBI 072	47.61696074	1.285824876	40	6	4	5
TBI 073	11.84341251	0.814264356	40	13	3	3
TBI 074	10.06801951	1.190310723	40	9	1	2
TBI 075	37.67464427	4.419093731	40	5	2	2
TBI 076	25.36052945	3.646337932	40	21	6	4
TBI 077	21.07924879	3.761648412	40	7	3	2
TBI 078	10.01677573	1.160522021	40	6	1	1
TBI 079	13.38632912	1.168007936	40	21	2	2
TBI 080	12.18723944	1.092091969	40	15	1	1
TBI 081	25.36549213	3.134550556	40	16	6	7
TBI 082	18.58540624	0.866971965	40	5	0	0
TBI 083	6.191120424	0.522826621	40	8	0	0
TBI 084	2.633460518	0.084481815	40	8	1	1
TBI 085	21.4099627	2.655752348	40	17	4	4
TBI 086	18.14679215	1.561314381	40	12	2	2
TBI 087	17.38688637	0.275156772	40	8	0	0
TBI 088	13.49917336	2.496028662	40	11	5	4
TBI 089	11.29641513	2.409699601	40	17	0	0
TBI 090	33.01801939	2.613315144	40	12	3	3
TBI 091	53.72778243	3.253103561	40	18	11	10
TBI 092	31.4890452	3.335741747	40	12	4	4
TBI 093	44.3391171	13.77693402	40	14	3	5
TBI 094	5.349989672	1.557513561	40	12	1	1
TBI 095	17.53414062	2.005922702	40	11	6	6
TBI 096	4.949354682	5.212009008	2	2	0	1
TBI 097	3.614231929	0.188247537	40	10	0	2
TBI 098	5.924771008	0.363675998	40	8	0	0
TBI 099	2.475207307	0.268928986	40	17	1	1
TBI 100	89.16902401	1.661882098	40	8	5	4
TBI 101	87.41789332	1.418430854	40	5	0	0
TBI 102	14.0938089	1.427338644	40	14	4	3
TBI 103	45.75361448	3.819852429	40	9	4	4
TBI 104	20.5961258	2.816142324	40	13	0	1
TBI 105	50.47620147	1.197399697	40	10	4	5
TBI 106	4.879338329	0.657268511	40	18	2	2
TBI 107	40.24937834	0.962644128	40	18	3	3

TBI 108	2.319360483	0.353460811	40	10	0	1
TBI 109	8.947088338	1.604656406	16	6	1	5
TBI 110	8.727249953	1.257566832	40	16	0	0
TBI 111	62.13325546	5.096635243	40	6	3	3
TBI 112	73.74613264	0.351517298	40	5	2	3

Table 4 Summary of Data Variance, Residual Variance, and Significant Spike Counts (all patients at minute-by-minute resolution for AMP)

Patient	Var data	Var model res	ACF org spikes	PACF org spikes	ACF model spikes	PACF model spikes
TBI 001	1.343340132	0.328208076	40	16	3	4
TBI 002	2.293270228	0.277561938	40	4	2	2
TBI 003	0.033950971	0.0034604	40	14	2	2
TBI 004	0.098123741	0.120967039	0	0	1	1
TBI 007	0.421577478	0.065190038	40	8	3	3
TBI 008	0.043892222	0.005038925	40	11	1	1
TBI 009	0.996906165	0.032187021	40	15	6	6
TBI 010	6.347041183	0.129213776	40	6	2	3
TBI 011	1.312277596	0.213840339	40	15	3	3
TBI 012	0.462132863	0.080305173	40	7	0	0
TBI 013	1.157081169	0.118919687	40	9	0	0
TBI 014	6.235668395	0.039473745	40	8	2	2
TBI 015	0.373739971	0.036940885	40	16	7	14
TBI 016	0.535529751	0.173978637	40	12	3	6
TBI 017	0.129681475	0.05467037	40	16	8	10
TBI 018	0.244679665	0.031328531	40	10	4	6
TBI 019	0.53535602	0.043162029	40	9	2	2
TBI 020	0.418860809	0.012523453	40	10	6	6
TBI 021	0.360069051	0.009375457	40	8	3	3
TBI 022	0.087812623	0.00649149	40	17	4	3
TBI 023	0.298002913	0.015042653	40	8	2	3
TBI 024	0.375828388	0.022713953	40	9	4	4
TBI 025	0.014143672	0.000972211	40	6	0	0
TBI 026	0.870126311	0.337256464	40	20	4	4
TBI 027	11.92212472	0.571789381	34	2	0	0
TBI 028	0.428491724	0.072199329	40	5	4	4
TBI 029	9.222276076	0.702653347	40	12	3	3
TBI 030	0.678317463	0.09170899	40	9	3	1
TBI 031	3.879065959	0.131475377	22	9	3	6
TBI 032	2.693738731	0.156684223	40	9	3	4
TBI 033	0.031237055	0.013479086	40	9	5	5
TBI 034	0.013505549	0.000891985	40	10	6	6
TBI 036	0.458545478	0.033138241	40	33	20	19
TBI 037	0.726783589	0.112287341	40	16	7	7
TBI 038	1.415467662	0.158541956	40	10	2	3
TBI 039	0.754187829	0.129954483	40	4	1	1
TBI 040	2.199989172	0.060258868	40	11	0	0
TBI 041	0.312547527	0.025969651	40	15	6	6
TBI 042	0.387784218	0.176371158	40	12	4	4
TBI 043	0.009088899	0.002822772	40	12	3	3
TBI 044	1.406372939	0.048415965	40	5	0	0
TBI 045	0.357953808	0.028984966	40	9	7	7
TBI 046	2.831491488	0.046052391	40	5	0	0
TBI 047	0.603317169	0.055163774	40	16	8	10
TBI 048	0.229417096	0.028562629	40	6	3	3
TBI 049	0.092535061	0.012429916	40	16	5	5
TBI 050	0.131344992	0.048349435	40	10	5	5
TBI 051	0.272216109	0.005253891	40	8	3	3
TBI 052	0.178086479	0.041510795	40	9	0	0
TBI 053	0.17703771	0.007135714	40	13	9	11

TBI 054	0.120238129	0.01331251	40	5	1	1
TBI 055	0.04458949	0.004439325	40	8	4	5
TBI 056	0.014316729	0.012281975	3	2	0	0
TBI 057	3.569392538	0.197457524	40	22	10	11
TBI 058	0.440942255	0.029971244	40	9	3	3
TBI 059	0.06431319	0.032033161	40	16	1	3
TBI 060	0.948292182	0.10982955	40	5	0	0
TBI 061	0.007634516	0.003148153	40	13	1	1
TBI 062	0.155563678	0.011886941	40	8	4	4
TBI 063	0.307571865	0.03461314	40	8	0	0
TBI 064	0.18061462	0.020803133	40	8	0	0
TBI 065	0.753440961	0.057827397	40	14	7	6
TBI 066	0.073513213	0.005912603	40	17	7	8
TBI 067	0.979082546	0.086219373	40	3	1	1
TBI 068	0.641463939	0.013394464	40	13	1	1
TBI 069	1.318329346	0.101846174	40	23	1	1
TBI 070	0.185022046	0.02727362	40	4	0	1
TBI 071	2.530668095	0.067842403	40	10	3	3
TBI 072	6.710503387	0.214237447	40	14	8	10
TBI 073	0.484636139	0.011947037	40	12	7	7
TBI 074	0.277096685	0.095297557	40	18	7	7
TBI 075	1.486125557	0.116571414	40	4	0	0
TBI 076	0.645418044	0.148216566	40	23	2	2
TBI 077	0.629424092	0.133246137	40	9	1	1
TBI 078	0.019209186	0.00221262	40	8	1	1
TBI 079	0.417676325	0.057531593	40	14	3	3
TBI 080	0.044791897	0.017220055	40	21	1	1
TBI 081	1.183804719	0.082886153	40	15	8	8
TBI 082	0.103996832	0.018424478	40	7	0	0
TBI 083	0.04395137	0.013358484	40	16	2	2
TBI 084	0.016857147	0.007414626	40	17	1	1
TBI 085	0.61498222	0.052421746	40	17	9	9
TBI 086	0.190603289	0.026546363	40	10	5	5
TBI 087	0.373547952	0.010920271	40	15	2	1
TBI 088	0.427141836	0.068219118	40	11	3	3
TBI 089	0.198899172	0.019610697	40	12	2	3
TBI 090	1.384396796	0.077851899	40	14	10	12
TBI 091	3.328747757	0.130482218	40	16	10	9
TBI 092	1.823582958	0.121793733	40	11	2	1
TBI 093	0.630876397	0.199425558	40	20	2	2
TBI 094	0.280304083	0.148654574	40	6	0	0
TBI 095	0.359190123	0.043814102	40	13	5	5
TBI 096	0.140210439	0.252006422	3	4	0	0
TBI 097	0.063993143	0.003781466	40	9	1	1
TBI 098	0.034260407	0.010855786	40	19	3	3
TBI 099	0.022710951	0.004343759	40	17	2	1
TBI 100	4.757124998	0.09389492	40	13	6	7
TBI 101	0.44398893	0.111418776	40	12	6	6
TBI 102	3.341908617	0.229569975	40	14	3	3
TBI 103	4.664995835	0.417131024	40	16	7	6
TBI 104	0.582508647	0.31994129	40	17	2	3
TBI 105	2.726413542	0.056364906	40	9	3	3
TBI 106	0.077123613	0.042809749	40	27	1	1
TBI 107	0.079593997	0.054014426	40	17	7	7
TBI 108	0.040924208	0.010816167	40	8	0	0
TBI 109	0.078921504	0.052309563	26	5	1	1
TBI 110	0.275766739	0.069077438	40	14	1	1
TBI 111	7.722836378	0.385442009	40	7	2	3
TBI 112	0.274307466	0.008567303	40	13	4	4

Table D.5 Summary of Data Variance, Residual Variance, and Significant Spike Counts (all patients at minute-by-minute resolution for **RAP**)

Patient	Var data	Var model res	ACF org spikes	PACF org spikes	ACF model spikes	PACF model spikes
TBI 001	0.1412515	0.070159938	40	17	6	6
TBI 002	0.129468786	0.070973082	22	6	4	5
TBI 003	0.303736781	0.099534592	40	8	2	2
TBI 004	0.081088963	0.081802522	1	1	0	0
TBI 007	0.220394564	0.104454374	25	4	3	4
TBI 008	0.243247676	0.131983562	11	4	2	2
TBI 009	0.265758508	0.128971031	40	15	3	2
TBI 010	0.065567075	0.041179102	8	4	0	0
TBI 011	0.156122664	0.075908695	40	18	10	9
TBI 012	0.137185019	0.062191102	21	4	2	1
TBI 013	0.038380234	0.020769834	6	5	0	0
TBI 014	0.226988344	0.097216753	20	6	7	7
TBI 015	0.249062888	0.114315375	40	9	7	7
TBI 016	0.245432782	0.103552744	40	10	3	3
TBI 017	0.270157474	0.141310431	33	1	1	2
TBI 018	0.433322242	0.122960649	40	8	1	3
TBI 019	0.270802434	0.097354065	40	11	2	3
TBI 020	0.178845439	0.06900749	40	25	7	6
TBI 021	0.1592727	0.068723601	40	18	6	5
TBI 022	0.241727085	0.108595488	40	15	7	7
TBI 023	0.199574822	0.087205538	35	8	0	0
TBI 024	0.150651424	0.071601673	40	8	3	3
TBI 025	0.360465375	0.160011105	13	6	6	7
TBI 026	0.248670542	0.128177218	40	8	3	4
TBI 027	0.198875002	0.080355394	19	7	2	2
TBI 028	0.267335613	0.124469042	40	9	5	5
TBI 029	0.228487805	0.129658932	40	14	2	2
TBI 030	0.168989639	0.072832695	23	1	2	3
TBI 031	0.570832286	0.121785389	35	6	2	4
TBI 032	0.223697803	0.119528482	25	4	2	2
TBI 033	0.357154683	0.169029392	20	4	3	3
TBI 034	0.299954673	0.146083555	40	5	0	0
TBI 036	0.139018384	0.065390222	40	9	3	3
TBI 037	0.201542126	0.081334675	40	18	5	3
TBI 038	0.159896225	0.069844247	40	12	0	0
TBI 039	0.215899736	0.091512222	34	7	2	3
TBI 040	0.160825525	0.072372323	40	9	4	5
TBI 041	0.180018002	0.081199784	39	6	4	5
TBI 042	0.281391818	0.132910462	40	9	2	3
TBI 043	0.292297839	0.146629363	40	8	5	5
TBI 044	0.201556902	0.099458121	22	6	1	2
TBI 045	0.163299125	0.079140004	40	10	5	6
TBI 046	0.087890007	0.045085374	10	3	3	3
TBI 047	0.294378248	0.141437383	36	4	1	1
TBI 048	0.329537719	0.150167293	37	5	1	1
TBI 049	0.354216239	0.168793758	40	14	6	5
TBI 050	0.237448831	0.127893757	12	6	2	3
TBI 051	0.38789464	0.185095875	25	5	4	3
TBI 052	0.451801269	0.137452089	40	6	1	1
TBI 053	0.29948899	0.097003591	40	14	3	4
TBI 054	0.094393531	0.067212536	10	3	2	2
TBI 055	0.331569396	0.144918929	40	11	4	5
TBI 056	0.415221004	0.288936762	7	7	1	3
TBI 057	0.12107862	0.060243334	40	20	9	8
TBI 058	0.269206065	0.119063577	40	19	8	8
TBI 059	0.239644162	0.119257502	40	3	0	0

TBI 060	0.183222724	0.106193035	28	3	0	0
TBI 061	0.263170505	0.12546849	32	5	3	3
TBI 062	0.373968292	0.157995046	16	5	1	1
TBI 063	0.189257062	0.098562334	27	4	2	2
TBI 064	0.416873558	0.189968092	36	4	2	3
TBI 065	0.177895434	0.085929203	29	5	3	3
TBI 066	0.22758353	0.106378819	40	14	8	7
TBI 067	0.161076046	0.085550426	12	4	3	3
TBI 068	0.31934334	0.138317772	40	8	3	3
TBI 069	0.147241898	0.072484398	38	10	2	2
TBI 070	0.364200356	0.156315925	17	3	0	0
TBI 071	0.1287753	0.058878032	34	6	4	4
TBI 072	0.250563826	0.106217166	38	4	2	3
TBI 073	0.211912393	0.097517151	40	14	5	5
TBI 074	0.235383185	0.112651905	40	8	2	2
TBI 075	0.251232415	0.105233391	40	8	3	4
TBI 076	0.150319996	0.07557991	40	10	2	3
TBI 077	0.202743169	0.099692366	40	8	2	2
TBI 078	0.350487187	0.181963517	4	3	0	0
TBI 079	0.168253314	0.069700859	35	9	4	4
TBI 080	0.315216263	0.1683715	40	8	4	4
TBI 081	0.146978659	0.057566577	40	11	5	5
TBI 082	0.263233461	0.12987111	14	6	3	3
TBI 083	0.358715999	0.147852695	29	9	6	7
TBI 084	0.315127065	0.141740705	30	11	6	5
TBI 085	0.134127951	0.070830416	39	6	3	3
TBI 086	0.196843926	0.08764298	40	18	5	6
TBI 087	0.18085509	0.081993391	40	15	6	4
TBI 088	0.084775108	0.043740211	35	12	6	7
TBI 089	0.283335967	0.123453535	40	18	2	2
TBI 090	0.222956546	0.076929373	40	17	3	3
TBI 091	0.090112254	0.039253186	40	22	3	3
TBI 092	0.203595545	0.084275289	40	18	4	4
TBI 093	0.190981587	0.085474574	40	12	6	6
TBI 094	0.306490751	0.164434451	18	3	2	2
TBI 095	0.144113211	0.066675476	40	5	1	1
TBI 096	0.301859576	0.158155105	9	6	0	2
TBI 097	0.231525838	0.106497988	40	8	1	1
TBI 098	0.277038629	0.131407275	39	12	5	5
TBI 099	0.259310022	0.141085614	38	8	2	2
TBI 100	0.120183335	0.05448055	40	22	7	7
TBI 101	0.256311834	0.119121748	40	8	2	3
TBI 102	0.289243285	0.137082761	40	15	2	2
TBI 103	0.154182022	0.070261691	40	15	8	7
TBI 104	0.297232126	0.140985497	40	14	0	0
TBI 105	0.288800164	0.10316541	40	15	1	0
TBI 106	0.284772004	0.136019806	40	6	1	0
TBI 107	0.425581549	0.186041656	40	14	7	8
TBI 108	0.205362702	0.113394438	36	4	0	0
TBI 109	0.375330545	0.217200451	8	4	5	9
TBI 110	0.242788623	0.120073816	40	6	4	4
TBI 111	0.108203624	0.046197093	27	8	4	4
TBI 112	0.176414156	0.085018341	40	7	1	1

Table D.6 Median of the Data Variance, Residual Variance, and Significant Spike Counts for total population at min-by-min resolution

Parameters	Var data	Var model res	ACF org spikes	PACF org spikes	ACF_model spikes	PACF_model spikes
ICP	18.57120	1.41843	40	9	2	3
AMP	0.41768	0.04842	40	11	3	3

RAP	0.23153	0.10523	40	8	3	3
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Table D.7 Mean of the Data Variance, Residual Variance, and Significant Spike Counts for total population at min-by-min resolution

Parameters	Var data	Var model res	ACF org spikes	PACF org spikes	ACF model spikes	PACF model spikes
ICP	29.78738	2.00069	38.48624	10.05505	2.72477	3.07339
AMP	1.15358	0.08891	38.60550	11.56881	3.35780	3.63303
RAP	0.23621	0.10882	32.44954	9	3.16514	3.34862

Table D.8 Median of residuals at different resolutions

Parameter	Minute by minute	10 min by 10 min	30 min by 30 min	Hour by hour
ICP	0.17941	0.28646	0.37397	0.41906
AMP	0.13549	0.21710	0.19870	0.19970
RAP	0.12564	0.18085	0.14078	0.11851

Appendix E. Section 4.3.4: A comparative analysis between clean and artifact data using optimal ARIMA

This appendix presents the optimal ARIMA models for artifact segments for each patient at both minute-by-minute and 10-minute intervals, selected based on the lowest AIC value. Each cell displays four values: the p, d, and q orders, along with the model's AIC score. m refers to minute. Comparative tables and figures between clean and artifact profiles are also provided, showing median and mean values of the optimal ARIMA model orders, as well as scatterplots of these orders.

AIC, Akaike information criterion; AMP, pulse amplitude of ICP; ARIMA, auto-regressive integrated moving average; ICP, intracranial pressure; p, d, and q-orders, three components of ARIMA model, defining autoregression, integrated, and a moving average part respectively; RAP, compensatory reserve index.

Table E.1 Optimal ARIMA models of artifact segments

Patient	ICP m by m	ICP 10m by 10m	AMP m by m	AMP 10m by 10m	RAP m by m	RAP 10m by 10m
TBI_001	[1, 1, 1, '216.851']	[6, 1, 1, '4255.733']	[1, 1, 6, '911.386']	[6, 1, 1, '1332.552']	[1, 1, 6, '59.114']	[6, 1, 5, '-192.534']
TBI_002	[1, 1, 1, '195.969']	[3, 1, 1, '798.246']	[4, 1, 4, '20.000']	[1, 1, 2, '390.750']	[2, 1, 9, '366.023']	[2, 1, 1, '-52.852']
TBI_003	[3, 1, 3, '151.597']	[4, 1, 3, '609.108']	[1, 1, 1, '654.294']	[2, 1, 2, '-613.493']	[1, 1, 1, '341.556']	[3, 1, 4, '102.301']
TBI_004	[1, 1, 1, '380.408']	[8, 1, 5, '19.483']	[1, 1, 2, '1958.890']	[10, 1, 1, '-8.337']	[1, 1, 9, '-184.189']	[1, 1, 1, '7.550']
TBI_007	[1, 1, 1, '260.029']	[1, 1, 1, '341.530']	[1, 1, 5, '1457.070']	[1, 1, 1, '-42.308']	[10, 1, 1, '804.155']	[1, 1, 1, '29.447']
TBI_008	[2, 1, 4, '1253.486']	[6, 1, 7, '640.823']	[5, 1, 8, '4040.300']	[1, 1, 5, '-234.704']	[1, 1, 3, '-1014.547']	[1, 1, 1, '133.499']
TBI_009	[1, 1, 5, '1390.931']	[3, 1, 1, '2728.697']	[8, 1, 8, '4457.610']	[2, 1, 5, '-198.338']	[4, 1, 10, '838.514']	[2, 1, 3, '405.306']
TBI_010	[3, 1, 4, '302.078']	[2, 1, 8, '829.657']	[1, 1, 2, '1253.633']	[8, 1, 2, '421.414']	[3, 1, 2, '582.267']	[2, 1, 4, '-123.974']
TBI_011	[4, 1, 1, '432.608']	[4, 1, 1, '3969.556']	[9, 1, 5, '1860.488']	[5, 1, 5, '1322.034']	[3, 1, 1, '1183.942']	[9, 1, 1, '-66.064']
TBI_012	[5, 1, 3, '1207.493']	[3, 1, 3, '932.354']	[10, 1, 10, '5313.922']	[3, 1, 4, '170.531']	[9, 1, 10, '2074.735']	[1, 1, 1, '34.510']
TBI_013	[6, 1, 6, '90.568']	[1, 1, 1, '285.451']	[9, 1, 5, '75.752']	[1, 1, 1, '116.816']	[3, 1, 1, '11.060']	[1, 1, 1, '-111.659']
TBI_014	[6, 1, 1, '981.569']	[6, 1, 2, '705.939']	[10, 1, 10, '4907.600']	[4, 1, 1, '170.705']	[9, 1, 10, '319.266']	[1, 1, 1, '149.620']
TBI_015	[1, 1, 4, '1744.311']	[4, 1, 10, '3273.361']	[8, 1, 3, '7903.675']	[6, 1, 7, '887.067']	[9, 1, 1, '1431.264']	[4, 1, 1, '325.832']
TBI_016	[1, 1, 1, '221.447']	[4, 1, 5, '577.298']	[5, 1, 10, '821.869']	[2, 1, 6, '92.695']	[6, 1, 1, '564.081']	[3, 1, 5, '35.309']
TBI_017	[1, 1, 1, '260.924']	[1, 1, 2, '841.047']	[4, 1, 1, '2207.630']	[5, 1, 6, '-46.309']	[8, 1, 4, '28.000']	[5, 1, 5, '144.457']
TBI_018	[1, 1, 1, '162.220']	[1, 1, 3, '433.669']	[3, 1, 2, '1149.084']	[1, 1, 2, '-13.491']	[1, 1, 1, '404.283']	[3, 1, 3, '89.550']
TBI_019	[5, 1, 2, '26.560']	[2, 1, 6, '408.893']	[1, 1, 1, '27.672']	[4, 1, 3, '13.428']	[2, 1, 1, '-74.780']	[8, 1, 7, '18.908']
TBI_020	[1, 1, 3, '1008.423']	[8, 1, 3, '4486.602']	[5, 1, 3, '4279.900']	[1, 1, 3, '5.157']	[9, 1, 9, '1891.217']	[3, 1, 1, '-23.169']
TBI_021	[3, 1, 1, '541.141']	[1, 1, 2, '2075.738']	[9, 1, 2, '1821.910']	[1, 1, 3, '-1094.246']	[1, 1, 2, '511.206']	[1, 1, 2, '-105.751']
TBI_022	[1, 1, 4, '672.260']	[3, 1, 4, '2732.960']	[7, 1, 9, '2462.705']	[6, 1, 3, '-1294.473']	[3, 1, 6, '839.036']	[1, 1, 2, '339.065']
TBI_023	[1, 1, 1, '251.917']	[5, 1, 8, '2102.452']	[1, 1, 4, '949.311']	[2, 1, 2, '286.001']	[2, 1, 5, '503.681']	[1, 1, 1, '140.425']
TBI_024	[3, 1, 7, '630.735']	[2, 1, 2, '1977.338']	[10, 1, 8, '2840.440']	[3, 1, 7, '213.528']	[7, 1, 9, '770.870']	[5, 1, 1, '46.978']

TBI_025	[1, 1, 4, '268.862']	[5, 1, 7, '673.930']	[6, 1, 3, '940.446']	[2, 1, 1, '-187.712']	[4, 1, 10, '161.285']	[1, 1, 1, '182.025']
TBI_026	[4, 1, 1, '366.193']	[3, 1, 1, '3079.708']	[2, 1, 5, '1669.426']	[4, 1, 7, '884.406']	[6, 1, 7, '845.558']	[2, 1, 1, '282.125']
TBI_027	[10, 1, 1, '4099.958']	[6, 1, 6, '3432.804']	[3, 1, 3, '18617.367']	[8, 1, 9, '1810.299']	[9, 1, 9, '6422.273']	[3, 1, 2, '46.304']
TBI_028	[3, 1, 8, '1982.529']	[6, 1, 5, '2481.023']	[10, 1, 10, '1639.158']	[1, 1, 1, '558.722']	[10, 1, 7, '3723.586']	[1, 1, 1, '228.778']
TBI_029	[2, 1, 4, '1868.183']	[9, 1, 9, '3676.162']	[7, 1, 5, '8724.573']	[4, 1, 6, '1817.830']	[7, 1, 7, '4065.914']	[3, 1, 1, '323.412']
TBI_030	[1, 1, 1, '840.829']	[2, 1, 5, '1440.883']	[1, 1, 2, '4871.952']	[2, 1, 1, '424.745']	[2, 1, 4, '2217.295']	[1, 1, 1, '125.002']
TBI_031	[6, 1, 1, '3583.410']	[1, 1, 1, '116.934']	[4, 1, 4, '11342.088']	[9, 1, 1, '65.009']	[9, 1, 10, '5250.503']	[10, 1, 1, '12.878']
TBI_032	[3, 1, 2, '629.617']	[4, 1, 6, '1243.360']	[1, 1, 9, '3071.748']	[8, 1, 6, '414.222']	[3, 1, 1, '871.735']	[1, 1, 1, '90.492']
TBI_033	[2, 1, 2, '99.774']	[1, 1, 2, '556.279']	[2, 1, 4, '420.894']	[1, 1, 1, '-196.827']	[2, 1, 1, '235.039']	[1, 1, 1, '134.205']
TBI_034	[1, 1, 2, '880.048']	[2, 1, 5, '608.336']	[6, 1, 2, '3311.861']	[2, 1, 1, '-560.840']	[1, 1, 1, '1979.590']	[1, 1, 1, '118.680']
TBI_036	[1, 1, 1, '603.420']	[5, 1, 7, '6284.400']	[2, 1, 2, '2793.023']	[10, 1, 8, '2447.168']	[6, 1, 10, '812.963']	[1, 1, 1, '-40.093']
TBI_037	[6, 1, 1, '1049.940']	[1, 1, 1, '3174.555']	[1, 1, 9, '6439.643']	[1, 1, 2, '692.762']	[1, 1, 1, '2653.677']	[6, 1, 7, '186.534']
TBI_038	[1, 1, 2, '327.503']	[3, 1, 10, '3651.071']	[1, 1, 1, '1631.377']	[2, 1, 8, '1418.069']	[2, 1, 5, '793.073']	[1, 1, 1, '163.865']
TBI_039	[1, 1, 3, '248.396']	[1, 1, 1, '1373.530']	[3, 1, 10, '1548.009']	[1, 1, 2, '461.798']	[7, 1, 5, '699.469']	[1, 1, 1, '147.763']
TBI_040	[2, 1, 2, '597.103']	[1, 1, 3, '2388.786']	[7, 1, 9, '2358.536']	[3, 1, 4, '507.213']	[6, 1, 9, '853.780']	[1, 1, 2, '98.532']
TBI_041	[7, 1, 1, '624.256']	[1, 1, 1, '2322.222']	[1, 1, 1, '4350.928']	[1, 1, 3, '218.837']	[1, 1, 3, '1400.580']	[3, 1, 1, '215.685']
TBI_042	[1, 1, 1, '132.493']	[1, 1, 1, '1491.790']	[1, 1, 1, '846.594']	[4, 1, 1, '275.034']	[4, 1, 7, '370.171']	[2, 1, 3, '229.795']
TBI_043	[6, 1, 1, '3412.524']	[1, 1, 1, '583.359']	[9, 1, 10, '4393.327']	[1, 1, 1, '-742.371']	[8, 1, 8, '-10858.220']	[1, 1, 2, '159.959']
TBI_044	[5, 1, 1, '899.183']	[3, 1, 4, '712.394']	[10, 1, 1, '8831.879']	[2, 1, 1, '165.178']	[6, 1, 1, '1444.800']	[6, 1, 1, '70.514']
TBI_045	[2, 1, 6, '688.985']	[4, 1, 3, '1595.632']	[1, 1, 1, '3162.513']	[2, 1, 1, '125.979']	[1, 1, 4, '-2944.605']	[2, 1, 5, '13.006']
TBI_046	[1, 1, 4, '57.821']	[2, 1, 8, '745.024']	[1, 1, 1, '125.272']	[2, 1, 10, '340.444']	[1, 1, 1, '-21.288']	[2, 1, 2, '-91.210']
TBI_047	[1, 1, 4, '95.827']	[1, 1, 1, '233.857']	[1, 1, 1, '725.657']	[1, 1, 2, '-20.787']	[1, 1, 1, '249.664']	[3, 1, 2, '43.998']
TBI_048	[2, 1, 1, '-9.027']	[1, 1, 3, '1656.563']	[10, 1, 1, '68.995']	[2, 1, 1, '-669.049']	[10, 1, 1, '33.094']	[1, 1, 2, '436.151']
TBI_049	[1, 1, 2, '488.865']	[2, 1, 4, '543.931']	[1, 1, 1, '2721.889']	[6, 1, 9, '7.473']	[9, 1, 2, '875.675']	[2, 1, 4, '75.450']
TBI_050	[1, 1, 1, '117.525']	[2, 1, 2, '779.306']	[1, 1, 1, '767.686']	[2, 1, 1, '-239.027']	[1, 1, 1, '210.167']	[1, 1, 2, '129.049']
TBI_051	[1, 1, 5, '414.880']	[1, 1, 1, '420.971']	[1, 1, 4, '2888.338']	[2, 1, 10, '-111.112']	[4, 1, 1, '248.949']	[1, 1, 1, '120.369']
TBI_052	[5, 1, 5, '136.822']	[4, 1, 8, '1055.686']	[1, 1, 2, '665.639']	[8, 1, 10, '-414.364']	[1, 1, 2, '291.463']	[3, 1, 7, '171.868']
TBI_053	[2, 1, 3, '105.092']	[4, 1, 3, '248.705']	[1, 1, 1, '230.665']	[2, 1, 2, '-69.739']	[1, 1, 1, '-60.925']	[2, 1, 3, '-34.805']
TBI_054	[1, 1, 1, '134.648']	[1, 1, 1, '1387.897']	[3, 1, 1, '-1697.984']	[1, 1, 4, '-662.759']	[1, 1, 2, '-1830.949']	[2, 1, 1, '240.594']
TBI_055	[6, 1, 1, '495.105']	[8, 1, 1, '26.408']	[9, 1, 3, '28.000']	[6, 1, 1, '-13.890']	[5, 1, 8, '203.978']	[9, 1, 1, '17.316']
TBI_056	[2, 1, 1, '327.771']	[9, 1, 9, '7011.416']	[1, 1, 2, '2266.753']	[7, 1, 1, '2779.937']	[1, 1, 8, '968.387']	[5, 1, 1, '443.905']

TBI_057	[4, 1, 3, '2222.079']	[1, 1, 1, '1432.209']	[5, 1, 5, '10260.114']	[2, 1, 2, '-44.341']	[3, 1, 5, '3337.734']	[1, 1, 1, '146.171']
TBI_058	[2, 1, 1, '322.791']	[2, 1, 2, '383.868']	[1, 1, 1, '2050.290']	[1, 1, 1, '-221.804']	[1, 1, 1, '599.655']	[1, 1, 1, '73.161']
TBI_059	[3, 1, 1, '58.209']	[1, 1, 2, '1363.277']	[1, 1, 5, '189.682']	[1, 1, 5, '471.852']	[2, 1, 1, '87.081']	[2, 1, 4, '35.108']
TBI_060	[2, 1, 1, '143.785']	[3, 1, 2, '258.540']	[2, 1, 5, '453.600']	[1, 1, 7, '-451.396']	[2, 1, 5, '204.925']	[2, 1, 1, '84.490']
TBI_061	[4, 1, 3, '95.894']	[1, 1, 1, '401.476']	[3, 1, 2, '195.117']	[3, 1, 7, '19.553']	[1, 1, 1, '-149.068']	[3, 1, 3, '88.883']
TBI_062	[4, 1, 2, '92.239']	[1, 1, 1, '1489.315']	[2, 1, 1, '-887.826']	[1, 1, 2, '35.883']	[4, 1, 1, '-721.733']	[2, 1, 2, '40.785']
TBI_063	[4, 1, 1, '467.747']	[1, 1, 1, '274.303']	[5, 1, 10, '3628.414']	[2, 1, 2, '-79.875']	[1, 1, 1, '1415.880']	[1, 1, 1, '76.839']
TBI_064	[1, 1, 1, '194.979']	[1, 1, 2, '465.404']	[5, 1, 4, '22.000']	[1, 1, 1, '120.083']	[1, 1, 1, '241.505']	[1, 1, 1, '10.605']
TBI_065	[5, 1, 1, '239.342']	[4, 1, 3, '1368.894']	[1, 1, 1, '1666.025']	[2, 1, 1, '-896.379']	[1, 1, 1, '782.385']	[1, 1, 1, '150.551']
TBI_066	[1, 1, 1, '240.558']	[7, 1, 1, '385.927']	[1, 1, 1, '1617.437']	[2, 1, 10, '158.461']	[1, 1, 1, '563.820']	[1, 1, 1, '33.999']
TBI_067	[3, 1, 3, '645.248']	[1, 1, 1, '1229.778']	[1, 1, 1, '4416.943']	[1, 1, 3, '-217.419']	[1, 1, 2, '1180.296']	[3, 1, 3, '296.879']
TBI_068	[1, 1, 4, '146.175']	[3, 1, 4, '4544.290']	[1, 1, 1, '906.955']	[1, 1, 2, '1296.419']	[1, 1, 1, '290.948']	[10, 1, 1, '15.428']
TBI_069	[2, 1, 1, '605.122']	[1, 1, 4, '126.313']	[7, 1, 4, '4050.266']	[1, 1, 1, '-26.652']	[1, 1, 2, '1771.818']	[2, 1, 1, '49.412']
TBI_070	[4, 1, 1, '73.125']	[7, 1, 4, '6316.318']	[1, 1, 1, '-93.274']	[2, 1, 2, '2622.449']	[2, 1, 1, '-71.552']	[1, 1, 1, '-38.552']
TBI_071	[3, 1, 3, '304.884']	[7, 1, 9, '36.000']	[5, 1, 2, '1276.778']	[6, 1, 9, '288.003']	[4, 1, 1, '552.057']	[3, 1, 1, '75.470']
TBI_072	[1, 1, 1, '155.511']	[2, 1, 3, '5265.377']	[4, 1, 2, '16.000']	[3, 1, 5, '-1026.621']	[1, 1, 2, '309.501']	[1, 1, 1, '602.585']
TBI_073	[2, 1, 4, '307.419']	[1, 1, 2, '2353.766']	[10, 1, 5, '34.000']	[6, 1, 10, '-38.469']	[1, 1, 2, '755.731']	[1, 1, 1, '72.476']
TBI_074	[3, 1, 3, '126.786']	[8, 1, 10, '40.000']	[1, 1, 1, '-50.894']	[3, 1, 6, '244.269']	[1, 1, 1, '-639.540']	[3, 1, 3, '93.193']
TBI_075	[3, 1, 3, '323.676']	[1, 1, 2, '3795.065']	[1, 1, 5, '2518.804']	[6, 1, 5, '668.983']	[5, 1, 1, '401.281']	[3, 1, 1, '37.733']
TBI_076	[2, 1, 2, '153.266']	[1, 1, 1, '2098.357']	[1, 1, 3, '1149.362']	[3, 1, 3, '643.225']	[1, 1, 3, '347.456']	[3, 1, 1, '119.313']
TBI_077	[2, 1, 6, '235.293']	[1, 1, 1, '561.375']	[1, 1, 1, '1869.856']	[3, 1, 9, '-312.053']	[1, 1, 1, '433.423']	[1, 1, 1, '131.781']
TBI_078	[10, 1, 8, '40.000']	[1, 1, 1, '989.121']	[5, 1, 4, '22.000']	[1, 1, 1, '140.132']	[1, 1, 10, '-4685.873']	[4, 1, 1, '37.465']
TBI_079	[4, 1, 6, '200.652']	[3, 1, 1, '2914.104']	[4, 1, 1, '630.640']	[1, 1, 1, '-1450.861']	[5, 1, 5, '-53.220']	[1, 1, 2, '532.785']
TBI_080	[2, 1, 2, '526.633']	[8, 1, 8, '5232.541']	[9, 1, 7, '1413.642']	[3, 1, 4, '1931.642']	[2, 1, 4, '-95.125']	[1, 1, 1, '49.576']
TBI_081	[1, 1, 1, '410.170']	[2, 1, 2, '324.380']	[1, 1, 2, '1671.767']	[1, 1, 3, '-106.536']	[6, 1, 1, '326.753']	[1, 1, 1, '76.542']
TBI_082	[1, 1, 1, '142.962']	[4, 1, 4, '615.931']	[8, 1, 4, '701.148']	[1, 1, 1, '-480.234']	[1, 1, 7, '16.887']	[1, 1, 6, '182.994']
TBI_083	[4, 1, 2, '192.671']	[1, 1, 1, '254.656']	[3, 1, 3, '519.270']	[1, 1, 1, '-724.082']	[1, 1, 1, '-70.222']	[1, 1, 1, '227.432']
TBI_084	[7, 1, 2, '176.973']	[9, 1, 8, '3805.534']	[1, 1, 1, '1396.861']	[8, 1, 7, '282.638']	[1, 1, 1, '675.169']	[1, 1, 1, '-56.330']
TBI_085	[4, 1, 5, '164.428']	[4, 1, 9, '4333.346']	[1, 1, 1, '794.102']	[4, 1, 1, '43.771']	[5, 1, 1, '141.663']	[1, 1, 2, '148.433']
TBI_086	[1, 1, 3, '653.506']	[1, 1, 2, '2362.099']	[1, 1, 1, '2196.813']	[4, 1, 2, '-1591.208']	[1, 1, 1, '-8.758']	[1, 1, 1, '99.391']
TBI_087	[3, 1, 1, '254.955']	[3, 1, 4, '5733.186']	[9, 1, 2, '350.266']	[7, 1, 1, '1185.601']	[9, 1, 10, '-338.154']	[1, 1, 1, '-719.332']

TBI_088	[2, 1, 1, '313.831']	[1, 1, 2, '2767.672']	[3, 1, 4, '2097.287']	[1, 1, 1, '-898.413']	[1, 1, 1, '799.464']	[1, 1, 1, '361.620']
TBI_089	[5, 1, 5, '374.758']	[2, 1, 7, '2391.440']	[2, 1, 2, '3375.603']	[7, 1, 3, '605.383']	[1, 1, 3, '1499.648']	[1, 1, 1, '212.776']
TBI_090	[2, 1, 9, '627.030']	[7, 1, 2, '6128.983']	[6, 1, 9, '4000.068']	[5, 1, 7, '2342.235']	[1, 1, 7, '980.755']	[6, 1, 8, '-668.544']
TBI_091	[1, 1, 4, '492.351']	[1, 1, 5, '3760.560']	[1, 1, 1, '4113.294']	[3, 1, 4, '1543.450']	[2, 1, 9, '2720.688']	[7, 1, 2, '261.090']
TBI_092	[3, 1, 1, '377.535']	[1, 1, 2, '5118.541']	[2, 1, 1, '2346.761']	[3, 1, 1, '1003.610']	[1, 1, 1, '802.367']	[1, 1, 2, '279.230']
TBI_093	[1, 1, 1, '440.220']	[6, 1, 6, '394.269']	[1, 1, 1, '2516.182']	[1, 1, 1, '54.721']	[2, 1, 1, '1282.904']	[1, 1, 1, '127.756']
TBI_094	[4, 1, 2, '244.423']	[1, 1, 1, '2364.346']	[1, 1, 5, '692.869']	[1, 1, 3, '126.146']	[4, 1, 3, '418.360']	[4, 1, 9, '9.800']
TBI_095	[1, 1, 1, '222.588']	[1, 1, 1, '96.413']	[10, 1, 8, '40.000']	[1, 1, 2, '34.204']	[2, 1, 3, '317.848']	[1, 1, 4, '4.547']
TBI_096	[1, 1, 4, '1859.860']	[2, 1, 7, '539.291']	[1, 1, 6, '6557.346']	[3, 1, 3, '-861.808']	[1, 1, 3, '3169.689']	[2, 1, 1, '164.963']
TBI_097	[4, 1, 3, '197.839']	[1, 1, 2, '1453.918']	[4, 1, 2, '768.896']	[9, 1, 6, '-722.735']	[1, 1, 1, '545.407']	[3, 1, 1, '291.945']
TBI_098	[1, 1, 4, '341.200']	[4, 1, 6, '1044.266']	[1, 1, 1, '2084.600']	[5, 1, 5, '-1355.549']	[6, 1, 6, '642.491']	[4, 1, 4, '28.276']
TBI_099	[4, 1, 4, '296.096']	[5, 1, 1, '5978.417']	[1, 1, 1, '2039.579']	[2, 1, 9, '2860.168']	[1, 1, 2, '960.570']	[4, 1, 6, '-204.319']
TBI_100	[6, 1, 1, '1032.526']	[8, 1, 6, '32.000']	[8, 1, 8, '4341.087']	[1, 1, 3, '135.282']	[7, 1, 3, '1694.936']	[1, 1, 2, '55.751']
TBI_101	[5, 1, 1, '833.134']	[1, 1, 1, '1168.088']	[1, 1, 2, '5578.883']	[6, 1, 2, '409.388']	[1, 1, 3, '1230.939']	[7, 1, 1, '166.367']
TBI_102	[9, 1, 1, '21.916']	[8, 1, 8, '8422.112']	[2, 1, 2, '118.470']	[1, 1, 9, '4707.190']	[2, 1, 1, '106.422']	[6, 1, 2, '55.531']
TBI_103	[9, 1, 10, '42.000']	[7, 1, 10, '1789.902']	[1, 1, 1, '1871.172']	[1, 1, 1, '486.303']	[3, 1, 1, '953.341']	[1, 1, 2, '242.016']
TBI_104	[4, 1, 3, '170.430']	[1, 1, 2, '1976.162']	[8, 1, 5, '763.837']	[1, 1, 2, '737.405']	[9, 1, 7, '169.564']	[1, 1, 1, '204.868']
TBI_105	[1, 1, 4, '531.766']	[3, 1, 5, '1840.146']	[3, 1, 3, '2150.159']	[8, 1, 9, '-964.441']	[10, 1, 8, '932.014']	[1, 1, 1, '458.617']
TBI_106	[3, 1, 3, '126.549']	[5, 1, 6, '1661.255']	[3, 1, 1, '470.235']	[5, 1, 1, '-602.737']	[1, 1, 1, '101.765']	[1, 1, 1, '545.032']
TBI_107	[10, 1, 7, '38.000']	[1, 1, 1, '648.972']	[4, 1, 8, '2108.791']	[1, 1, 1, '-625.873']	[10, 1, 2, '1380.588']	[2, 1, 1, '96.404']
TBI_108	[1, 1, 1, '176.033']	[1, 1, 1, '335.184']	[9, 1, 10, '516.831']	[3, 1, 3, '14.186']	[8, 1, 4, '141.479']	[1, 1, 6, '55.569']
TBI_109	[1, 1, 1, '212.494']	[4, 1, 8, '2406.468']	[10, 1, 10, '998.789']	[6, 1, 5, '369.640']	[5, 1, 5, '396.094']	[1, 1, 2, '367.743']
TBI_110	[5, 1, 6, '398.988']	[5, 1, 1, '3183.328']	[2, 1, 4, '1697.653']	[5, 1, 1, '1905.199']	[7, 1, 7, '1046.452']	[1, 1, 1, '-224.253']
TBI_111	[5, 1, 1, '1689.427']	[2, 1, 7, '1897.303']	[1, 1, 4, '12588.356']	[9, 1, 10, '-324.208']	[3, 1, 1, '1771.921']	[3, 1, 1, '58.025']
TBI_112	[1, 1, 2, '930.173']	[3, 1, 1, '1124.876']	[10, 1, 8, '3149.498']	[7, 1, 10, '1.010']	[8, 1, 7, '-708.170']	[1, 1, 1, '179.101']

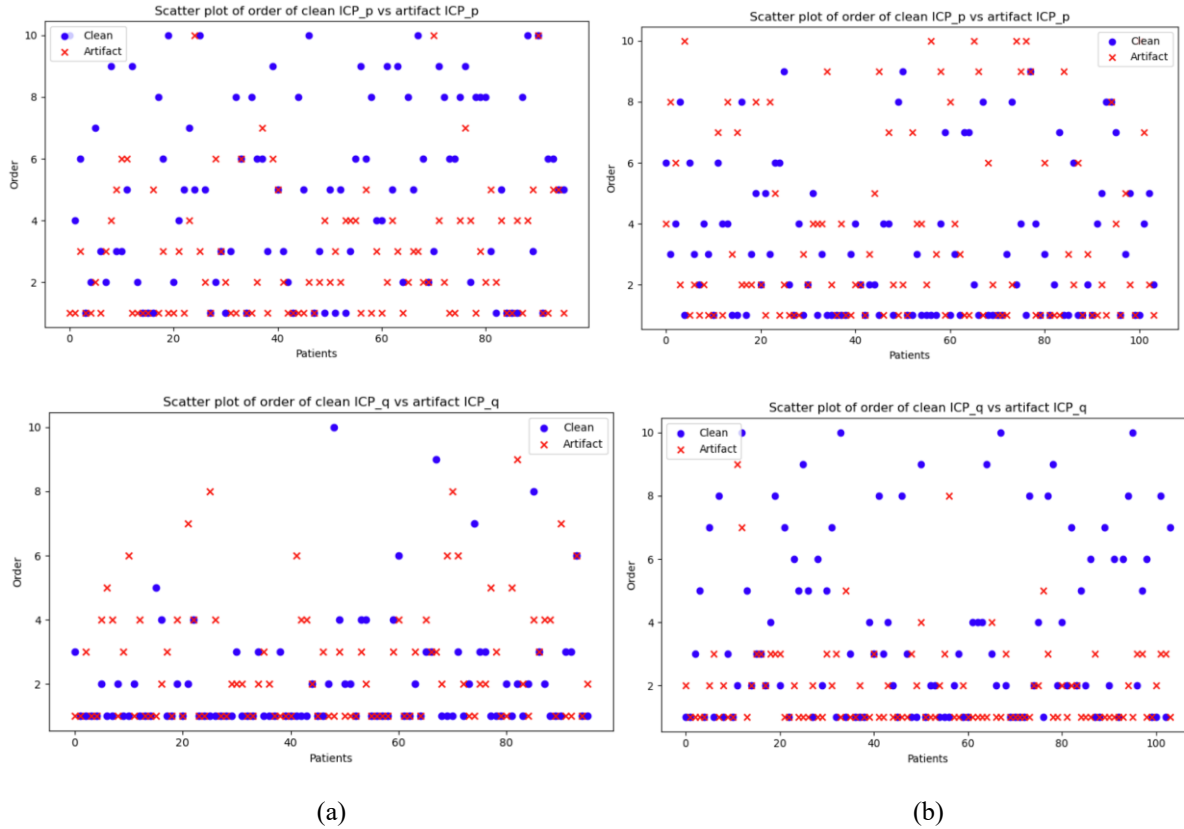
Table E.2 Median of the orders of optimal ARIMA models

Parameter	Minute-by-minute				10-minute-by-10-minute			
	Clean		Artifact		Clean		Artifact	
	p-order	q-order	p-order	q-order	p-order	q-order	p-order	q-order
ICP	3	5	2	3	3	3	2	1
AMP	3	3	2	2	2	3	1	1
RAP	5	1	2	2	1	1	1	1

Table E.3 Mean of the orders of optimal ARIMA models

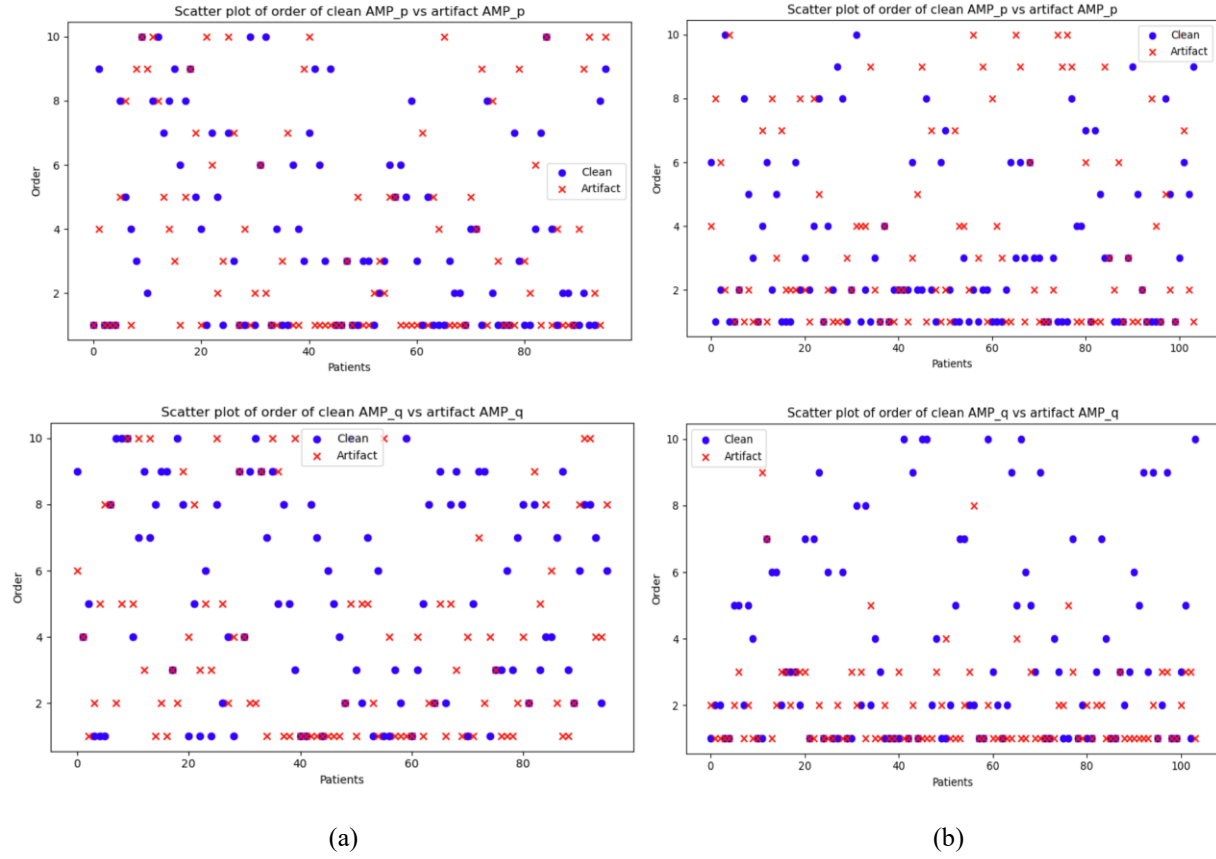
Parameter	Minute-by-minute				10-minute-by-10-minute			
	Clean		Artifact		Clean		Artifact	
	p-order	q-order	p-order	q-order	p-order	q-order	p-order	q-order
ICP	3.91743	5.28440	3.82569	3.78899	3.23077	3.69231	3.65385	1.87500
AMP	4.49541	4.20183	3.57798	3.72477	3.26923	3.72115	3.34615	2.35577
RAP	5.12844	2.06422	2.95413	2.62385	2.34615	2.02885	2.93269	2.44231

Figure E.1 Scatterplots for ICP p-orders and q-orders at different resolutions for each patient



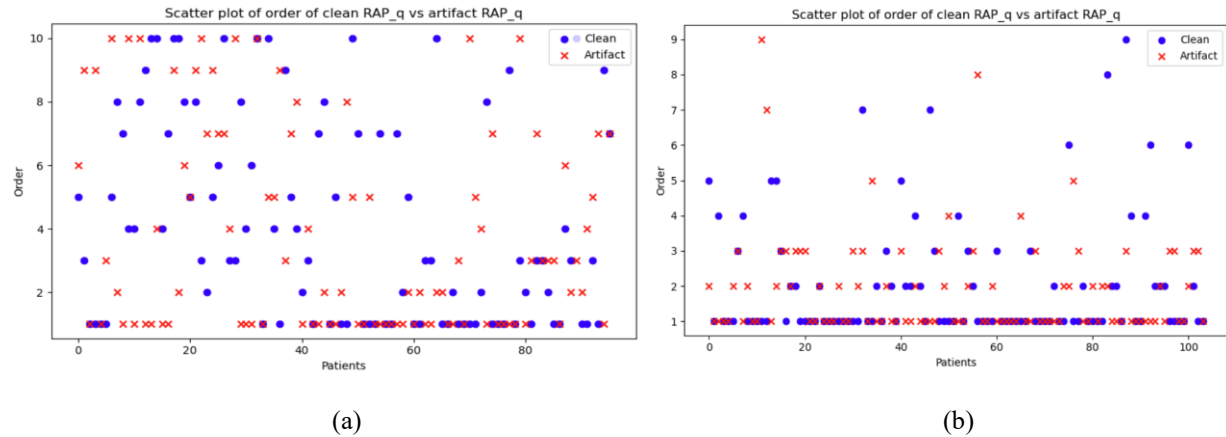
The figure demonstrates the value of the p-orders and q-orders from the optimal ARIMA models of ICP's clean vs artifact data at (a) Minute-by-minute resolution and (b) 10-minute-by-10-minute resolution. The blue circles correspond to the orders of the clean data, whereas the red crosses represent the orders of the artifact segment. If a red cross overlaps a blue circle, the value of the order for that patient is the same. If they don't overlap, the values differ.

Figure E.2 Scatterplots for AMP p -orders and q -orders at different resolutions for each patient



The figure demonstrates the value of the q orders from the optimal ARIMA models of RAP's clean vs artifact group at (a) Minute-by-minute resolution and (b) 10-minute-by-10-minute resolution.

Figure E.3 Scatterplots for RAP q -orders at different resolutions for each patient



The figure demonstrates the value of the q orders from the optimal ARIMA models of RAP's clean vs artifact group at (a) Minute-by-minute resolution and (b) 10-minute-by-10-minute resolution.

Appendix F. Section 4.3.4: Evaluation of the potential features for identifying artifacts

This appendix presents the values of the evaluation parameters for the potential features of identifying artifacts at the minute-by-minute resolution and 10-minute-by-10-minute resolution.

AMP, pulse amplitude of ICP; ARIMA, auto-regressive integrated moving average; ICP, intracranial pressure, RAP, compensatory reserve index; RAP-ICP, cross-correlation between residuals of RAP and ICP; RAP-AMP, cross-correlation between residuals of RAP and AMP.

Table F.1: Evaluation of potential features at the minute-by-minute resolution

	Total data	True artifacts	Predicted artifacts	False positives	Success rate (%)
Difference of the optimal ARIMA models					
ICP	4129	238	155	2398	65.258
AMP			148	2335	62.115
RAP			200	2212	84.038
Medians of the variance of residuals					
ICP	4129	238	167	1997	70.212
AMP			136	1897	56.916
RAP			218	1846	91.666
Median of the maximum cross-correlation of residuals					
RAP-ICP	4129	238	88	1985	37.011
RAP-AMP			146	1856	61.6

Table F.2: Evaluation of potential features at the 10-minute-by-10-minute resolution

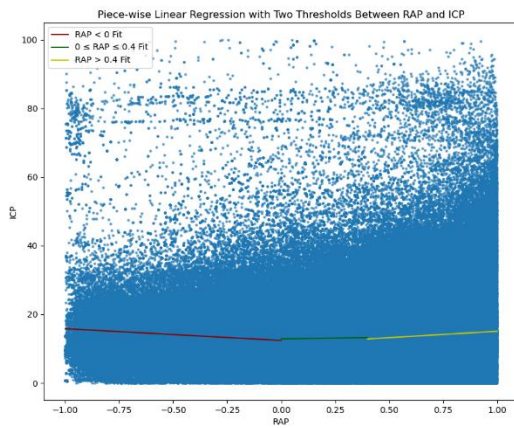
Parameter	Total data	True artifacts	Predicted artifacts	False positives	Success rate (%)
Difference of the optimal ARIMA models					
ICP	415	19	11	290	55.336
AMP			10	298	54.128
RAP			8	312	43.089
Medians of the variance of residuals					
ICP	415	19	16	223	85.092
AMP			14	222	74.264
RAP			16	219	84.411
Median of the maximum cross-correlation of residuals					
RAP-ICP	415	19	1	240	6.512
RAP-AMP			7	240	35.829

Appendix G. Section 5.3.2: General descriptive relationships between RAP and other physiological variables

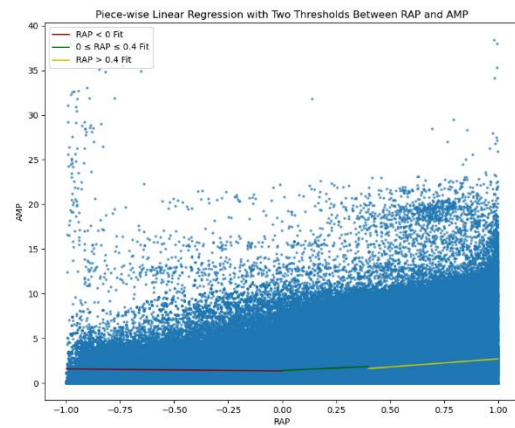
This appendix presents scatterplots and box plots, along with the median physiological measurements and formal comparison results across different groups segmented based on RAP thresholds. Additionally, it includes a reverse analysis, examining the response of RAP through median measurements and statistical comparisons in relation to other physiological thresholds. This appendix also includes %time spent within certain threshold ranges.

AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; IQR, interquartile range; MAP, mean arterial pressure; P_{ax}, pulse amplitude index; PbtO₂, brain tissue oxygenation; PR_x, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

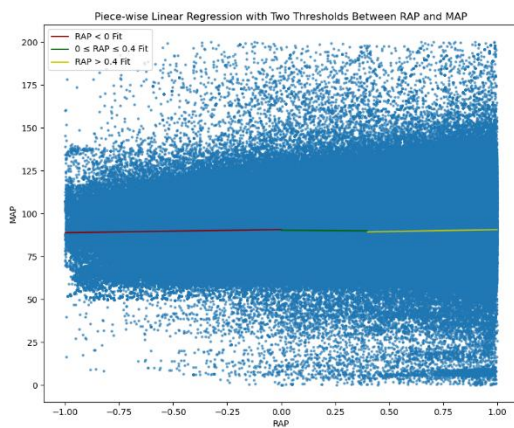
Figure G.1 Scatterplots across the entire population with piecewise linear regression (based on RAP thresholds) for the physiological variables at minute-by-minute resolution



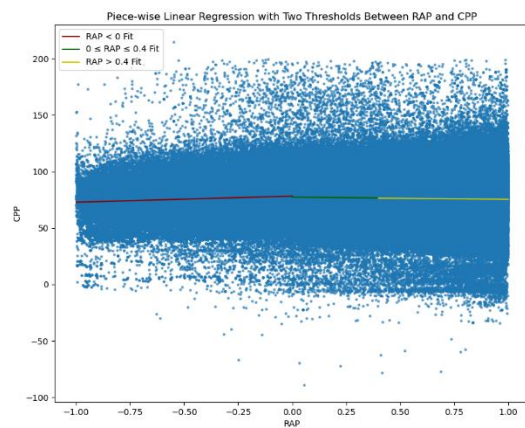
(a) RAP-ICP scatterplot



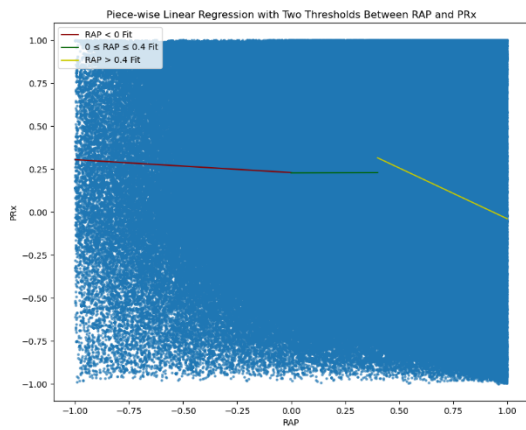
(b) RAP-AMP scatterplot



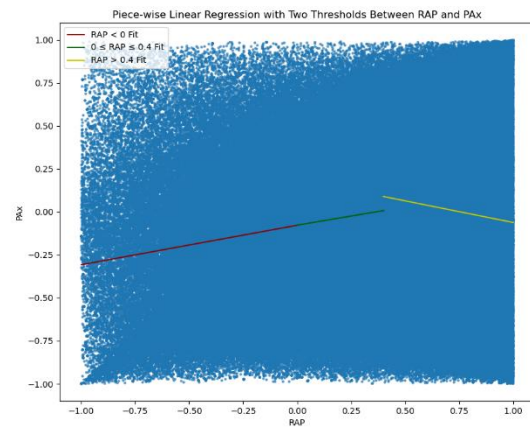
(c) RAP-MAP scatterplot



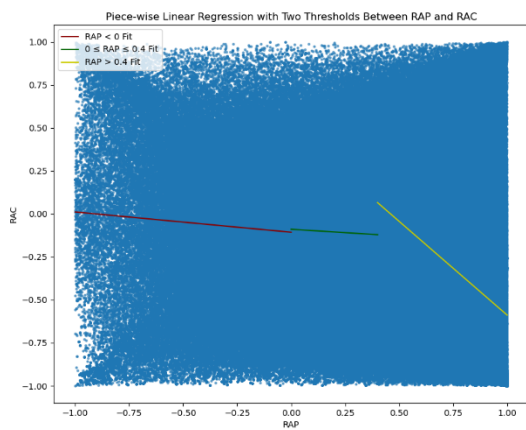
(d) RAP-CPP scatterplot



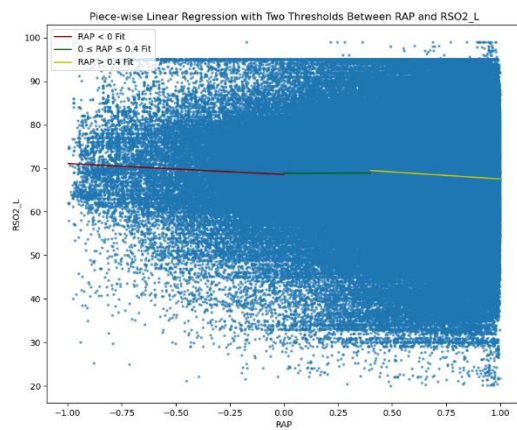
(e) RAP-PRx scatterplot



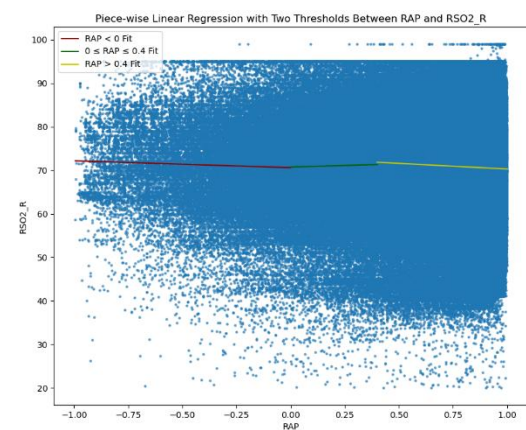
(f) RAP-PAX scatterplot



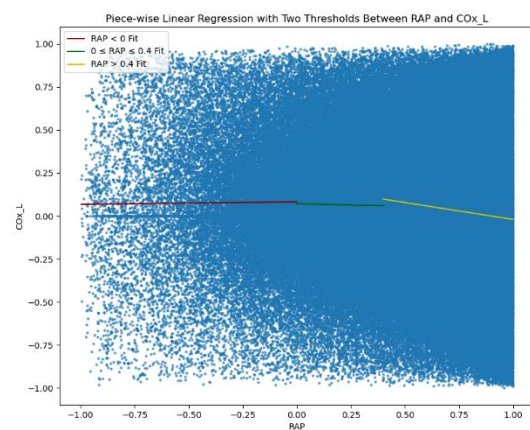
(g) RAP-RAC scatterplot



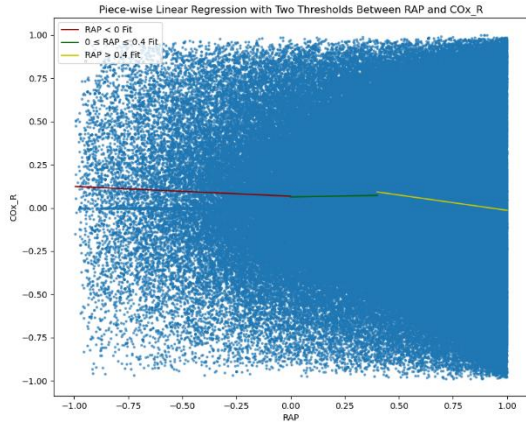
(h) RAP-rSO2_L scatterplot



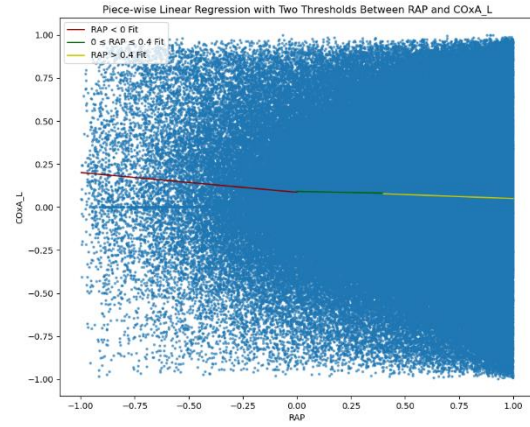
(i) RAP-rSO2_R scatterplot



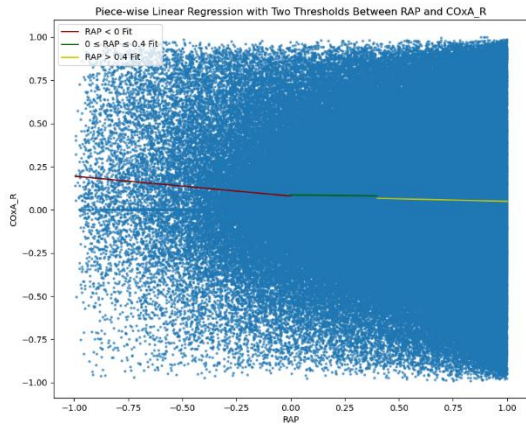
(j) RAP-COx_L scatterplot



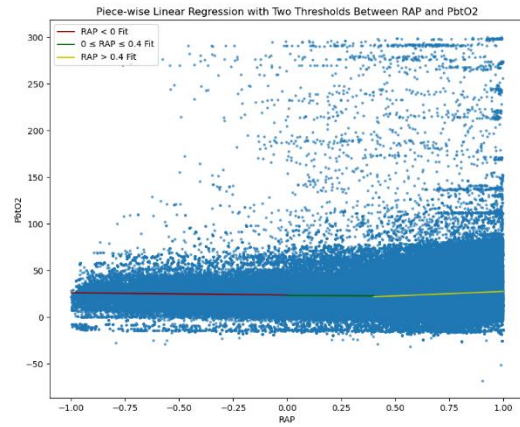
(k) RAP-COx_R scatterplot



(l) RAP-COx_A_L scatterplot



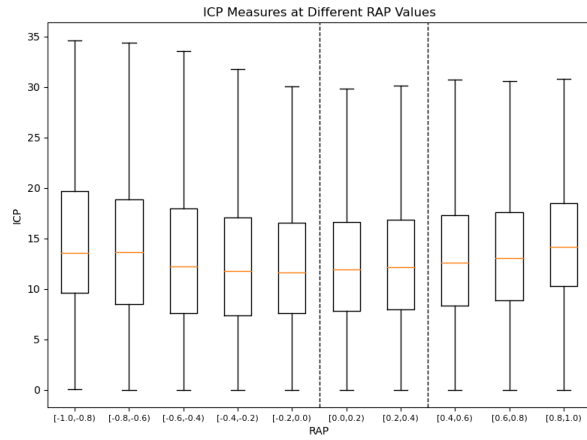
(m) RAP-COx_A_R scatterplot



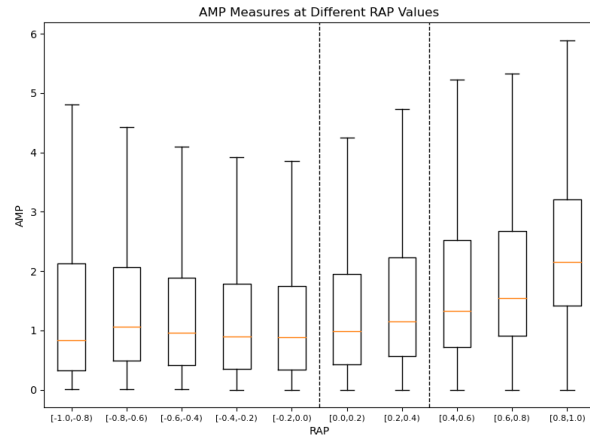
(n) RAP-PbtO2 scatterplot

This figure documents the scatterplots for the physiologic signals (a) ICP (b) AMP (c) MAP (d) CPP (e) PRx (f) PAX (g) RAC (h) rSO₂_L (i) rSO₂_R (j) COx_L (k) COx_L (l) COx_A_L (m) COx_A_R (n) PbtO₂ at the minute-by-minute resolution with respect to RAP across the whole population with piecewise linear regression, which was derived based on RAP threshold ranges. The green, yellow and red solid lines correspond to the $0 \leq \text{RAP} \leq 0.4$, $\text{RAP} > 0.4$, and $\text{RAP} < 0$ segments, respectively.

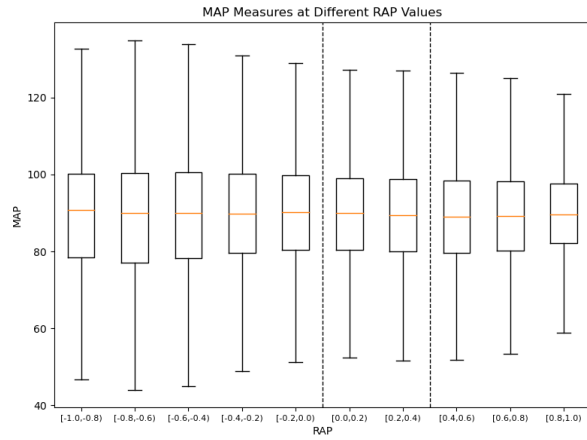
Figure G.2 Boxplots across the entire population for the physiological variables



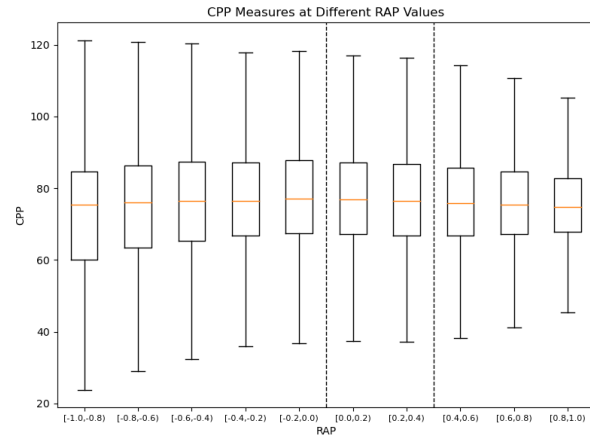
(a) RAP-ICP boxplot



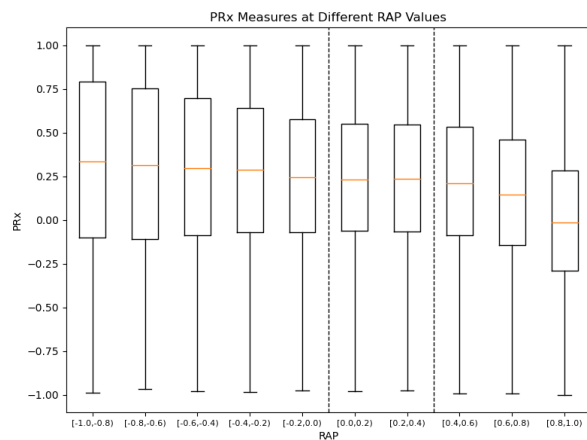
(b) RAP-AMP boxplot



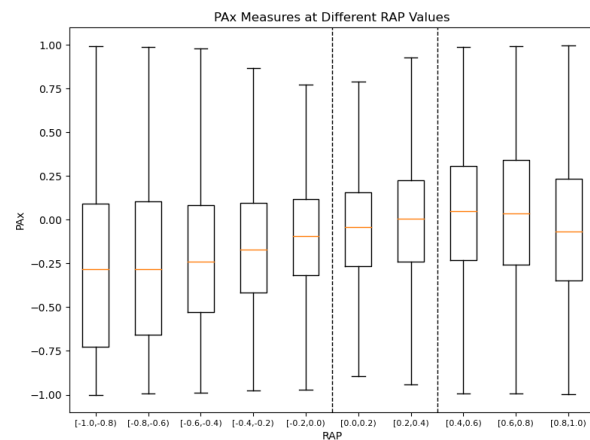
(c) RAP-MAP boxplot



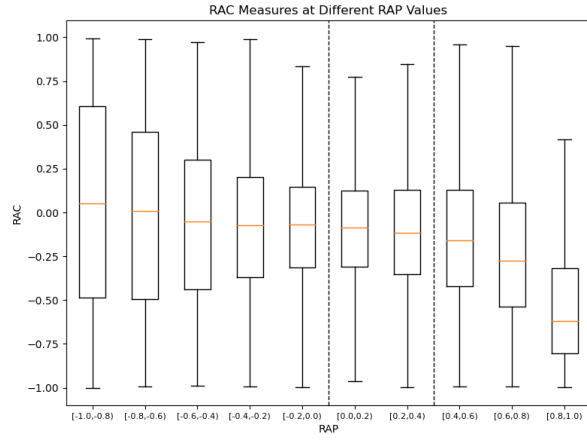
(d) RAP-CPP boxplot



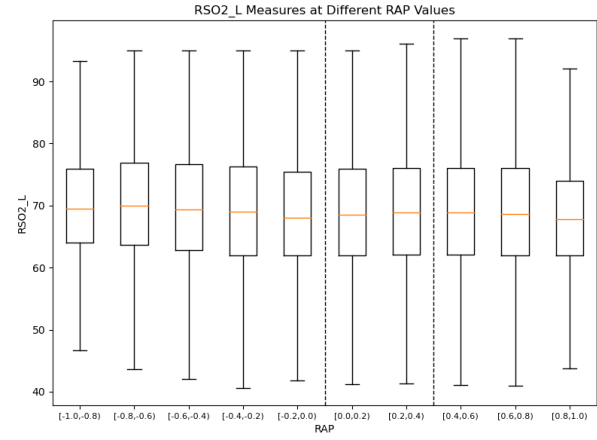
(e) RAP-PRx boxplot



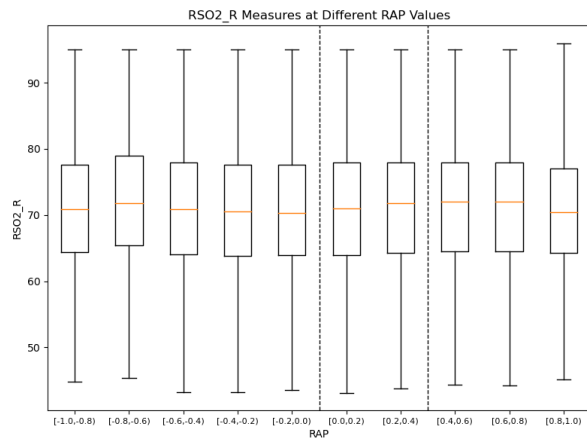
(f) RAP-PAx boxplot



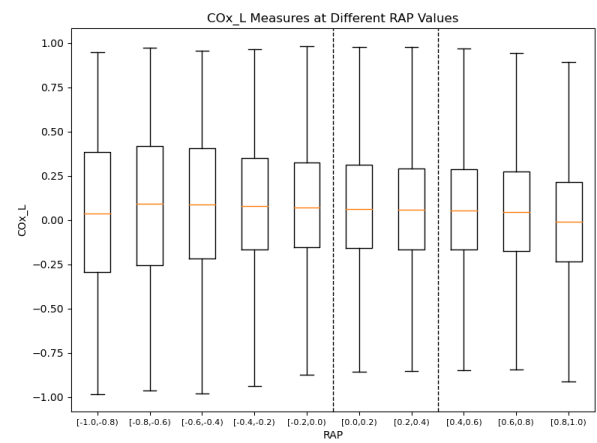
(g) RAP-RAC boxplot



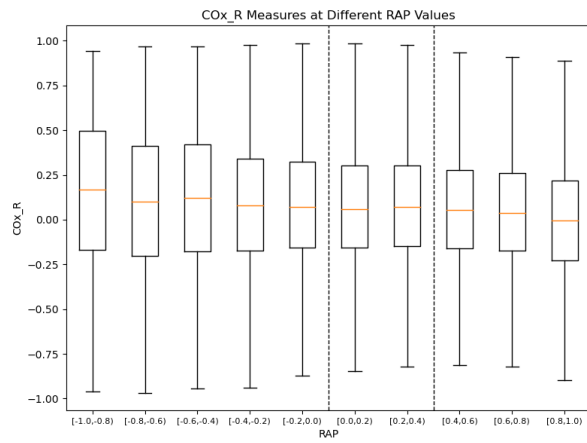
(h) RAP-rSO2_L boxplot



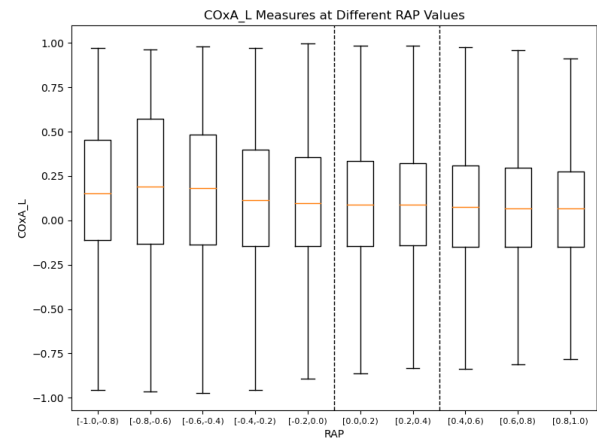
(i) RAP-rSO2_R boxplot



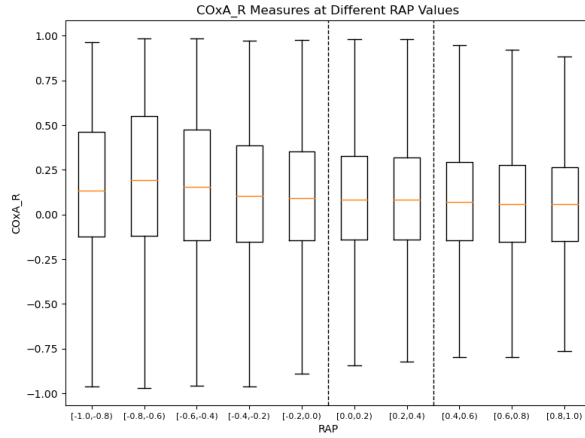
(j) RAP-Cox_L boxplot



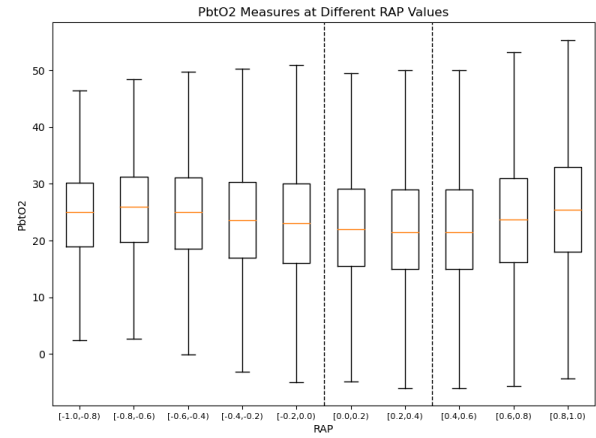
(k) RAP-Cox_R boxplot



(l) RAP-CoxA_L boxplot



(k) RAP-CoxA_R boxplot



(l) RAP-PbtO2 boxplot

This figure documents the boxplots for the physiologic signals (a) ICP (b) AMP (c) MAP (d) CPP (e) PRx (f) PAX (g) RAC (h) rSO2_L (i) rSO2_R (j) COx_L (k) COx_L (l) COxA_L (m) COxA_R (n) PbtO2 with respect to RAP across the whole population. Each bin covers the 0.2 range of RAP, starting from [-1, -0.8] to [0.8, 1]. The entire plot is segmented into three parts based on the RAP threshold ranges, which are separated by vertical dashed lines.

Table G.1 Median physiology measures across the RAP states with formal comparison and % time spent of parameters within different RAP states at their threshold ranges

RAP Thresholds				
Parameter	RAP < 0 (IQR)	0 ≤ RAP ≤ 0.4 (IQR)	RAP > 0.4 (IQR)	p-value
RAP	-0.234(-0.458—0.1)	0.239(0.134—0.326)	0.873(0.722—0.949)	3.05e-19
ICP	12.03(7.7—17.3)	12.06(7.891—16.75)	13.71(9.697—18.14)	0.021
AMP	0.913(0.362—1.822)	1.081(0.506—2.119)	1.93(1.174—3.052)	3.94e-09
MAP	90.06(79.64—100.1)	89.66(80.11—98.9)	89.46(81.44—97.85)	0.008
CPP	76.69(66.38—87.2)	76.63(67.04—86.9)	75.07(67.58—83.53)	0.638
PRx	0.271(-0.078—0.638)	0.233(-0.064—0.548)	0.047(-0.238—0.36)	0.035
PAx	-0.147(-0.423—0.107)	-0.015(-0.25—0.2)	-0.03(-0.314—0.272)	0.184
RAC	-0.06(-0.364—0.214)	-0.103(-0.336—0.126)	-0.485(-0.739—0.131)	1.00e-04
RSO2_L	69.29(62.67—76.485)	69.03(62.54—76.39)	68.02(62.08—74.94)	0.093
RSO2_R	71.01(64.325—78.32)	71.96(64.53—78.16)	71.29(64.57—77.71)	0.152
COx_L	0.076(-0.172—0.35)	0.058(-0.159—0.298)	0.009(-0.215—0.234)	0.170
COx_R	0.085(-0.166—0.352)	0.066(-0.15—0.301)	0.013(-0.206—0.233)	0.508
COxA_L	0.115(-0.14—0.402)	0.085(-0.14—0.323)	0.065(-0.15—0.28)	0.669
COxA_R	0.11(-0.141—0.395)	0.084(-0.138—0.32)	0.059(-0.146—0.268)	0.827
PbtO2	24.0(17.31—30.56)	21.66(15.01—29.0)	24.67(17.24—32.0)	0.819
% time spent within the thresholds of the parameters				

% time spent within ICP thresholds	ICP < 20	ICP ≥ 20	ICP < 20	ICP ≥ 20	ICP < 20	ICP ≥ 20
	91.29%(75.06%—99.03%)	8.71%(0.97%—24.94%)	94.11%(79.5%—99.14%)	5.89%(0.86%—20.5%)	95.07%(80.42%—99.38%)	4.93%(0.62%—19.58%)
	ICP < 22	ICP ≥ 22	ICP < 22	ICP ≥ 22	ICP < 22	ICP ≥ 22
	95.5%(84.62%—100.0%)	4.5%(0.0%—15.38%)	96.98%(89.06%—99.69%)	3.02%(0.31%—10.94%)	97.92%(89.57%—99.8%)	2.08%(0.2%—10.43%)
% time spent within CPP thresholds	CPP < 60	CPP ≥ 60	CPP < 60	CPP ≥ 60	CPP < 60	CPP ≥ 60
	3.72%(0.55%—11.03%)	96.28%(88.97%—99.45%)	3.66%(0.89%—9.38%)	96.34%(90.62%—99.11%)	4.54%(1.21%—9.35%)	95.46%(90.65%—98.79%)
	CPP < 70	CPP ≥ 70	CPP < 70	CPP ≥ 70	CPP < 70	CPP ≥ 70
	24.19%(9.65%—48.57%)	75.81%(51.43%—90.35%)	24.41%(9.38%—47.42%)	75.59%(52.58%—90.62%)	34.25%(14.63%—54.07%)	65.75%(45.93%—85.37%)
% time spent within PRx thresholds	PRx < 0	PRx ≥ 0	PRx < 0	PRx ≥ 0	PRx < 0	PRx ≥ 0
	25.83%(13.29%—39.79%)	74.17%(60.21%—86.71%)	27.27%(16.67%—39.54%)	72.73%(60.46%—83.33%)	42.11%(25.78%—55.92%)	57.89%(44.08%—74.22%)
	PRx < 0.25	PRx ≥ 0.25	PRx < 0.25	PRx ≥ 0.25	PRx < 0.25	PRx ≥ 0.25
	45.11%(27.25%—61.72%)	54.89%(38.28%—72.75%)	50.91%(33.8%—65.83%)	49.09%(34.17%—66.2%)	67.84%(49.99%—78.08%)	32.16%(21.92%—50.01%)
	PRx < 0.35	PRx ≥ 0.35	PRx < 0.35	PRx ≥ 0.35	PRx < 0.35	PRx ≥ 0.35
	52.93%(34.72%—69.48%)	47.07%(30.52%—65.28%)	61.0%(44.16%—74.54%)	39.0%(25.46%—55.84%)	75.66%(60.52%—84.96%)	24.34%(15.04%—39.48%)
% time spent within PAx thresholds	PAx < 0	PAx ≥ 0	PAx < 0	PAx ≥ 0	PAx < 0	PAx ≥ 0
	65.87%(52.96%—80.68%)	34.13%(19.32%—47.04%)	53.61%(41.02%—66.4%)	46.39%(33.6%—58.98%)	49.26%(32.33%—64.97%)	50.74%(35.03%—67.67%)
	PAx < 0.25	PAx ≥ 0.25	PAx < 0.25	PAx ≥ 0.25	PAx < 0.25	PAx ≥ 0.25
	86.86%(77.61%—93.26%)	13.14%(6.74%—22.39%)	83.94%(71.73%—89.42%)	16.06%(10.58%—28.27%)	75.49%(59.28%—85.6%)	24.51%(14.4%—40.72%)
% time spent within RAC thresholds	RAC < 0	RAC ≥ 0	RAC < 0	RAC ≥ 0	RAC < 0	RAC ≥ 0

	53.42%(41.0%—71.98%)	46.58%(28.02%—59.0%)	65.0%(51.54%—77.42%)	35.0%(22.58%—48.46%)	81.76%(66.19%—92.08%)	18.24%(7.92%—33.81%)
% time spent within rSO ₂ _L thresholds	rSO ₂ _L < 60	rSO ₂ _L ≥ 60	rSO ₂ _L < 60	rSO ₂ _L ≥ 60	rSO ₂ _L < 60	rSO ₂ _L ≥ 60
	7.65%(0.0%—36.09%)	92.35%(63.91%—100.0%)	7.25%(0.07%—37.7%)	92.75%(62.3%—99.93%)	6.15%(0.21%—39.16%)	93.85%(60.84%—99.79%)
	rSO ₂ _L < 70	rSO ₂ _L ≥ 70	rSO ₂ _L < 70	rSO ₂ _L ≥ 70	rSO ₂ _L < 70	rSO ₂ _L ≥ 70
	60.43%(14.12%—94.57%)	39.57%(5.43%—85.88%)	61.73%(15.01%—94.46%)	38.27%(5.54%—84.99%)	63.33%(16.83%—95.02%)	36.67%(4.98%—83.17%)
	rSO ₂ _L < 80	rSO ₂ _L ≥ 80	rSO ₂ _L < 80	rSO ₂ _L ≥ 80	rSO ₂ _L < 80	rSO ₂ _L ≥ 80
	98.18%(80.61%—100.0%)	1.82%(0.0%—19.39%)	99.06%(82.05%—100.0%)	0.94%(0.0%—17.95%)	99.36%(84.1%—100.0%)	0.64%(0.0%—15.9%)
	rSO ₂ _L < 90	rSO ₂ _L ≥ 90	rSO ₂ _L < 90	rSO ₂ _L ≥ 90	rSO ₂ _L < 90	rSO ₂ _L ≥ 90
	100.0%(100.0%—100.0%)	0.0%(0.0%—0.0%)	100.0%(100.0%—100.0%)	0.0%(0.0%—0.0%)	100.0%(99.99%—100.0%)	0.0%(0.0%—0.01%)
% time spent within rSO ₂ _R thresholds	rSO ₂ _R < 60	rSO ₂ _R ≥ 60	rSO ₂ _R < 60	rSO ₂ _R ≥ 60	rSO ₂ _R < 60	rSO ₂ _R ≥ 60
	3.06%(0.0%—25.5%)	96.94%(74.5%—100.0%)	3.38%(0.0%—31.1%)	96.62%(68.9%—100.0%)	3.49%(0.0%—28.1%)	96.51%(71.9%—100.0%)
	rSO ₂ _R < 70	rSO ₂ _R ≥ 70	rSO ₂ _R < 70	rSO ₂ _R ≥ 70	rSO ₂ _R < 70	rSO ₂ _R ≥ 70
	44.22%(9.72%—87.34%)	55.78%(12.66%—90.28%)	40.8%(12.16%—89.35%)	59.2%(10.65%—87.84%)	50.97%(11.12%—91.85%)	49.03%(8.15%—88.88%)
	rSO ₂ _R < 80	rSO ₂ _R ≥ 80	rSO ₂ _R < 80	rSO ₂ _R ≥ 80	rSO ₂ _R < 80	rSO ₂ _R ≥ 80
	97.88%(74.32%—100.0%)	2.12%(0.0%—25.68%)	98.16%(78.55%—100.0%)	1.84%(0.0%—21.45%)	98.57%(80.81%—100.0%)	1.43%(0.0%—19.19%)
	rSO ₂ _R < 90	rSO ₂ _R ≥ 90	rSO ₂ _R < 90	rSO ₂ _R ≥ 90	rSO ₂ _R < 90	rSO ₂ _R ≥ 90
	100.0%(100.0%—100.0%)	0.0%(0.0%—0.0%)	100.0%(99.97%—100.0%)	0.0%(0.0%—0.03%)	100.0%(99.77%—100.0%)	0.0%(0.0%—0.23%)
% time spent within COx_L thresholds	COx_L < 0	COx_L ≥ 0	COx_L < 0	COx_L ≥ 0	COx_L < 0	COx_L ≥ 0
	38.32%(30.12%—48.87%)	61.68%(51.13%—69.88%)	38.92%(29.21%—47.51%)	61.08%(52.49%—70.79%)	42.33%(33.83%—52.61%)	57.67%(47.39%—66.17%)

	COx_L < 0.20	COx_L ≥ 0.20	COx_L < 0.20	COx_L ≥ 0.20	COx_L < 0.20	COx_L ≥ 0.20	
	66.67%(56.83%—77.69%)	33.33%(22.31%—43.17%)	67.15%(58.93%—75.12%)	32.85%(24.88%—41.07%)	75.11%(68.12%—80.54%)	24.89%(19.46%—31.88%)	
% time spent within COx_R thresholds	COx_R < 0	COx_R ≥ 0	COx_R < 0	COx_R ≥ 0	COx_R < 0	COx_R ≥ 0	
	38.34%(28.28%—47.89%)	61.66%(52.11%—71.72%)	36.2%(27.79%—46.44%)	63.8%(53.56%—72.21%)	42.22%(31.91%—50.3%)	57.78%(49.7%—68.09%)	
	COx_R < 0.20	COx_R ≥ 0.20	COx_R < 0.20	COx_R ≥ 0.20	COx_R < 0.20	COx_R ≥ 0.20	
	67.29%(55.33%—76.51%)	32.71%(23.49%—44.67%)	70.02%(59.33%—78.93%)	29.98%(21.07%—40.67%)	76.26%(68.38%—83.12%)	23.74%(16.88%—31.62%)	
% time spent within COx-a_L thresholds	COx-a_L < 0	COx-a_L ≥ 0	COx-a_L < 0	COx-a_L ≥ 0	COx-a_L < 0	COx-a_L ≥ 0	
	36.63%(26.67%—46.05%)	63.37%(53.95%—73.33%)	35.88%(28.99%—46.28%)	64.12%(53.72%—71.01%)	36.34%(30.42%—44.95%)	63.66%(55.05%—69.58%)	
	COx-a_L < 0.20	COx-a_L ≥ 0.20	COx-a_L < 0.20	COx-a_L ≥ 0.20	COx-a_L < 0.20	COx-a_L ≥ 0.20	
	62.04%(50.0%—71.4%)	37.96%(28.6%—50.0%)	64.0%(55.23%—74.35%)	36.0%(25.65%—44.77%)	69.36%(61.77%—76.1%)	30.64%(23.9%—38.23%)	
% time spent within COx-a_R thresholds	COx-a_R < 0	COx-a_R ≥ 0	COx-a_R < 0	COx-a_R ≥ 0	COx-a_R < 0	COx-a_R ≥ 0	
	35.29%(26.05%—47.33%)	64.71%(52.67%—73.95%)	35.33%(28.0%—45.16%)	64.67%(54.84%—72.0%)	38.46%(28.52%—44.81%)	61.54%(55.19%—71.48%)	
	COx-a_R < 0.20	COx-a_R ≥ 0.20	COx-a_R < 0.20	COx-a_R ≥ 0.20	COx-a_R < 0.20	COx-a_R ≥ 0.20	
	64.73%(50.06%—74.24%)	35.27%(25.76%—49.94%)	68.08%(54.55%—75.64%)	31.92%(24.36%—45.45%)	72.16%(63.9%—80.09%)	27.84%(19.91%—36.1%)	
% time spent within PbtO ₂ thresholds	PbtO ₂ < 15	PbtO ₂ ≥ 15	PbtO ₂ < 15	PbtO ₂ ≥ 15	PbtO ₂ < 15	PbtO ₂ ≥ 15	
	12.37%(2.69%—65.69%)	87.63%(34.31%—97.31%)	12.42%(1.98%—69.96%)	87.58%(30.04%—98.02%)	7.57%(1.41%—70.3%)	92.43%(29.7%—98.59%)	
	PbtO ₂ < 25	PbtO ₂ ≥ 25	PbtO ₂ < 25	PbtO ₂ ≥ 25	PbtO ₂ < 25	PbtO ₂ ≥ 25	
	63.94%(23.49%—94.08%)	36.06%(5.92%—76.51%)	67.7%(32.68%—95.37%)	32.3%(4.63%—67.32%)	67.09%(20.1%—96.55%)	32.91%(3.45%—79.9%)	

Table G.2 Median physiology measures across the thresholds of different physiologic variables with formal comparison and % time spent of RAP within different RAP states at the threshold ranges

ICP Thresholds							
Parameter	ICP < 20			ICP ≥ 20			p-value
ICP	12.11(8.437—15.49)			23.64(21.5—27.58)			9.83e-20
RAP	0.812(0.525—0.933)			0.853(0.594—0.95)			0.535
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.69%(2.06%—10.26%)	10.77%(6.05%—17.69%)	83.93%(72.05%—91.68%)	6.25%(2.2%—14.24%)	10.34%(4.59%—17.93%)	81.33%(67.68%—92.42%)	
Parameter	ICP < 22			ICP ≥ 22			p-value
ICP	12.57(8.785—16.37)			26.25(24.01—30.89)			5.23e-11
RAP	0.816(0.532—0.935)			0.845(0.579—0.948)			0.725
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.66%(2.16%—9.97%)	10.67%(5.85%—17.44%)	83.92%(72.19%—91.68%)	6.21%(1.98%—15.52%)	11.14%(4.29%—19.0%)	79.7%(64.38%—92.96%)	
CPP Thresholds							
Parameter	CPP < 60			CPP ≥ 60			p-value
CPP	54.46(48.67—57.86)			76.78(69.79—85.17)			8.92e-10
RAP	0.719(0.406—0.904)			0.83(0.558—0.939)			0.139
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.36%(1.15%—11.03%)	9.66%(3.71%—20.0%)	83.67%(67.98%—93.76%)	4.79%(2.23%—9.43%)	10.33%(5.65%—17.65%)	84.1%(72.68%—92.06%)	
Parameter	CPP < 70			CPP ≥ 70			p-value
CPP	64.05(59.04—67.29)			80.68(75.15—88.19)			6.96e-49
RAP	0.818(0.539—0.934)			0.823(0.543—0.938)			0.006
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	3.76%(1.48%—9.11%)	8.48%(3.81%—16.04%)	87.36%(74.43%—94.17%)	5.3%(2.49%—10.4%)	11.23%(6.23%—19.67%)	82.59%(68.22%—91.09%)	
PRx Thresholds							
Parameter	PRx < 0			PRx ≥ 0			p-value

PRx	-0.262(-0.447—0.123)			0.35(0.164—0.605)			1.30e-51
RAP	0.881(0.675—0.955)			0.761(0.455—0.913)			1.76e-09
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	3.12%(1.27%—8.98%)	7.69%(3.68%—15.6%)	88.26%(74.42%—94.77%)	6.12%(3.0%—11.38%)	12.86%(6.88%—20.67%)	80.86%(66.37%—89.69%)	
Parameter	PRx < 0.25			PRx ≥ 0.25			p-value
PRx	-0.124(-0.346—0.058)			0.528(0.375—0.74)			7.99e-50
RAP	0.863(0.633—0.949)			0.721(0.4—0.895)			6.86e-05
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	3.51%(1.47%—8.51%)	8.77%(4.65%—16.8%)	87.33%(73.38%—93.42%)	8.84%(4.18%—15.44%)	15.52%(8.5%—22.38%)	75.33%(60.93%—85.68%)	
Parameter	PRx < 0.35			PRx ≥ 0.35			p-value
PRx	-0.081(-0.316—0.122)			0.605(0.464—0.792)			4.74e-36
RAP	0.856(0.619—0.947)			0.701(0.377—0.886)			9.47e-06
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.36%(1.15%—11.03%)	9.66%(3.71%—20.0%)	83.67%(67.98%—93.76%)	4.79%(2.23%—9.43%)	10.33%(5.65%—17.65%)	84.1%(72.68%—92.06%)	
PAx Thresholds							
Parameter	PAx < 0			PAx ≥ 0			p-value
PAx	-0.293(-0.486—0.141)			0.275(0.128—0.477)			5.89e-63
RAP	0.842(0.54—0.945)			0.798(0.543—0.925)			0.257
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	6.7%(3.12%—14.18%)	11.46%(6.1%—19.23%)	81.07%(64.03%—89.64%)	3.3%(1.5%—6.96%)	10.23%(5.22%—17.72%)	85.85%(75.64%—92.76%)	
Parameter	PAx < 0.25			PAx ≥ 0.25			p-value
PAx	-0.17(-0.4—0.029)			0.457(0.342—0.615)			4.13e-29
RAP	0.828(0.518—0.94)			0.804(0.587—0.924)			0.215
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	5.92%(2.67%—12.04%)	12.04%(6.07%—20.37%)	81.31%(66.25%—90.92%)	2.76%(1.15%—6.59%)	7.92%(3.93%—14.97%)	88.85%(78.44%—94.53%)	

RAC Thresholds							
Parameter	RAC < 0			RAC ≥ 0			p-value
RAC	-0.546(-0.76—0.298)			0.247(0.109—0.449)			1.64e-31
RAP	0.865(0.639—0.95)			0.608(0.278—0.817)			6.99e-08
% time spent within RAC thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	3.73%(1.56%—8.56%)	9.0%(4.52%—15.8%)	86.36%(74.79%—93.53%)	10.54%(5.59%—19.46%)	17.62%(11.01%—25.66%)	69.39%(54.07%—80.8%)	
rSO ₂ _L Thresholds							
Parameter	rSO ₂ _L < 60			rSO ₂ _L ≥ 60			p-value
rSO ₂ _L	54.89(49.31—57.96)			71.0(66.34—76.44)			1.01e-13
RAP	0.856(0.623—0.941)			0.846(0.585—0.945)			0.973
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	2.84%(0.47%—10.01%)	8.66%(2.13%—18.37%)	85.76%(70.49%—96.75%)	4.93%(2.4%—10.93%)	10.32%(5.33%—17.25%)	84.17%(71.05%—91.67%)	
Parameter	rSO ₂ _L < 70			rSO ₂ _L ≥ 70			p-value
rSO ₂ _L	63.29(58.11—66.91)			75.42(71.63—79.97)			1.43e-24
RAP	0.864(0.622—0.949)			0.824(0.554—0.937)			0.044
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	3.49%(1.44%—8.83%)	8.67%(3.82%—19.34%)	86.18%(72.84%—93.69%)	5.76%(2.18%—11.85%)	11.51%(4.89%—20.15%)	82.2%(65.31%—89.78%)	
Parameter	rSO ₂ _L < 80			rSO ₂ _L ≥ 80			p-value
rSO ₂ _L	67.99(62.0—72.13)			84.03(81.67—88.6)			2.49e-11
RAP	0.858(0.607—0.948)			0.767(0.499—0.904)			0.097
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.63%(2.14%—10.22%)	9.37%(4.9%—17.73%)	84.8%(72.34%—92.33%)	6.06%(2.01%—13.87%)	13.7%(6.71%—23.28%)	78.68%(59.04%—88.96%)	
Parameter	rSO ₂ _L < 90			rSO ₂ _L ≥ 90			p-value
rSO ₂ _L	69.08(62.94—74.5)			94.35(91.99—94.99)			0.003
RAP	0.851(0.595—0.945)			0.75(0.466—0.875)			0.328

% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.75%(2.17%—10.11%)	10.21%(5.11%—18.45%)	84.17%(72.01%—91.98%)	2.16%(0.0%—12.92%)	8.47%(0.0%—19.51%)	82.91%(58.58%—100.0%)	
rSO ₂ _R Thresholds							
Parameter	rSO ₂ _R < 60			rSO ₂ _R ≥ 60			p-value
rSO ₂ _R	55.36(50.46—58.07)			74.03(67.99—79.0)			3.20e-09
RAP	0.825(0.558—0.935)			0.845(0.584—0.943)			0.490
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	3.48%(0.14%—9.49%)	8.88%(2.14%—25.45%)	85.07%(51.55%—94.75%)	4.96%(2.36%—10.27%)	9.64%(4.53%—18.95%)	84.28%(69.81%—92.36%)	
Parameter	rSO ₂ _R < 70			rSO ₂ _R ≥ 70			p-value
rSO ₂ _R	63.81(58.99—66.99)			78.0(74.04—80.32)			4.18e-24
RAP	0.86(0.603—0.949)			0.827(0.565—0.936)			0.375
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	3.82%(1.79%—10.68%)	8.53%(3.97%—18.01%)	86.07%(69.49%—94.03%)	5.06%(2.52%—11.35%)	12.77%(5.11%—21.49%)	80.68%(65.59%—90.98%)	
Parameter	rSO ₂ _R < 80			rSO ₂ _R ≥ 80			p-value
rSO ₂ _R	70.26(63.97—76.16)			84.0(81.67—87.5)			2.67e-11
RAP	0.853(0.597—0.946)			0.781(0.501—0.911)			0.002
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.75%(2.27%—11.31%)	8.83%(4.87%—19.22%)	85.47%(67.95%—91.91%)	6.71%(3.43%—12.95%)	11.61%(6.15%—25.61%)	79.17%(60.59%—88.93%)	
Parameter	rSO ₂ _R < 90			rSO ₂ _R ≥ 90			p-value
rSO ₂ _R	72.0(65.0—78.83)			93.5(91.39—94.99)			0.003
RAP	0.844(0.584—0.943)			0.757(0.454—0.897)			0.037
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.65%(2.4%—10.78%)	9.54%(5.14%—18.61%)	84.58%(72.38%—92.05%)	5.36%(0.0%—16.67%)	9.53%(0.0%—28.38%)	79.35%(52.9%—100.0%)	
COx_L Thresholds							

Parameter	COx L < 0			COx L ≥ 0			p-value
COx L	-0.217(-0.379—0.1)			0.231(0.107—0.414)			5.90e-23
RAP	0.87(0.634—0.953)			0.822(0.547—0.934)			0.023
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.12%(1.99%—10.4%)	9.66%(4.5%—17.03%)	86.33%(73.37%—93.25%)	5.64%(2.55%—10.65%)	11.01%(5.65%—19.87%)	81.92%(68.46%—90.45%)	
Parameter	COx L < 0.20			COx L ≥ 0.20			p-value
COx L	-0.105(-0.292—0.043)			0.386(0.281—0.554)			3.61e-05
RAP	0.861(0.618—0.949)			0.807(0.513—0.93)			0.781
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.28%(2.0%—10.02%)	9.42%(4.83%—16.2%)	84.92%(71.34%—93.17%)	6.25%(3.27%—12.44%)	12.4%(7.13%—20.19%)	80.05%(65.99%—89.25%)	
COx_R Thresholds							
Parameter	COx R < 0			COx R ≥ 0			p-value
COx R	-0.212(-0.372—0.098)			0.228(0.107—0.409)			1.62e-22
RAP	0.865(0.624—0.951)			0.818(0.536—0.932)			0.157
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.36%(1.98%—9.71%)	8.97%(4.33%—18.53%)	86.04%(72.04%—93.49%)	5.31%(2.75%—11.34%)	10.9%(5.96%—20.53%)	83.33%(67.38%—90.38%)	
Parameter	COx R < 0.20			COx R ≥ 0.20			p-value
COx R	-0.1(-0.283—0.046)			0.384(0.279—0.549)			1.49e-07
RAP	0.855(0.607—0.946)			0.805(0.5—0.929)			0.245
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.06%(2.1%—10.23%)	8.7%(4.87%—18.39%)	86.63%(72.87%—93.26%)	6.61%(3.33%—12.39%)	11.68%(6.79%—21.33%)	78.93%(64.53%—88.56%)	
COx-a_L Thresholds							
Parameter	COx-a L < 0			COx-a L ≥ 0			p-value
COx-a L	-0.197(-0.356—0.089)			0.247(0.118—0.424)			1.10e-09
RAP	0.855(0.607—0.947)			0.849(0.579—0.946)			0.087
	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	

% time spent within RAP thresholds	4.16%(1.87%—10.0%)	10.32%(4.53%—19.37%)	84.24%(73.27%—93.48%)	4.87%(2.29%—10.25%)	9.85%(5.03%—18.6%)	82.96%(70.33%—92.46%)	
Parameter	COx-a L < 0.20			COx-a L ≥ 0.20			p-value
COx-a L	-0.073(-0.252—0.064)			0.386(0.283—0.545)			3.62e-13
RAP	0.858(0.612—0.948)			0.838(0.548—0.944)			0.260
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.11%(1.71%—9.76%)	10.27%(4.83%—17.31%)	85.05%(70.15%—93.78%)	6.42%(3.03%—13.21%)	10.83%(6.78%—20.08%)	82.27%(65.16%—90.21%)	
COx-a_R Thresholds							
Parameter	COx-a R < 0			COx-a R ≥ 0			p-value
COx-a R	-0.19(-0.342—0.086)			0.238(0.114—0.413)			1.08e-15
RAP	0.848(0.597—0.945)			0.843(0.566—0.944)			0.296
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.32%(2.01%—9.96%)	9.45%(4.87%—18.73%)	86.17%(69.57%—92.45%)	4.95%(2.62%—11.85%)	10.1%(5.5%—20.15%)	83.66%(68.85%—91.91%)	
Parameter	COx-a R < 0.20			COx-a R ≥ 0.20			p-value
COx-a R	-0.069(-0.242—0.064)			0.382(0.28—0.54)			3.40e-09
RAP	0.851(0.601—0.945)			0.833(0.533—0.943)			0.401
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	3.72%(1.87—10.38)	9.14(4.39—18.19)	86.38(71.31—93.11)	6.07(3.33—12.33)	10.6(6.73—21.04)	82.78(66.06—89.92)	
PbtO2 Thresholds							
Parameter	PbtO2 < 15			PbtO2 ≥ 15			p-value
PbtO2	8.775(5.288—11.99)			27.0(21.26—33.37)			2.91e-18
RAP	0.774(0.494—0.926)			0.828(0.57—0.935)			0.939
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	5.15%(2.29%—10.49%)	9.96%(3.18%—21.1%)	82.08%(62.5%—91.63%)	5.78%(2.37%—13.88%)	9.98%(4.87%—17.09%)	83.21%(65.2%—92.13%)	
Parameter	PbtO2 < 20			PbtO2 ≥ 20			p-value

PbtO ₂	12.99(7.732—17.0)			29.0(24.31—35.0)			7.78e-20
RAP	0.767(0.485—0.92)			0.84(0.596—0.938)			0.601
% time spent within RAP thresholds	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	RAP < 0	0 ≤ RAP ≤ 0.4	RAP > 0.4	
	4.76%(2.37%— 12.56%)	11.9%(4.97%— 22.7%)	81.07%(63.96%— 90.73%)	5.66%(2.27%— 12.5%)	10.04%(4.64%— 18.66%)	84.22%(64.24%— 93.21%)	

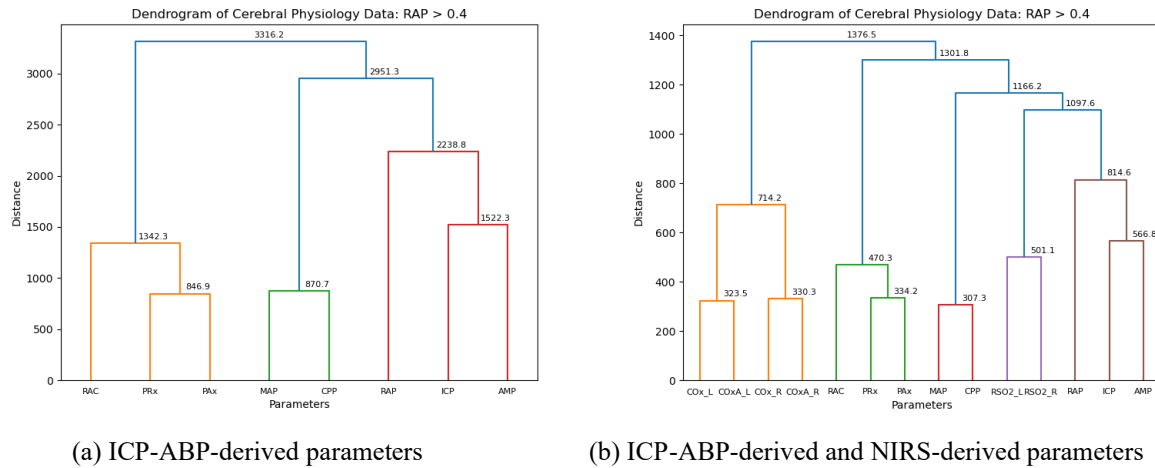
Appendix H. Section 5.3.4: Application of Semi-supervised Machine Learning Models for Clustering Parameters - Agglomerative Hierarchical Clustering (AHC)

This appendix presents the AHC dendrograms for the entire cohort at lower temporal resolutions, along with the dendrograms derived from the sub-group analyses. A summary table of the cophenetic correlation coefficients for these dendrograms is provided at the end of the appendix.

ABP, arterial blood pressure; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation ; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

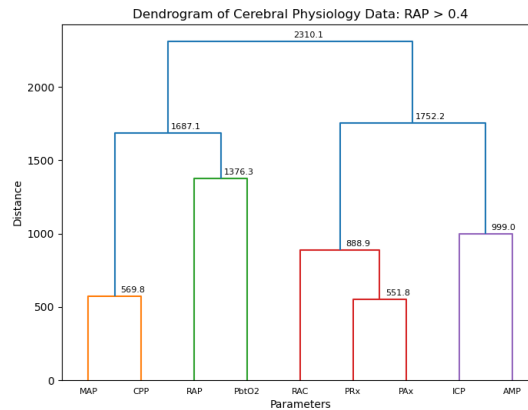
Sub-group analysis

Figure H.1 Dendrograms at minute-by-minute resolution across RAP > 0.4 state



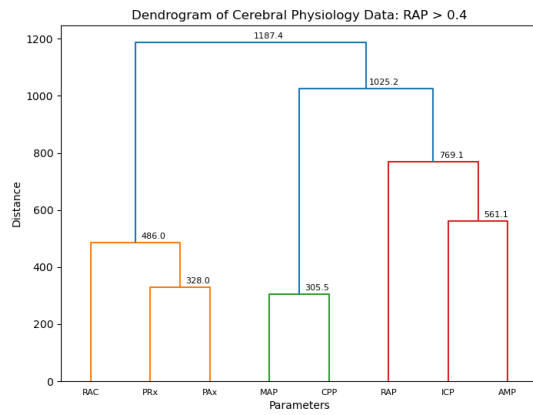
(a) ICP-ABP-derived parameters

(b) ICP-ABP-derived and NIRS-derived parameters

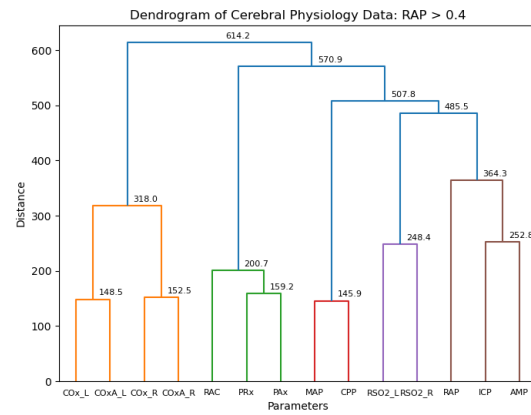


(c) ICP-ABP-derived parameters and PbtO₂

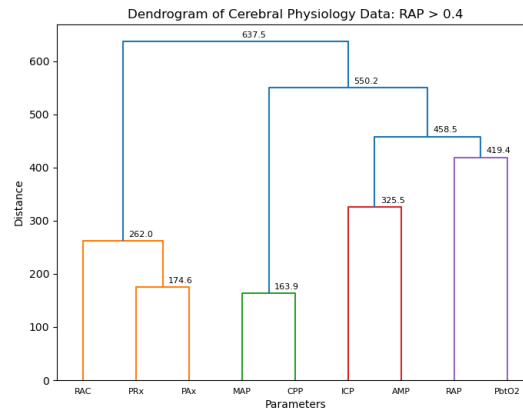
Figure H.2 Dendrograms at 5-minute-by-5-minute resolution across RAP > 0.4 state



(a) ICP-ABP-derived parameters

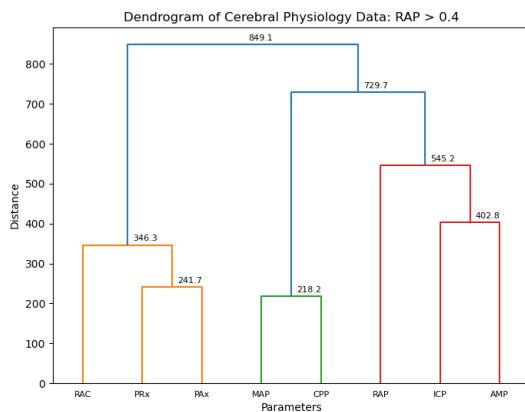


(b) ICP-ABP-derived and NIRS-derived parameters

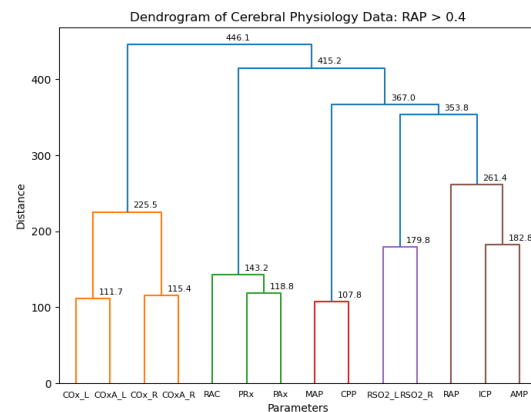


(c) ICP-ABP-derived parameters and PbtO₂

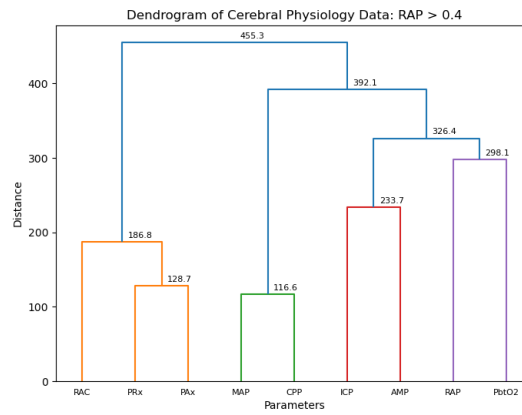
Figure H.3 Dendrograms at 10-minute-by-10-minute resolution across RAP > 0.4 state



(a) ICP-ABP-derived parameters

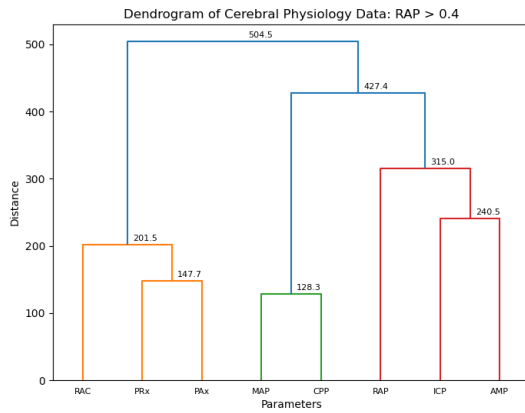


(b) ICP-ABP-derived and NIRS-derived parameters

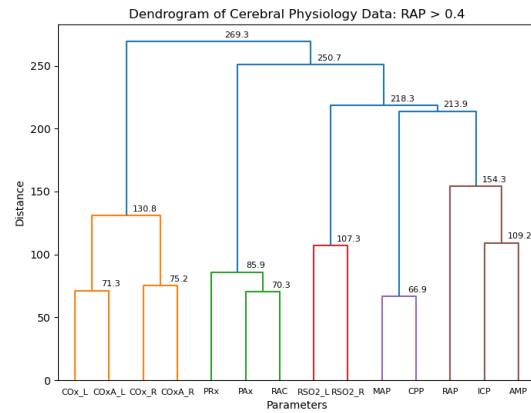


(c) ICP-ABP-derived parameters and PbtO₂

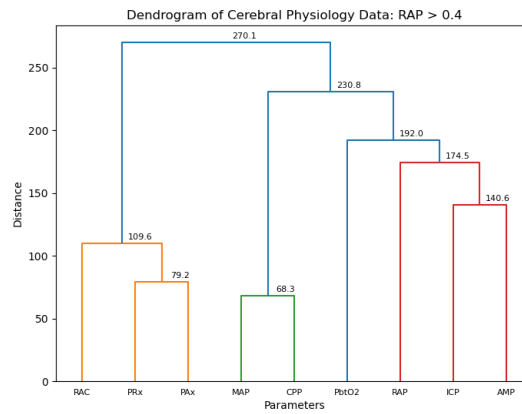
Figure H.4 Dendrograms at 30-minute-by-30-minute resolution across RAP > 0.4 state



(a) ICP-ABP-derived parameters

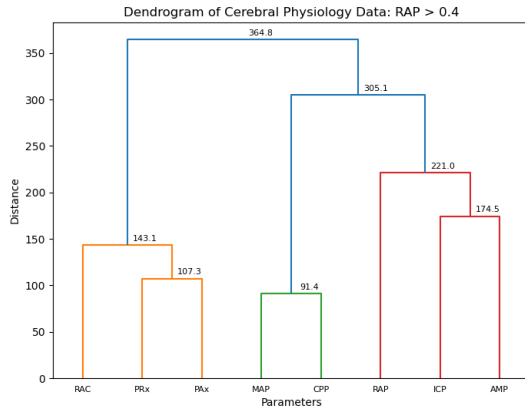


(b) ICP-ABP-derived and NIRS-derived parameters

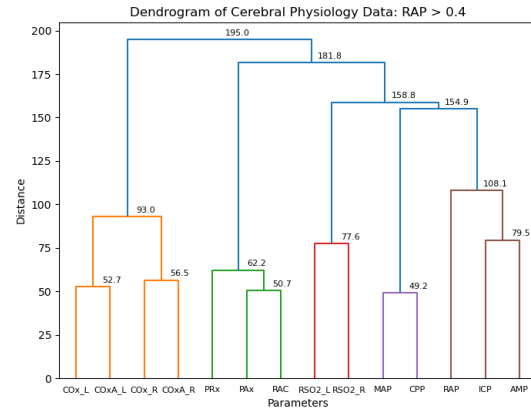


(c) ICP-ABP-derived parameters and PbtO₂

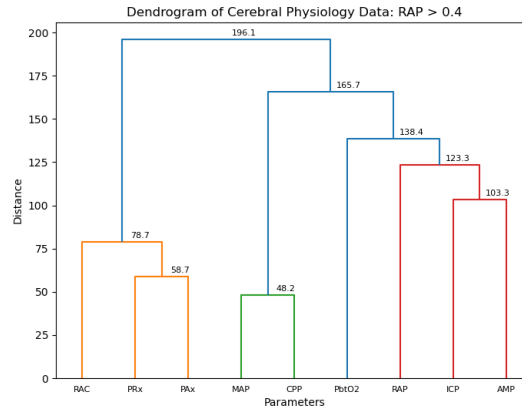
Figure H.5 Dendrograms at hour-by-hour resolution across $RAP > 0.4$ state



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

Table H.1 The cophenetic correlations for the dendrograms across all the resolutions at sub-group level

Minute-by-minute			
Sub-groups	ICP-ABP-derived parameters	ICP-ABP-derived and NIRS-derived parameters	ICP-ABP-derived parameters and PbtO ₂
$RAP < 0$	0.9	0.86	0.86
$0 \leq RAP \leq 0.4$	0.91	0.86	0.88
$RAP > 0.4$	0.89	0.9	0.91
5-minute-by-5-minute			
Sub-groups	ICP-ABP-derived parameters	ICP-ABP-derived and NIRS-derived parameters	ICP-ABP-derived parameters and PbtO ₂
$RAP < 0$	0.87	0.86	0.87
$0 \leq RAP \leq 0.4$	0.9	0.88	0.84
$RAP > 0.4$	0.89	0.89	0.84
10-minute-by-10-minute			
Sub-groups	ICP-ABP-derived parameters	ICP-ABP-derived and NIRS-derived parameters	ICP-ABP-derived parameters and PbtO ₂
$RAP < 0$	0.87	0.87	0.86
$0 \leq RAP \leq 0.4$	0.9	0.88	0.84
$RAP > 0.4$	0.89	0.89	0.83

30-minute-by-30-minute			
Sub-groups	ICP-ABP-derived parameters	ICP-ABP-derived and NIRS-derived parameters	ICP-ABP-derived parameters and PbtO ₂
RAP < 0	0.91	0.89	0.85
$0 \leq \text{RAP} \leq 0.4$	0.89	0.88	0.87
RAP > 0.4	0.88	0.88	0.82
Hour-by-hour			
Sub-groups	ICP-ABP-derived parameters	ICP-ABP-derived and NIRS-derived parameters	ICP-ABP-derived parameters and PbtO ₂
RAP < 0	0.91	0.86	0.83
$0 \leq \text{RAP} \leq 0.4$	0.88	0.88	0.85
RAP > 0.4	0.88	0.88	0.82

Appendix I. Section 5.3.4: Application of Semi-supervised Machine Learning Models - Principal Component Analysis (PCA)

This appendix displays the scree plots of the explained variance ratio and cumulative explained variance ratio across all data resolutions, derived from the principal components following PCA application to the full cohort. Additionally, it includes PCA biplots for the lower resolutions, based on the first two principal components. Biplots for the subgroup analyses are also presented in this appendix.

ABP, arterial blood pressure; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation ; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

Sub-group analysis

Figure I.1 PCA biplots at minute-by-minute resolution across RAP > 0.4 state

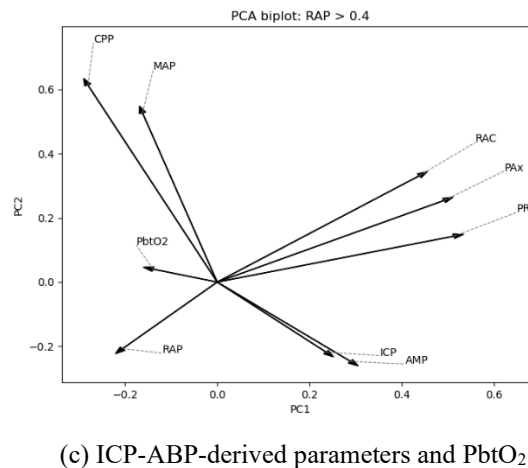
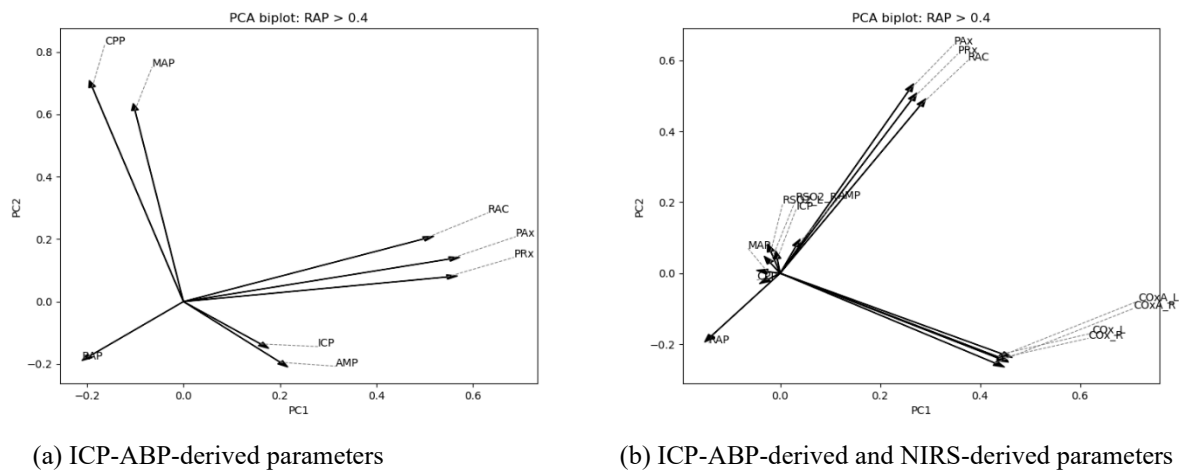
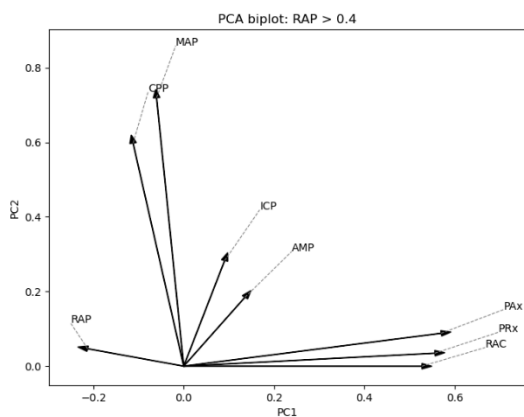
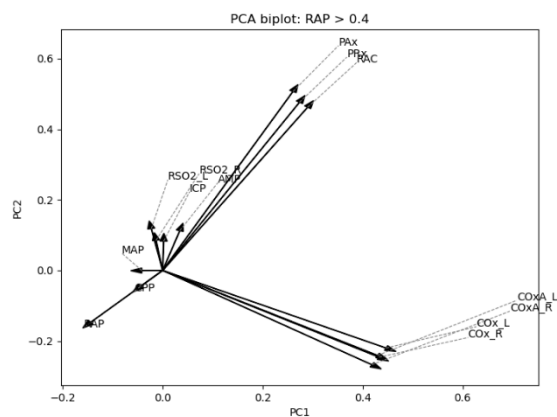


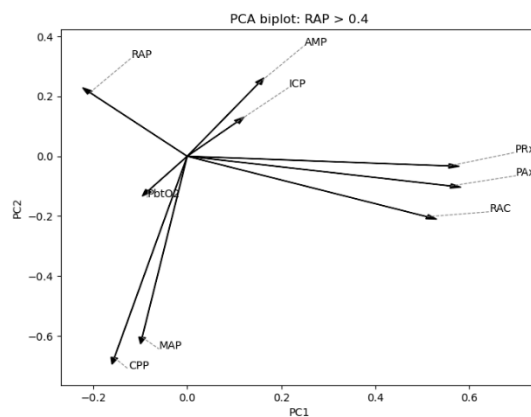
Figure I.2 PCA biplots at 5-minute-by-5-minute resolution across RAP > 0.4 state



(a) ICP-ABP-derived parameters

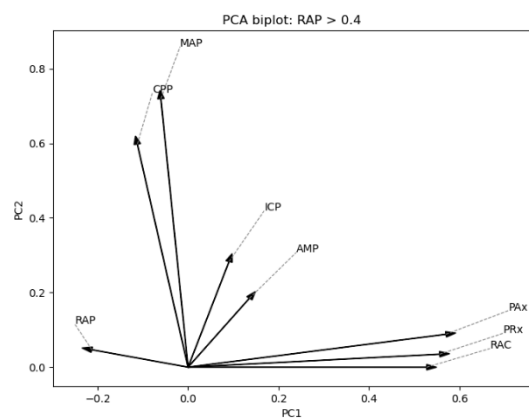


(b) ICP-ABP-derived and NIRS-derived parameters

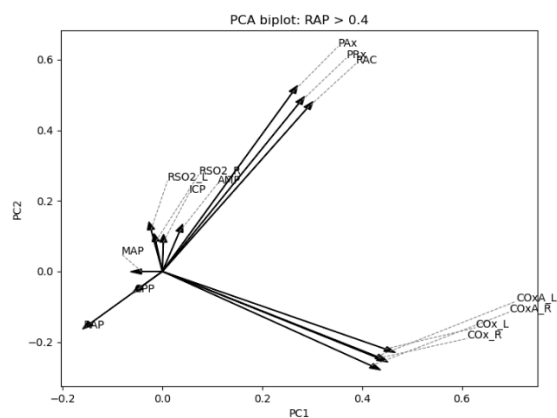


(c) ICP-ABP-derived parameters and PbtO₂

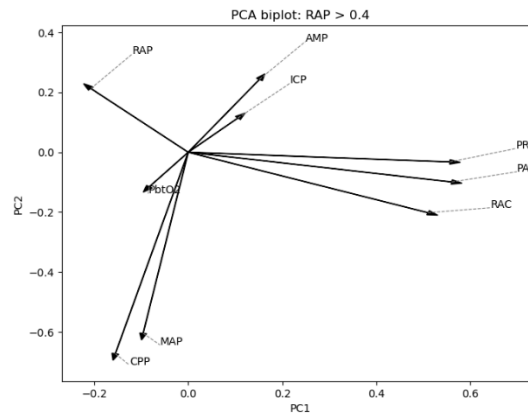
Figure I.3 PCA biplots at 5-minute-by-5-minute resolution across $RAP > 0.4$ state



(a) ICP-ABP-derived parameters

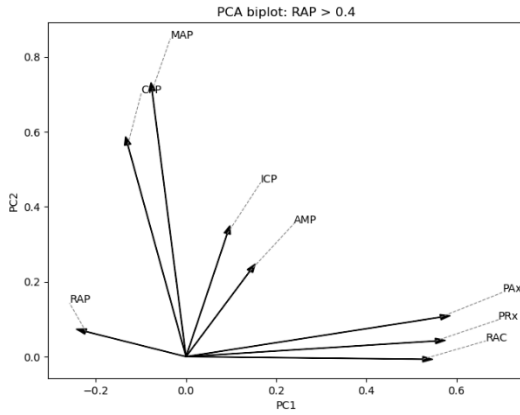


(b) ICP-ABP-derived and NIRS-derived parameters

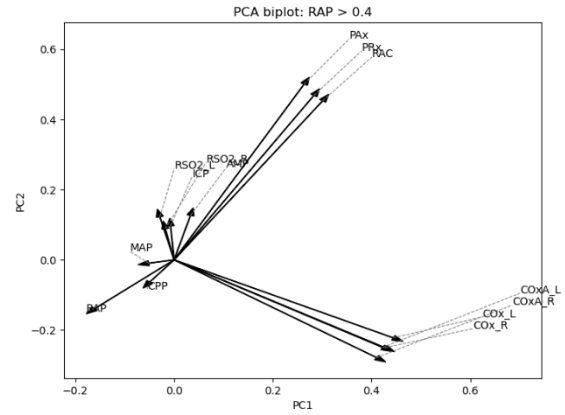


(c) ICP-ABP-derived parameters and PbtO₂

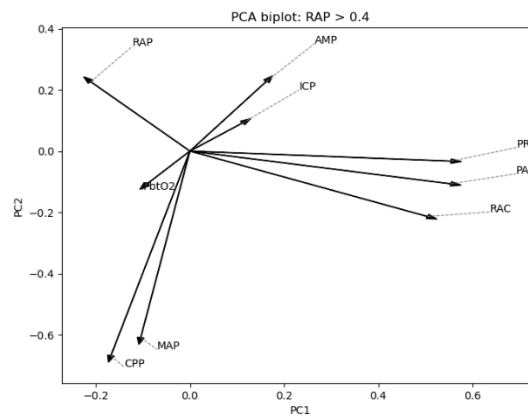
Figure I.4 PCA biplots at 10-minute-by-10-minute resolution across RAP > 0.4 state



(a) ICP-ABP-derived parameters

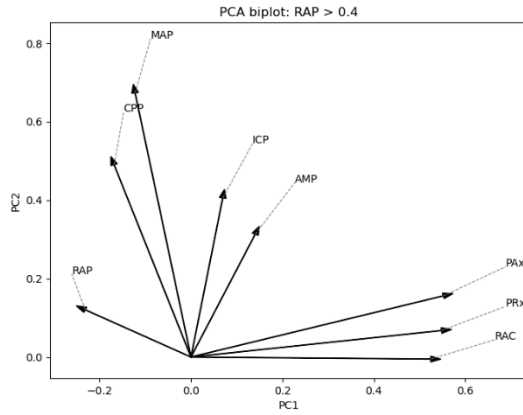


(b) ICP-ABP-derived and NIRS-derived parameters

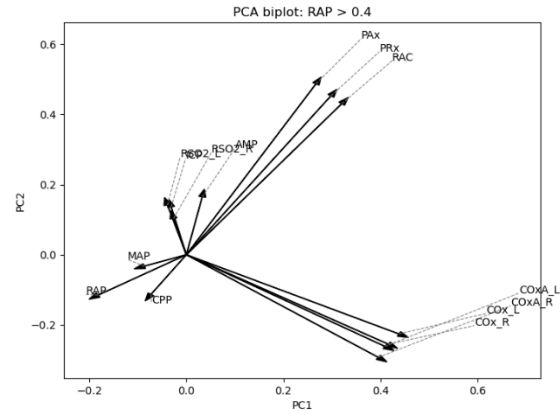


(c) ICP-ABP-derived parameters and PbtO₂

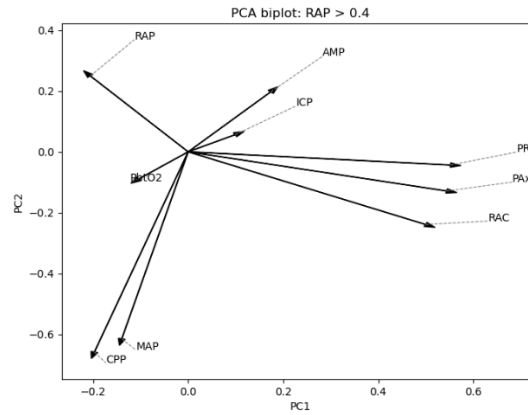
Figure I.5 PCA biplots at 30-minute-by-30-minute resolution across $RAP > 0.4$ state



(a) ICP-ABP-derived parameters

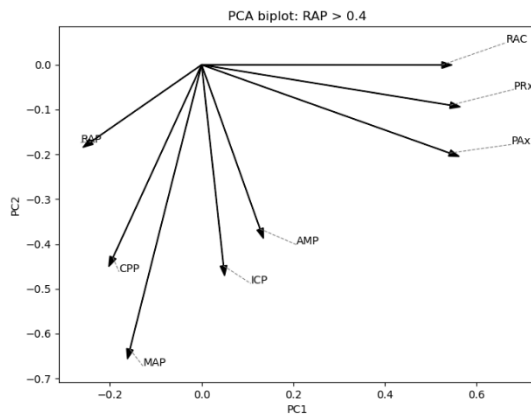


(b) ICP-ABP-derived and NIRS-derived parameters

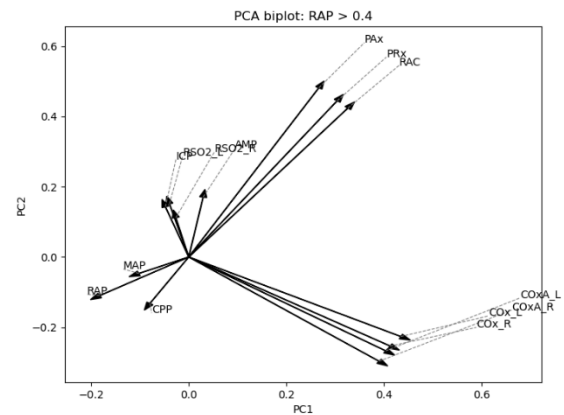


(c) ICP-ABP-derived parameters and PbtO₂

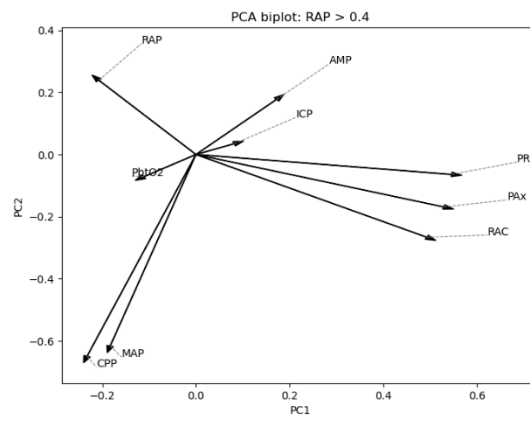
Figure I.6 PCA biplots at hour-by-hour resolution across $RAP > 0.4$ state



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

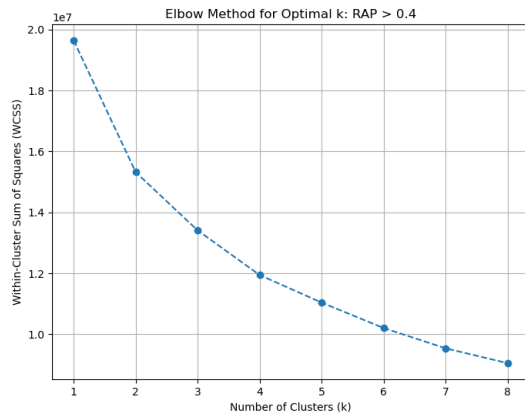
Appendix J. Section 5.3.4: Application of Semi-supervised Machine Learning Models – K-Means Clustering Analysis (KMCA)

This appendix contains the number of clusters (k) vs *within-cluster sum of squared errors (WCSS)* graphs for the application of the elbow method to determine the optimal k for KMCA. These plots are provided for both lower-resolution data and sub-group analyses. The KMCA results for sub-group analyses are also summarized at the end of the appendix.

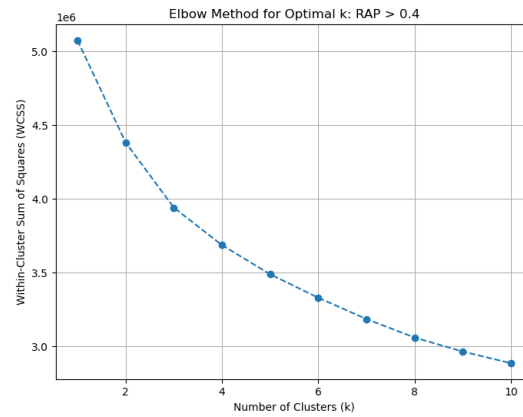
ABP, arterial blood pressure; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere; WCSS, within-cluster sum of squared errors

Sub-group analysis

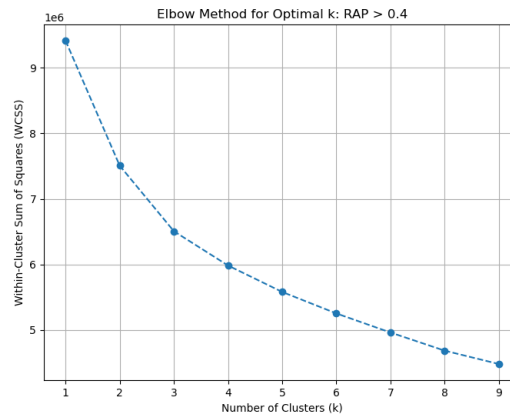
Figure J.1 Application of the elbow method at minute-by-minute resolution across RAP > 0.4 state



(a) ICP-ABP-derived parameters

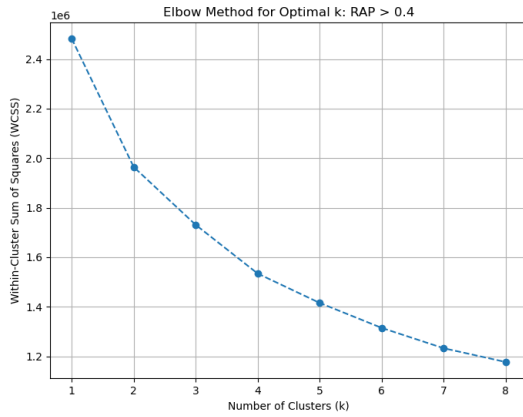


(b) ICP-ABP-derived and NIRS-derived parameters

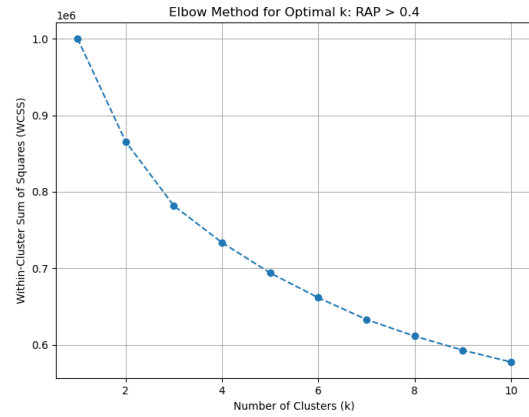


(c) ICP-ABP-derived parameters and PbtO₂

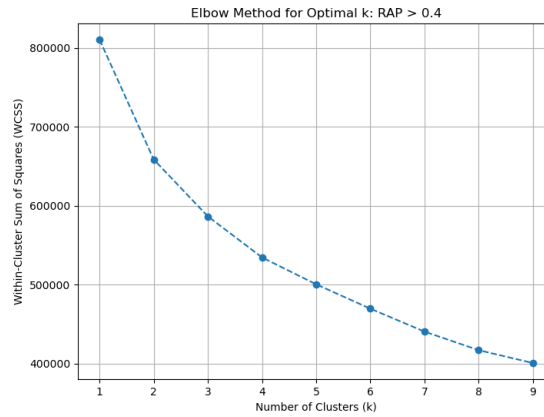
Figure J.2 Application of the elbow method at 5-minute-by-5-minute resolution across $RAP > 0.4$ state



(a) ICP-ABP-derived parameters

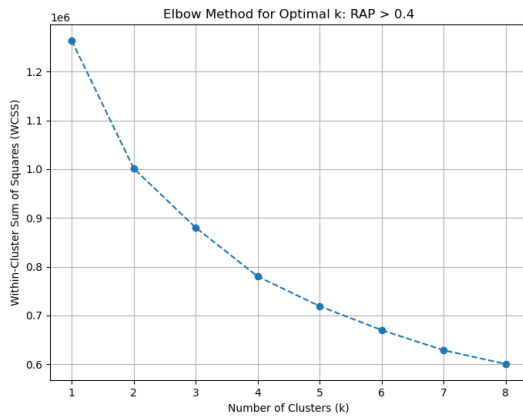


(b) ICP-ABP-derived and NIRS-derived parameters

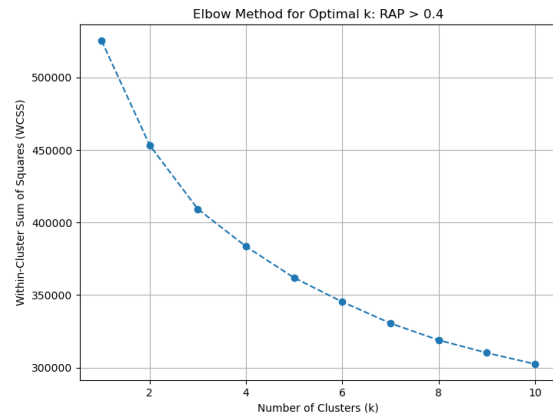


(c) ICP-ABP-derived parameters and PbtO₂

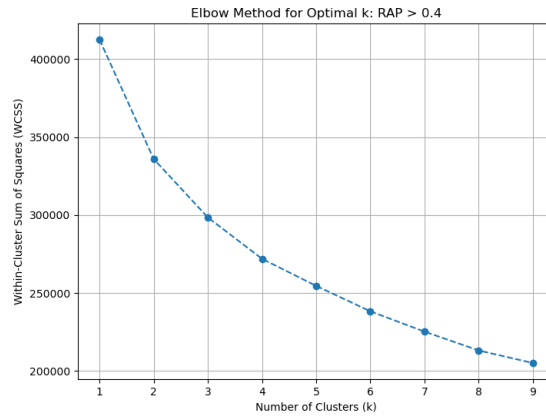
Figure J.3 Application of the elbow method at 10-minute-by-10-minute resolution across $RAP > 0.4$ state



(a) ICP-ABP-derived parameters

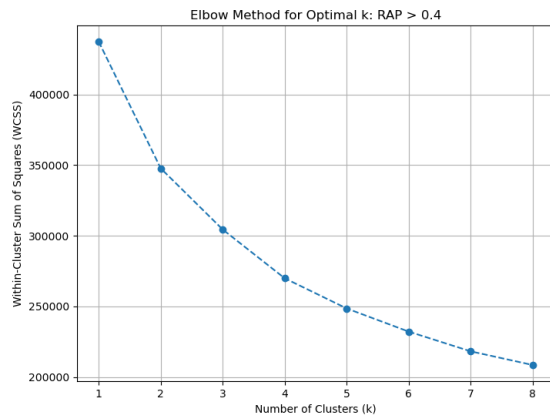


(b) ICP-ABP-derived and NIRS-derived parameters

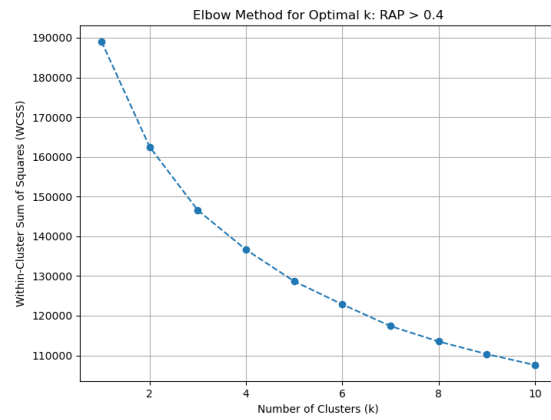


(c) ICP-ABP-derived parameters and PbtO₂

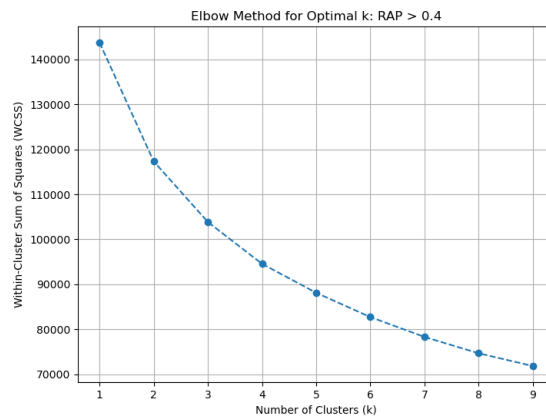
Figure J.4 Application of the elbow method at 30-minute-by-30-minute resolution across $RAP > 0.4$ state



(a) ICP-ABP-derived parameters

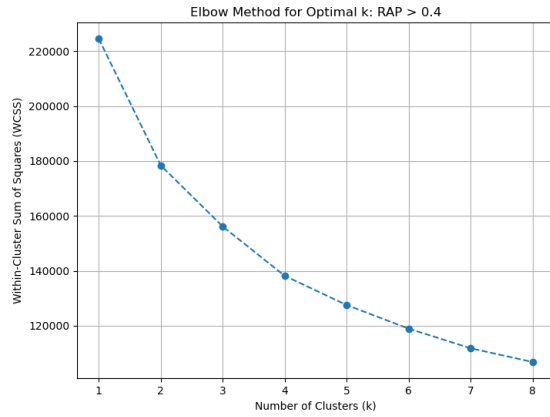


(b) ICP-ABP-derived and NIRS-derived parameters

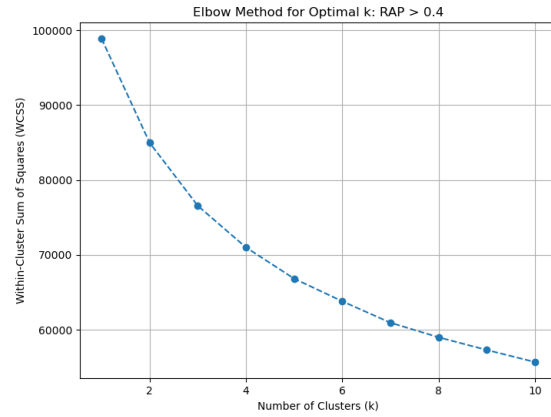


(c) ICP-ABP-derived parameters and PbtO₂

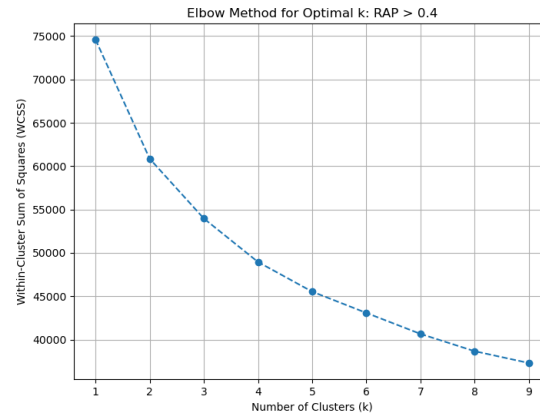
Figure J.5 Application of the elbow method at hour-by-hour resolution across $RAP > 0.4$ state



(a) ICP-ABP-derived parameters



(b) ICP-ABP-derived and NIRS-derived parameters



(c) ICP-ABP-derived parameters and PbtO₂

Table J.1 Clusters generated from KMCA across all resolutions at $RAP < 0$

Minute-by-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	RAP, AMP, PRx, PAx, RAC	MAP, CPP	ICP
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	RAP, AMP, PRx, PAx, RAC	MAP, CPP	ICP, PbtO ₂
5-minute-by-5-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC

10-minute-by-10-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
30-minute-by-30-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
Hour-by-hour			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	RAP, AMP, PRx, PAx, RAC	RAP, AMP, PRx, PAx, RAC	RAP, AMP, PRx, PAx, RAC

Table J.2 Clusters generated from KMCA across all resolutions at $0 \leq RAP \leq 0.4$ state

Minute-by-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	RAP, AMP, PRx, PAx, RAC	MAP, CPP	ICP, PbtO ₂
5-minute-by-5-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
10-minute-by-10-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC

30-minute-by-30-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
Hour-by-hour			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC

Table J.3 Clusters generated from KMCA across all resolutions at RAP > 0.4 state

Minute-by-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
5-minute-by-5-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
10-minute-by-10-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC
30-minute-by-30-minute			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, COx_L, COx_R, COx-a_L, COx-a_R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC

Hour-by-hour			
	Cluster 1	Cluster 2	Cluster 3
ICP-ABP-derived parameters	ICP	MAP, CPP	RAP, AMP, PRx, PAx, RAC
ICP-ABP-derived and NIRS-derived parameters	rSO ₂ _L, rSO ₂ _R	RAP, ICP, AMP, PRx, PAx, RAC, CO _x _L, CO _x _R, CO _{x-a} _L, CO _{x-a} _R	MAP, CPP
ICP-ABP-derived parameters and PbtO ₂	ICP, PbtO ₂	MAP, CPP	RAP, AMP, PRx, PAx, RAC

Appendix K. Section 5.3.5: Application of Vector Autoregressive Integrated Moving Average (VARIMA) Impulse Response Function (IRF) Analysis

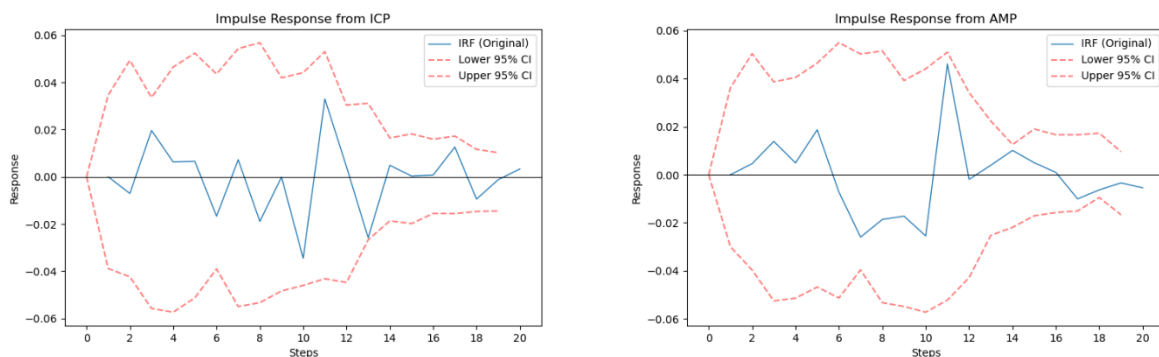
This appendix contains the IRF plots generated from the orthogonal impulse physiological parameters to RAP. Each IRF plot also demonstrates the 95% confidence interval range/boundary with red dashed lines. Prior to IRF analysis, the VARIMA optimal model was required to be calculated. The median optimal VARIMA models for each RAP-X pair (where X is other physiological parameters) are also depicted in this appendix. The results of the subgroup-level analysis for the percentage of RAP responsiveness are summarized in a table located at the end of the appendix.

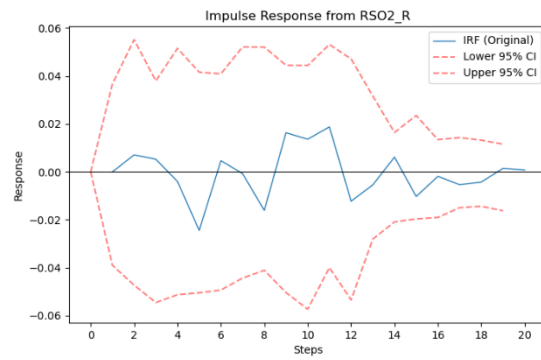
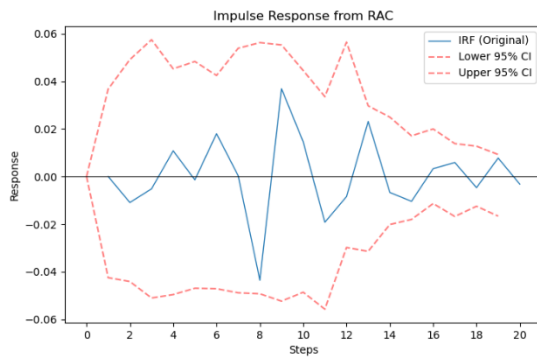
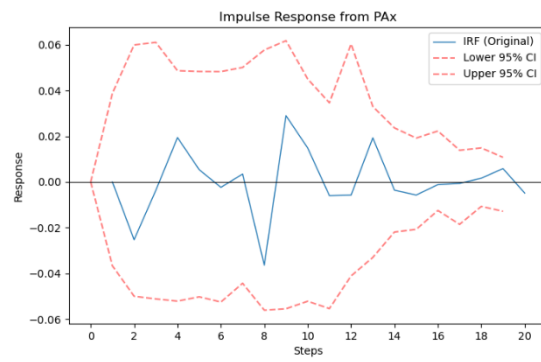
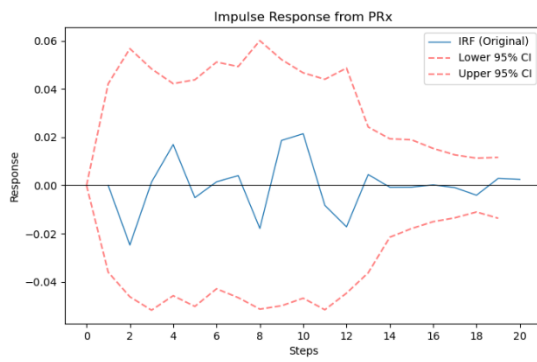
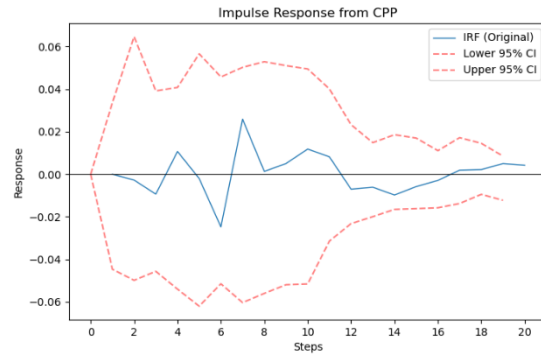
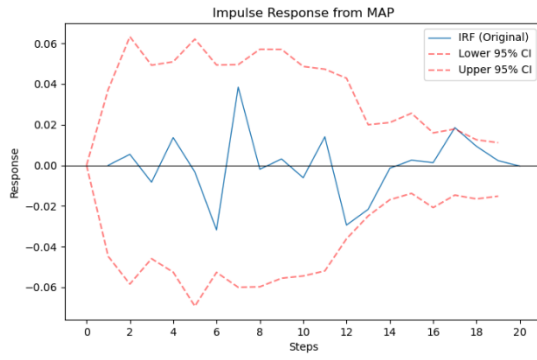
Δ , first-order differenced; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NA, not applicable; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation ; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

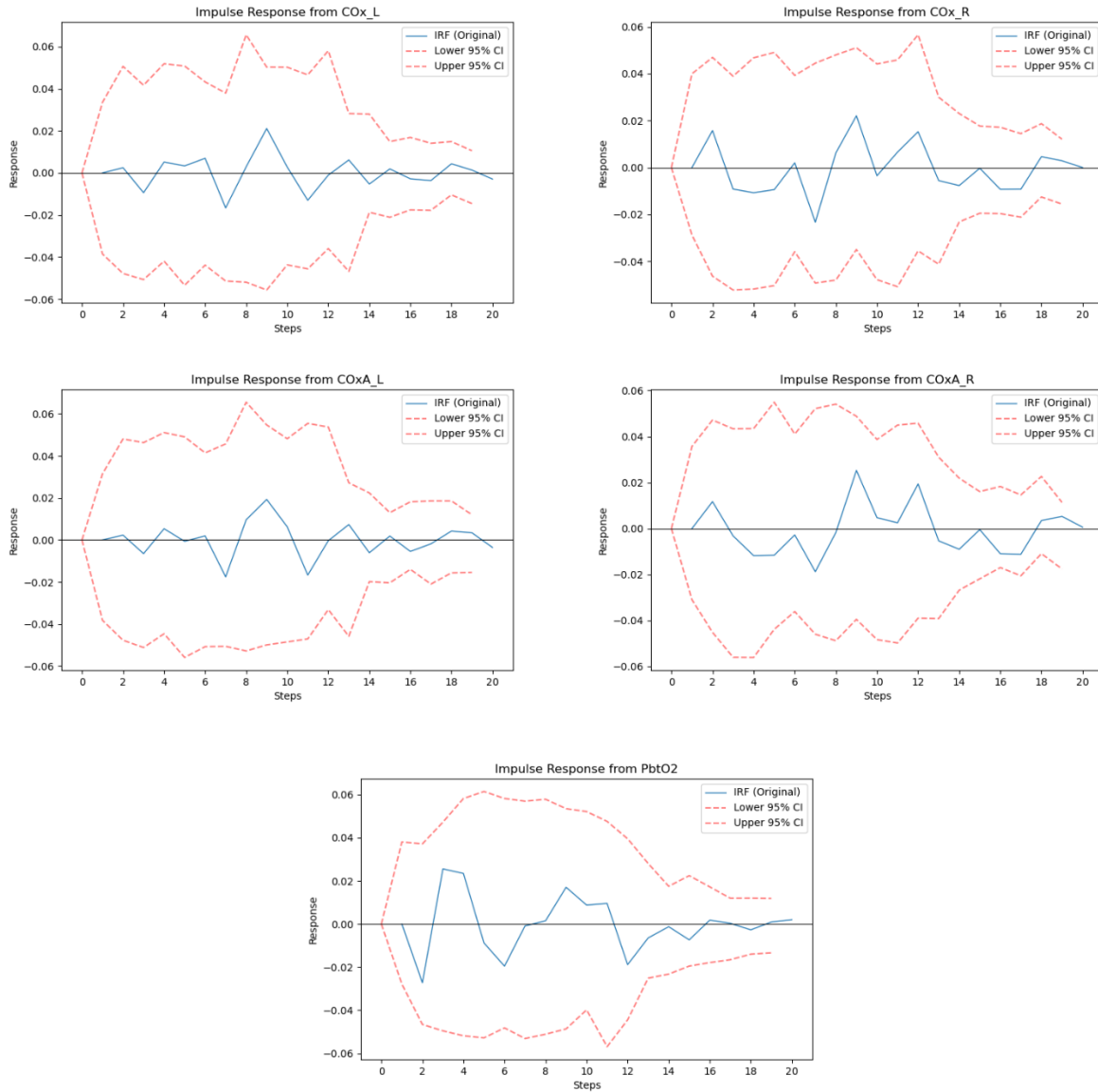
Table K.1 Median optimal VARIMA models across whole population

Parameter pair	Minute-by-minute	5-minute-by-5-minute	10-minute-by-10-minute
RAP-ICP	[10, 1, 10]	[6, 1, 6]	[4, 1, 5]
RAP-AMP	[10, 1, 9]	[6, 1, 5]	[4, 1, 5]
RAP-MAP	[10, 1, 10]	[6, 1, 6]	[4, 1, 5]
RAP-CPP	[10, 1, 10]	[6, 1, 6]	[4, 1, 5]
RAP-PRx	[10, 1, 6]	[5, 1, 6]	[4, 1, 5]
RAP-PAX	[10, 1, 6]	[6, 1, 6]	[4, 1, 5]
RAP-RAC	[10, 1, 6]	[3, 1, 3]	[2, 1, 3]
RAP-rSO ₂ _L	[10, 1, 10]	[4, 1, 4]	[3, 1, 3]
RAP-rSO ₂ _R	[10, 1, 9]	[4, 1, 4]	[3, 1, 3]
RAP-COx_L	[10, 1, 6]	[4, 1, 4]	[2, 1, 3]
RAP-COx_R	[10, 1, 6]	[3, 1, 3]	[2, 1, 3]
RAP-COx-a_L	[10, 1, 6]	[4, 1, 4]	[2, 1, 3]
RAP-COx-a_R	[10, 1, 7]	[6, 1, 6]	[4, 1, 5]
RAP-PbtO ₂	[10, 1, 10]	[5, 1, 4]	[3, 1, 4]

Figure K.1 VARIMA IRF plots at minute-by-minute resolution for patient CAHR-101

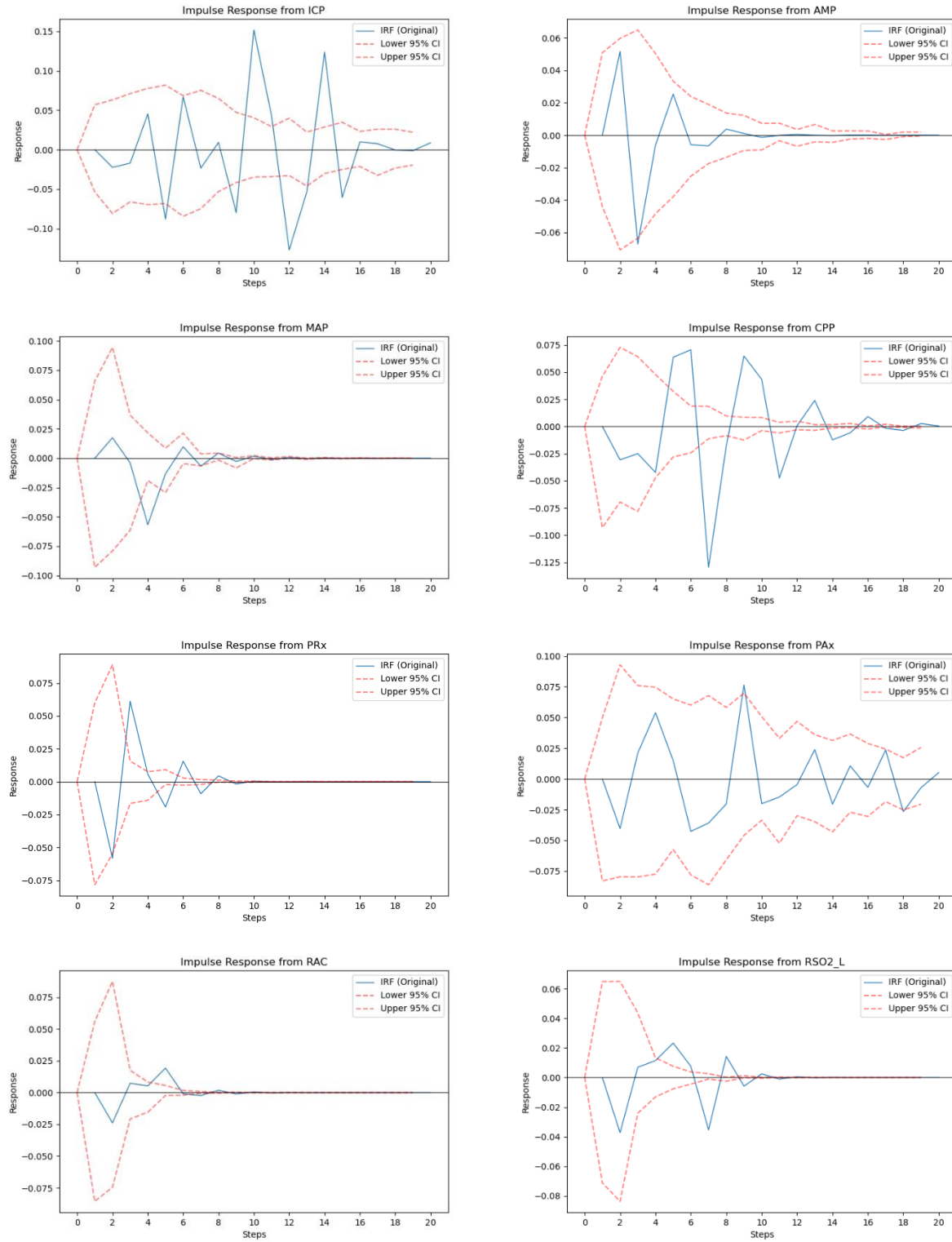






In this figure, the impulse response for rSO_2_L is absent because the corresponding VARIMA model failed to fit the data due to an insufficient number of data points, resulting in an error and no output from the analysis..

Figure K.2 VARIMA IRF plots at 5-minute-by-5-minute resolution for patient CAHR-101



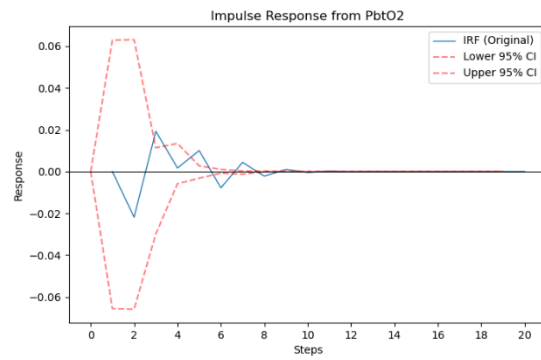
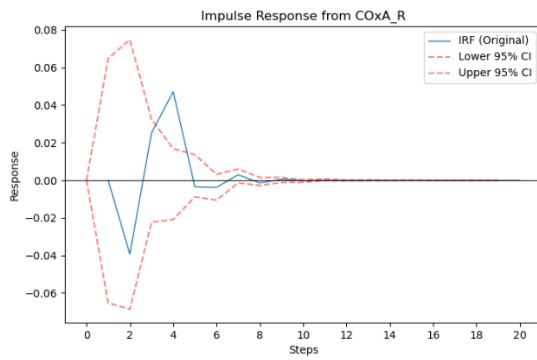
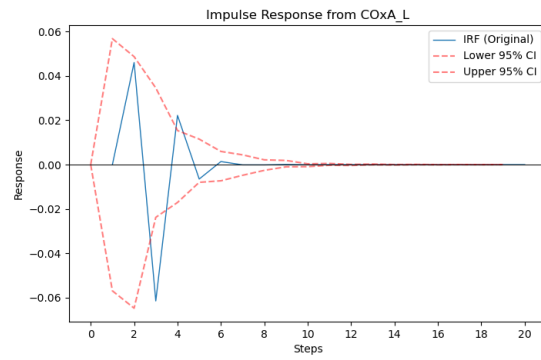
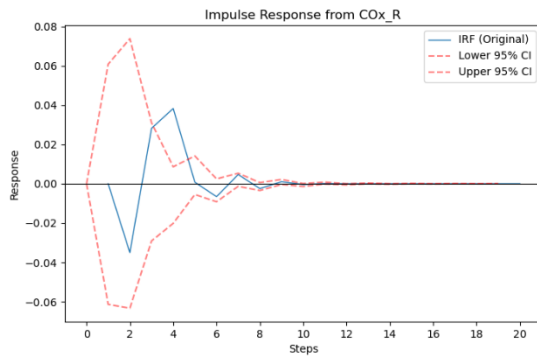
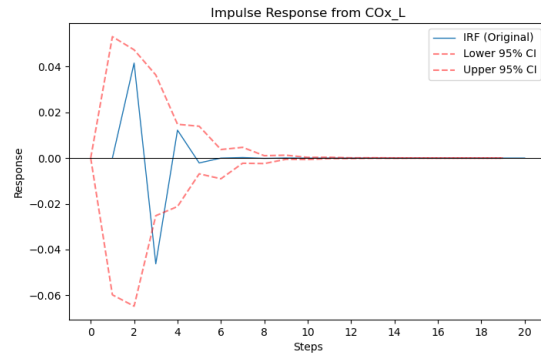
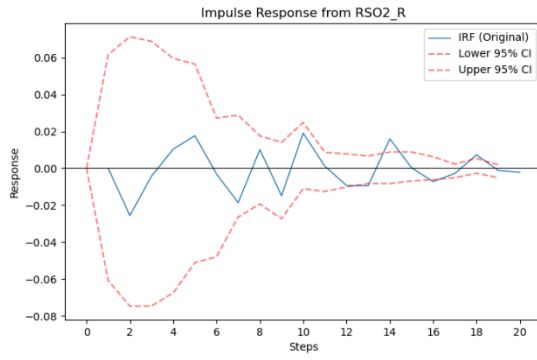
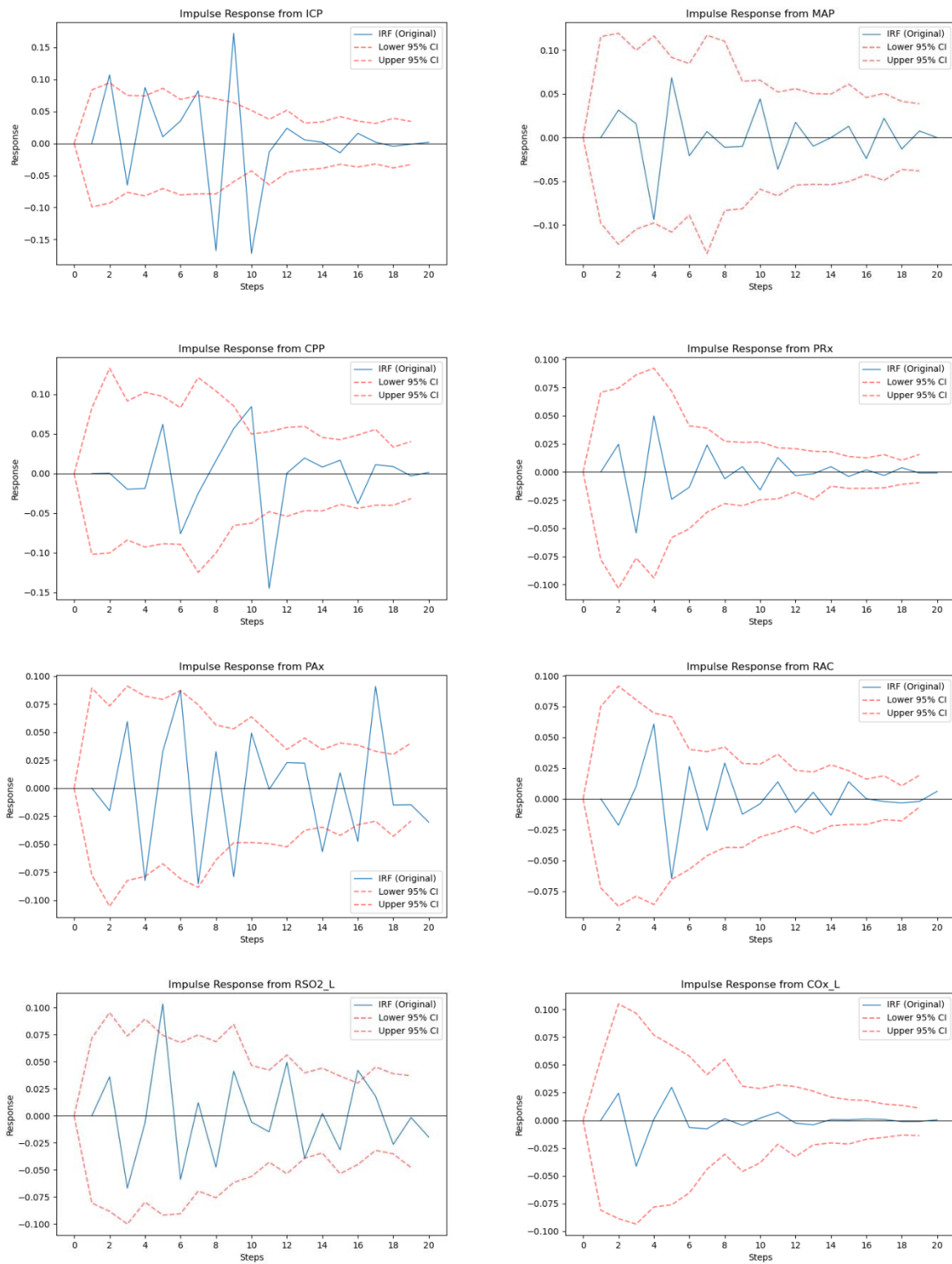
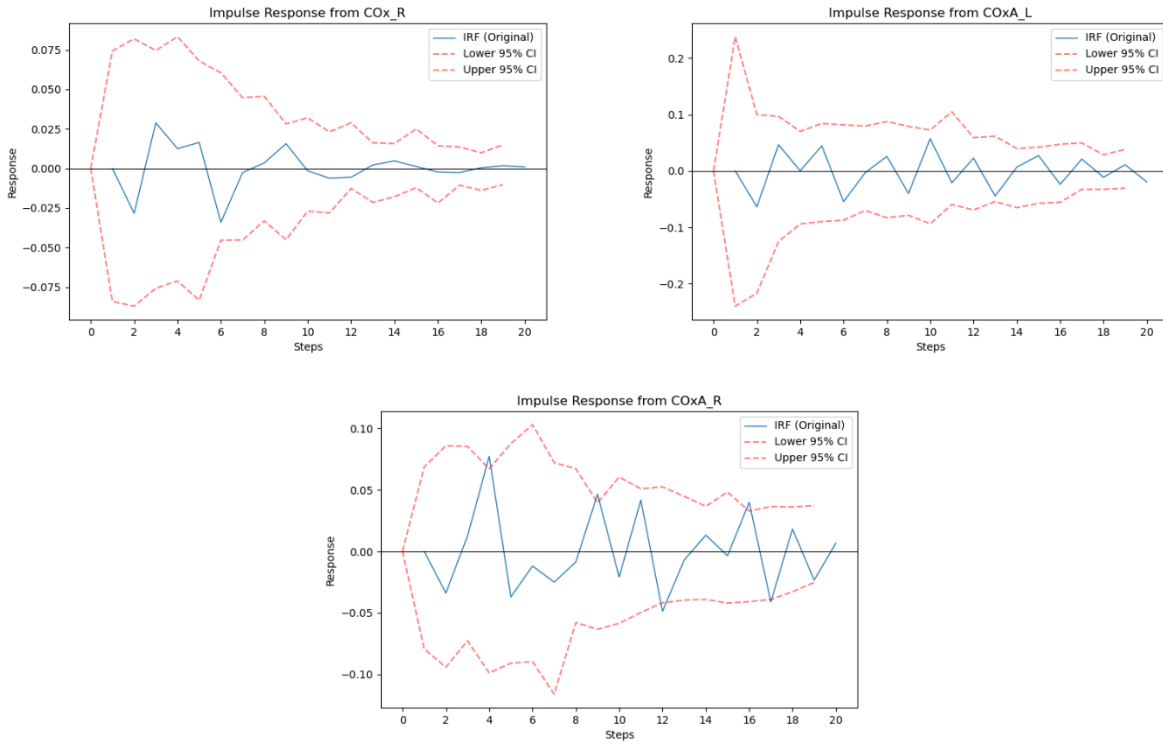


Figure K.3 VARIMA IRF plots at 10-minute-by-10-minute resolution for patient CAHR-101





In this figure, the impulse response for AMP, rSO₂_R, PbtO₂ is absent because the corresponding VARIMA model failed to fit the data due to an insufficient number of data points, resulting in an error and no output from the analysis.

Table K.2 Responsiveness of RAP to the orthogonal impulse of cerebral physiological parameters across RAP states

RAP < 0						
Direction	Minute-by-minute		5-minute-by-5-minute		10-minute-by-10-minute	
	>0.1%	NA	>0.1%	NA	>0.1%	NA
$\Delta\text{ICP} \rightarrow \Delta\text{RAP}$	83.33%(5)	0	16.67%(1)	0	66.67%(4)	0
$\Delta\text{AMP} \rightarrow \Delta\text{RAP}$	83.33%(5)	0	50.00%(3)	0	50.00%(3)	0
$\Delta\text{MAP} \rightarrow \Delta\text{RAP}$	100.00%(6)	0	66.67%(4)	0	50.00%(3)	0
$\Delta\text{CPP} \rightarrow \Delta\text{RAP}$	33.33%(2)	0	16.67%(1)	0	50.00%(3)	0
$\Delta\text{PRx} \rightarrow \Delta\text{RAP}$	83.33%(5)	0	33.33%(2)	0	50.00%(3)	0
$\Delta\text{PAx} \rightarrow \Delta\text{RAP}$	100.00%(6)	0	50.00%(3)	0	66.67%(4)	0
$\Delta\text{RAC} \rightarrow \Delta\text{RAP}$	100.00%(6)	0	50.00%(3)	0	33.33%(2)	0
$\Delta\text{rSO}_2_L \rightarrow \Delta\text{RAP}$	100.00%(1)	0	0.00%(0)	0	0.00%(0)	0
$\Delta\text{rSO}_2_R \rightarrow \Delta\text{RAP}$	100.00%(1)	0	0.00%(0)	0	0.00%(0)	0
$\Delta\text{COx}_L \rightarrow \Delta\text{RAP}$	100.00%(1)	0	0.00%(0)	0	0.00%(0)	0
$\Delta\text{COx}_R \rightarrow \Delta\text{RAP}$	0.00%(0)	0	0.00%(0)	0	0.00%(0)	0
$\Delta\text{COx-a}_L \rightarrow \Delta\text{RAP}$	0.00%(0)	0	0.00%(0)	0	0.00%(0)	0
$\Delta\text{COx-a}_R \rightarrow \Delta\text{RAP}$	0.00%(0)	0	0.00%(0)	0	0.00%(0)	0
$\Delta\text{PbtO}_2 \rightarrow \Delta\text{RAP}$	100.00%(4)	0	50.00%(2)	0	25.00%(1)	0

0 ≤ RAP ≤ 0.4						
Direction	Minute-by-minute		5-minute-by-5-minute		10-minute-by-10-minute	
	>0.1%	NA	>0.1%	NA	>0.1%	NA
ΔICP→ΔRAP	84.00%(21)	0	64.00%(16)	0	60.00%(15)	0
ΔAMP→ΔRAP	84.00%(21)	0	60.00%(15)	0	52.00%(13)	0
ΔMAP→ΔRAP	80.00%(20)	0	68.00%(17)	0	52.00%(13)	0
ΔCPP→ΔRAP	80.00%(20)	0	80.00%(20)	0	52.00%(13)	0
ΔPRx→ΔRAP	72.00%(18)	0	40.00%(10)	0	44.00%(11)	0
ΔPAX→ΔRAP	80.00%(20)	0	40.00%(10)	0	48.00%(12)	0
ΔRAC→ΔRAP	80.00%(20)	0	52.00%(13)	0	40.00%(10)	0
ΔrSO ₂ _L→ΔRAP	75.00%(9)	1	41.67%(5)	1	66.67%(8)	1
ΔrSO ₂ _R→ΔRAP	91.67%(11)	2	66.67%(8)	2	66.67%(8)	2
ΔCOx_L→ΔRAP	58.33%(7)	1	41.67%(5)	1	16.67%(2)	1
ΔCOx_R→ΔRAP	66.67%(8)	0	41.67%(5)	0	25.00%(3)	0
ΔCOx-a_L→ΔRAP	83.33%(10)	0	50.00%(6)	0	41.67%(5)	0
ΔCOx-a_R→ΔRAP	66.67%(8)	0	58.33%(7)	0	41.67%(5)	0
ΔPbtO ₂ →ΔRAP	100.00%(4)	0	75.00%(3)	0	100.00%(4)	0
RAP > 0.4						
Direction	Minute-by-minute		5-minute-by-5-minute		10-minute-by-10-minute	
	>0.1%	NA	>0.1%	NA	>0.1%	NA
ΔICP→ΔRAP	77.30%(269)	0	63.79%(222)	0	64.37%(224)	0
ΔAMP→ΔRAP	74.43%(259)	0	61.78%(215)	0	59.20%(206)	0
ΔMAP→ΔRAP	72.41%(252)	0	67.24%(234)	0	58.62%(204)	0
ΔCPP→ΔRAP	71.26%(248)	0	66.38%(231)	0	56.90%(198)	0
ΔPRx→ΔRAP	78.74%(274)	0	54.31%(189)	0	43.10%(150)	0
ΔPAX→ΔRAP	77.59%(270)	0	52.59%(183)	0	38.51%(134)	0
ΔRAC→ΔRAP	79.31%(276)	0	55.75%(194)	0	41.67%(145)	0
ΔrSO ₂ _L→ΔRAP	75.19%(97)	13	67.44%(87)	13	61.24%(79)	13
ΔrSO ₂ _R→ΔRAP	75.40%(95)	14	70.63%(89)	14	57.94%(73)	14
ΔCOx_L→ΔRAP	74.02%(94)	11	40.16%(51)	11	34.65%(44)	11
ΔCOx_R→ΔRAP	76.98%(97)	13	46.03%(58)	13	32.54%(41)	13
ΔCOx-a_L→ΔRAP	80.49%(99)	4	45.53%(56)	4	32.52%(40)	4
ΔCOx-a_R→ΔRAP	81.15%(99)	4	44.26%(54)	4	30.33%(37)	4
ΔPbtO ₂ →ΔRAP	60.19%(65)	0	66.67%(72)	0	62.96%(68)	0

Appendix L. Section 5.3.5: Application of Granger causality testing

This appendix includes tables summarizing the results of the sub-group Granger causality analyses across the three data resolutions. For each RAP–X pair (where X denotes another cerebral physiological parameter), four categories are presented: $\Delta X \rightarrow \Delta RAP$, indicating RAP's response to an orthogonal impulse from X; $\Delta RAP \rightarrow \Delta X$, indicating the reverse relationship; NS, denoting the number of cases with non-significant results; and NA, representing cases where results could not be obtained due to insufficient data. To calculate the percentage values in these tables, the NA cases were excluded from the total number of patients.

Δ , first-order differenced; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NA, not applicable, NS, not significant; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation ; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

Table L.1 Granger causality testing across the resolutions for RAP < 0 state

Parameters	Direction	Minute-by-minute	5-minute-by-5-minute	10-minute-by-10-minute
ΔICP & ΔRAP	$\Delta ICP \rightarrow \Delta RAP$	7.59%(28)	9.82%(32)	4.78%(12)
	$\Delta RAP \rightarrow \Delta ICP$	14.09%(52)	7.67%(25)	9.16%(23)
	NS	78.32%(289)	82.52%(269)	86.06%(216)
	NA	10	53	128
ΔAMP & ΔRAP	$\Delta AMP \rightarrow \Delta RAP$	6.5%(24)	6.12%(20)	5.95%(15)
	$\Delta RAP \rightarrow \Delta AMP$	10.3%(38)	4.89%(16)	5.56%(14)
	NS	83.2%(307)	88.99%(291)	88.49%(223)
	NA	10	52	127
ΔMAP & ΔRAP	$\Delta MAP \rightarrow \Delta RAP$	4.05%(15)	7.12%(23)	5.2%(13)
	$\Delta RAP \rightarrow \Delta MAP$	10.27%(38)	5.88%(19)	5.6%(14)
	NS	85.68%(317)	87.0%(281)	89.2%(223)
	NA	9	56	129
ΔCPP & ΔRAP	$\Delta CPP \rightarrow \Delta RAP$	6.23%(23)	8.07%(26)	6.05%(15)
	$\Delta RAP \rightarrow \Delta CPP$	10.03%(37)	7.14%(23)	6.05%(15)
	NS	83.74%(309)	84.78%(273)	87.9%(218)
	NA	10	57	131

ΔPR_x & ΔRAP	$\Delta PR_x \rightarrow \Delta RAP$	10.05%(37)	4.02%(13)	4.82%(12)
	$\Delta RAP \rightarrow \Delta PR_x$	9.24%(34)	5.57%(18)	9.64%(24)
	NS	80.71%(297)	90.4%(292)	85.54%(213)
	NA	11	56	130
ΔPA_x & ΔRAP	$\Delta PA_x \rightarrow \Delta RAP$	10.33%(38)	5.26%(17)	8.03%(20)
	$\Delta RAP \rightarrow \Delta PA_x$	10.33%(38)	7.74%(25)	7.63%(19)
	NS	79.35%(292)	87.0%(281)	84.34%(210)
	NA	11	56	130
ΔRAC & ΔRAP	$\Delta RAC \rightarrow \Delta RAP$	13.86%(51)	5.26%(17)	7.23%(18)
	$\Delta RAP \rightarrow \Delta RAC$	9.24%(34)	7.12%(23)	5.22%(13)
	NS	76.9%(283)	87.62%(283)	87.55%(218)
	NA	11	56	130
ΔrSO_2_L & ΔRAP	$\Delta rSO_2_L \rightarrow \Delta RAP$	5.88%(8)	5.88%(7)	7.59%(6)
	$\Delta RAP \rightarrow \Delta rSO_2_L$	9.56%(13)	5.04%(6)	3.8%(3)
	NS	84.56%(115)	89.08%(106)	88.61%(70)
	NA	20	37	77
ΔrSO_2_R & ΔRAP	$\Delta rSO_2_R \rightarrow \Delta RAP$	7.41%(10)	4.31%(5)	7.89%(6)
	$\Delta RAP \rightarrow \Delta rSO_2_L$	11.11%(15)	4.31%(5)	6.58%(5)
	NS	81.48%(110)	91.38%(106)	85.53%(65)
	NA	20	39	79
ΔCO_x_L & ΔRAP	$\Delta CO_x_L \rightarrow \Delta RAP$	7.52%(10)	5.93%(7)	5.41%(4)
	$\Delta RAP \rightarrow \Delta CO_x_L$	9.02%(12)	2.54%(3)	5.41%(4)
	NS	83.46%(111)	91.53%(108)	89.19%(66)
	NA	19	34	78
ΔCO_x_R & ΔRAP	$\Delta CO_x_R \rightarrow \Delta RAP$	8.27%(11)	10.43%(12)	9.33%(7)
	$\Delta RAP \rightarrow \Delta CO_x_R$	6.77%(9)	4.35%(5)	4.0%(3)
	NS	84.96%(113)	85.22%(98)	86.67%(65)
	NA	19	37	77
$\Delta CO_x\text{-}a_L$ & ΔRAP	$\Delta CO_x\text{-}a_L \rightarrow \Delta RAP$	5.43%(7)	7.89%(9)	6.76%(5)

	$\Delta RAP \rightarrow \Delta COx-a_L$	10.08%(13)	4.39%(5)	8.11%(6)
	NS	84.5%(109)	87.72%(100)	85.14%(63)
	NA	11	26	66
$\Delta COx-a_R$ & ΔRAP	$\Delta COx-a_R \rightarrow \Delta RAP$	6.2%(8)	4.5%(5)	9.59%(7)
	$\Delta RAP \rightarrow \Delta COx-a_R$	8.53%(11)	7.21%(8)	8.22%(6)
	NS	85.27%(110)	88.29%(98)	82.19%(60)
	NA	11	29	67
$\Delta PbtO_2$ & ΔRAP	$\Delta PbtO_2 \rightarrow \Delta RAP$	4.59%(5)	12.5%(12)	6.41%(5)
	$\Delta RAP \rightarrow \Delta PbtO_2$	8.26%(9)	4.17%(4)	8.97%(7)
	NS	87.16%(95)	83.33%(80)	84.62%(66)
	NA	7	20	38

Table L.2 Granger causality testing across the resolutions for $0 \leq RAP \leq 0.4$ state

Parameters	Direction	Minute-by-minute	5-minute-by-5-minute	10-minute-by-10-minute
ΔICP & ΔRAP	$\Delta ICP \rightarrow \Delta RAP$	7.59%(28)	9.82%(32)	4.78%(12)
	$\Delta RAP \rightarrow \Delta ICP$	14.09%(52)	7.67%(25)	9.16%(23)
	NS	78.32%(289)	82.52%(269)	86.06%(216)
	NA	10	53	128
ΔAMP & ΔRAP	$\Delta AMP \rightarrow \Delta RAP$	6.5%(24)	6.12%(20)	5.95%(15)
	$\Delta RAP \rightarrow \Delta AMP$	10.3%(38)	4.89%(16)	5.56%(14)
	NS	83.2%(307)	88.99%(291)	88.49%(223)
	NA	10	52	127
ΔMAP & ΔRAP	$\Delta MAP \rightarrow \Delta RAP$	4.05%(15)	7.12%(23)	5.2%(13)
	$\Delta RAP \rightarrow \Delta MAP$	10.27%(38)	5.88%(19)	5.6%(14)
	NS	85.68%(317)	87.0%(281)	89.2%(223)
	NA	9	56	129
ΔCPP & ΔRAP	$\Delta CPP \rightarrow \Delta RAP$	6.23%(23)	8.07%(26)	6.05%(15)
	$\Delta RAP \rightarrow \Delta CPP$	10.03%(37)	7.14%(23)	6.05%(15)
	NS	83.74%(309)	84.78%(273)	87.9%(218)

	NA	10	57	131
ΔPR_x & ΔRAP	$\Delta PR_x \rightarrow \Delta RAP$	10.05%(37)	4.02%(13)	4.82%(12)
	$\Delta RAP \rightarrow \Delta PR_x$	9.24%(34)	5.57%(18)	9.64%(24)
	NS	80.71%(297)	90.4%(292)	85.54%(213)
	NA	11	56	130
ΔPA_x & ΔRAP	$\Delta PA_x \rightarrow \Delta RAP$	10.33%(38)	5.26%(17)	8.03%(20)
	$\Delta RAP \rightarrow \Delta PA_x$	10.33%(38)	7.74%(25)	7.63%(19)
	NS	79.35%(292)	87.0%(281)	84.34%(210)
	NA	11	56	130
ΔRAC & ΔRAP	$\Delta RAC \rightarrow \Delta RAP$	13.86%(51)	5.26%(17)	7.23%(18)
	$\Delta RAP \rightarrow \Delta RAC$	9.24%(34)	7.12%(23)	5.22%(13)
	NS	76.9%(283)	87.62%(283)	87.55%(218)
	NA	11	56	130
ΔrSO_2_L & ΔRAP	$\Delta rSO_2_L \rightarrow \Delta RAP$	5.88%(8)	5.88%(7)	7.59%(6)
	$\Delta RAP \rightarrow \Delta rSO_2_L$	9.56%(13)	5.04%(6)	3.8%(3)
	NS	84.56%(115)	89.08%(106)	88.61%(70)
	NA	20	37	77
ΔrSO_2_R & ΔRAP	$\Delta rSO_2_R \rightarrow \Delta RAP$	7.41%(10)	4.31%(5)	7.89%(6)
	$\Delta RAP \rightarrow \Delta rSO_2_L$	11.11%(15)	4.31%(5)	6.58%(5)
	NS	81.48%(110)	91.38%(106)	85.53%(65)
	NA	20	39	79
ΔrSO_2_R & ΔRAP	$\Delta CO_x_L \rightarrow \Delta RAP$	7.52%(10)	5.93%(7)	5.41%(4)
	$\Delta RAP \rightarrow \Delta CO_x_L$	9.02%(12)	2.54%(3)	5.41%(4)
	NS	83.46%(111)	91.53%(108)	89.19%(66)
	NA	19	34	78
ΔCO_x_R & ΔRAP	$\Delta CO_x_R \rightarrow \Delta RAP$	8.27%(11)	10.43%(12)	9.33%(7)
	$\Delta RAP \rightarrow \Delta CO_x_R$	6.77%(9)	4.35%(5)	4.0%(3)
	NS	84.96%(113)	85.22%(98)	86.67%(65)
	NA	19	37	77

$\Delta\text{COx-a_L}$ & ΔRAP	$\Delta\text{COx-a_L} \rightarrow \Delta\text{RAP}$	5.43%(7)	7.89%(9)	6.76%(5)
	$\Delta\text{RAP} \rightarrow \Delta\text{COx-a_L}$	10.08%(13)	4.39%(5)	8.11%(6)
	NS	84.5%(109)	87.72%(100)	85.14%(63)
	NA	11	26	66
$\Delta\text{COx-a_R}$ & ΔRAP	$\Delta\text{COx-a_R} \rightarrow \Delta\text{RAP}$	6.2%(8)	4.5%(5)	9.59%(7)
	$\Delta\text{RAP} \rightarrow \Delta\text{COx-a_R}$	8.53%(11)	7.21%(8)	8.22%(6)
	NS	85.27%(110)	88.29%(98)	82.19%(60)
	NA	11	29	67
ΔPbtO_2 & ΔRAP	$\Delta\text{PbtO}_2 \rightarrow \Delta\text{RAP}$	4.59%(5)	12.5%(12)	6.41%(5)
	$\Delta\text{RAP} \rightarrow \Delta\text{PbtO}_2$	8.26%(9)	4.17%(4)	8.97%(7)
	NS	87.16%(95)	83.33%(80)	84.62%(66)
	NA	7	20	38

Table L.3 Granger causality testing across the resolutions for $\text{RAP} > 0.4$ state

Parameters	Direction	Minute-by-minute	5-minute-by-5-minute	10-minute-by-10-minute
ΔICP & ΔRAP	$\Delta\text{ICP} \rightarrow \Delta\text{RAP}$	17.94%(68)	30.5%(115)	26.67%(100)
	$\Delta\text{RAP} \rightarrow \Delta\text{ICP}$	27.18%(103)	17.51%(66)	15.73%(59)
	NS	54.88%(208)	51.99%(196)	57.6%(216)
	NA	0	2	4
ΔAMP & ΔRAP	$\Delta\text{AMP} \rightarrow \Delta\text{RAP}$	14.25%(54)	44.03%(166)	31.73%(119)
	$\Delta\text{RAP} \rightarrow \Delta\text{AMP}$	41.16%(156)	15.12%(57)	17.87%(67)
	NS	44.59%(169)	40.85%(154)	50.4%(189)
	NA	0	2	4
ΔMAP & ΔRAP	$\Delta\text{MAP} \rightarrow \Delta\text{RAP}$	26.91%(102)	42.97%(162)	26.47%(99)
	$\Delta\text{RAP} \rightarrow \Delta\text{MAP}$	20.58%(78)	11.94%(45)	9.09%(34)
	NS	52.51%(199)	45.09%(170)	64.44%(241)
	NA	0	2	5
ΔCPP & ΔRAP	$\Delta\text{CPP} \rightarrow \Delta\text{RAP}$	25.07%(95)	45.62%(172)	29.95%(112)
	$\Delta\text{RAP} \rightarrow \Delta\text{CPP}$	22.96%(87)	12.47%(47)	12.83%(48)

	NS	51.98%(197)	41.91%(158)	57.22%(214)
	NA	0	2	5
ΔPR_x & ΔRAP	$\Delta PR_x \rightarrow \Delta RAP$	38.79%(147)	14.85%(56)	12.27%(46)
	$\Delta RAP \rightarrow \Delta PR_x$	17.41%(66)	16.98%(64)	15.47%(58)
	NS	43.8%(166)	68.17%(257)	72.27%(271)
	NA	0	2	4
ΔPA_x & ΔRAP	$\Delta PA_x \rightarrow \Delta RAP$	39.58%(150)	11.67%(44)	10.13%(38)
	$\Delta RAP \rightarrow \Delta PA_x$	21.11%(80)	19.63%(74)	14.4%(54)
	NS	39.31%(149)	68.7%(259)	75.47%(283)
	NA	0	2	4
ΔRAC & ΔRAP	$\Delta RAC \rightarrow \Delta RAP$	45.38%(172)	13.26%(50)	13.33%(50)
	$\Delta RAP \rightarrow \Delta RAC$	19.26%(73)	22.81%(86)	15.73%(59)
	NS	35.36%(134)	63.93%(241)	70.93%(266)
	NA	0	2	4
ΔrSO_2_L & ΔRAP	$\Delta rSO_2_L \rightarrow \Delta RAP$	17.14%(24)	20.44%(28)	8.09%(11)
	$\Delta RAP \rightarrow \Delta rSO_2_L$	24.29%(34)	15.33%(21)	17.65%(24)
	NS	58.57%(82)	64.23%(88)	74.26%(101)
	NA	16	19	20
ΔrSO_2_R & ΔRAP	$\Delta rSO_2_R \rightarrow \Delta RAP$	12.32%(17)	20.59%(28)	6.67%(9)
	$\Delta RAP \rightarrow \Delta rSO_2_L$	28.26%(39)	13.97%(19)	7.41%(10)
	NS	59.42%(82)	65.44%(89)	85.93%(116)
	NA	17	19	20
ΔrSO_2_R & ΔRAP	$\Delta CO_x_L \rightarrow \Delta RAP$	10.79%(15)	5.88%(8)	8.21%(11)
	$\Delta RAP \rightarrow \Delta CO_x_L$	25.9%(36)	23.53%(32)	18.66%(25)
	NS	63.31%(88)	70.59%(96)	73.13%(98)
	NA	13	16	18
ΔCO_x_R & ΔRAP	$\Delta CO_x_R \rightarrow \Delta RAP$	15.22%(21)	5.15%(7)	5.97%(8)
	$\Delta RAP \rightarrow \Delta CO_x_R$	17.39%(24)	31.62%(43)	17.16%(23)
	NS	67.39%(93)	63.24%(86)	76.87%(103)

	NA	14	16	18
$\Delta\text{COx-a_L}$ & ΔRAP	$\Delta\text{COx-a_L} \rightarrow \Delta\text{RAP}$	11.11%(15)	8.33%(11)	10.0%(13)
	$\Delta\text{RAP} \rightarrow \Delta\text{COx-a_L}$	27.41%(37)	16.67%(22)	19.23%(25)
	NS	61.48%(83)	75.0%(99)	70.77%(92)
	NA	5	8	10
$\Delta\text{COx-a_R}$ & ΔRAP	$\Delta\text{COx-a_R} \rightarrow \Delta\text{RAP}$	13.43%(18)	6.06%(8)	6.92%(9)
	$\Delta\text{RAP} \rightarrow \Delta\text{COx-a_R}$	23.88%(32)	19.7%(26)	13.85%(18)
	NS	62.69%(84)	74.24%(98)	79.23%(103)
	NA	6	8	10
ΔPbtO_2 & ΔRAP	$\Delta\text{PbtO}_2 \rightarrow \Delta\text{RAP}$	15.93%(18)	14.29%(16)	11.93%(13)
	$\Delta\text{RAP} \rightarrow \Delta\text{PbtO}_2$	21.24%(24)	19.64%(22)	11.93%(13)
	NS	62.83%(71)	66.07%(74)	76.15%(83)
	NA	3	4	7

Appendix M. Section 5.3.5: Application of cross-correlation analysis

This appendix presents tables summarizing the cross-correlation analysis results across three data resolutions at the sub-group levels. Each table reports the median of the maximum correlation values along with their interquartile range (IQR), as well as the median of the absolute lag values (with IQR) at which peak correlation occurred. Instances labelled as NA indicate patient examples where the analysis could not be performed due to insufficient data.

Δ , first-order differenced; AMP, pulse amplitude of ICP; COx_L, cerebral oxygenation index of left hemisphere; COx_R, cerebral oxygenation index of right hemisphere; COx-a_L, COx with ABP of left hemisphere; COx-a_R, COx with ABP of the right hemisphere; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial pressure; NA, not applicable; PAX, pulse amplitude index; PbtO₂, brain tissue oxygenation; PRx, pressure reactivity index; RAC, a cerebral autoregulation index; RAP, index of cerebral compensatory reserve; rSO₂_L, regional cerebral oxygen saturation of left hemisphere; rSO₂_R, regional cerebral oxygen saturation of the right hemisphere.

Table M.1 Δ RAP- Δ X cross-correlation analysis across the resolutions for RAP < 0 state

Parameter pair	Minute-by-minute			5-minute-by-5-minute			10-minute-by-10-minute		
	Maximum correlation	Maximum lag	NA	Maximum correlation	Maximum lag	NA	Maximum correlation	Maximum lag	NA
Δ RAP- Δ ICP	0.192(0.13—0.274)	4.0(0.0—10.0)	3	0.364(0.262—0.479)	5.0(1.0—10.0)	18	0.468(0.362—0.576)	2.0(0.0—6.0)	58
Δ RAP- Δ AMP	0.175(0.122—0.288)	5.0(1.0—11.0)	3	0.37(0.266—0.5)	5.0(1.0—11.0)	18	0.473(0.359—0.56)	2.0(0.0—5.0)	57
Δ RAP- Δ MAP	0.171(0.115—0.263)	6.0(2.0—13.25)	3	0.37(0.268—0.483)	5.0(2.0—9.0)	17	0.448(0.321—0.552)	2.0(0.0—7.0)	56
Δ RAP- Δ CPP	0.167(0.116—0.266)	6.0(2.0—14.0)	3	0.365(0.257—0.483)	4.0(1.0—10.0)	18	0.455(0.337—0.537)	2.0(0.0—7.0)	62
Δ RAP- Δ PRx	0.196(0.132—0.306)	3.0(0.0—11.0)	3	0.364(0.283—0.5)	4.0(1.0—9.0)	16	0.478(0.359—0.548)	2.0(0.0—6.0)	58
Δ RAP- Δ PAX	0.245(0.153—0.352)	0.0(0.0—7.0)	3	0.377(0.293—0.5)	2.0(0.0—8.0)	16	0.479(0.363—0.554)	1.0(0.0—5.0)	58
Δ RAP- Δ RAC	0.224(0.151—0.349)	1.0(0.0—8.0)	3	0.391(0.296—0.5)	2.0(0.0—7.0)	16	0.476(0.365—0.563)	1.0(0.0—5.0)	58
Δ RAP- Δ rSO ₂ _L	0.205(0.153—0.316)	7.0(2.0—13.75)	14	0.415(0.316—0.528)	3.0(1.0—8.0)	20	0.5(0.419—0.602)	1.0(0.0—4.25)	28
Δ RAP- Δ rSO ₂ _R	0.208(0.144—0.322)	7.0(2.0—14.75)	13	0.394(0.285—0.498)	4.0(1.0—8.0)	18	0.5(0.408—0.568)	1.0(0.0—5.0)	30
Δ RAP- Δ COx_L	0.226(0.16—0.311)	7.0(1.0—15.0)	11	0.445(0.362—0.51)	3.0(1.0—7.75)	18	0.5(0.42—0.597)	1.0(0.0—3.0)	28

$\Delta\text{RAP}-\Delta\text{CO}_x \text{ R}$	0.217(0.156—0.311)	7.0(2.0—14.0)	10	0.44(0.329—0.528)	4.0(1.0—8.0)	18	0.5(0.433—0.576)	1.0(0.0—4.0)	31
$\Delta\text{RAP}-\Delta\text{CO}_x\text{-a L}$	0.226(0.155—0.316)	5.0(1.0—11.0)	9	0.429(0.369—0.517)	3.0(1.0—6.0)	16	0.508(0.438—0.596)	1.0(0.0—3.0)	26
$\Delta\text{RAP}-\Delta\text{CO}_x\text{-a R}$	0.218(0.157—0.313)	7.0(2.75—12.0)	8	0.435(0.343—0.514)	3.0(1.0—8.0)	16	0.5(0.398—0.602)	1.0(0.0—4.0)	29
$\Delta\text{RAP}-\Delta\text{PbO}_2$	0.157(0.106—0.251)	6.0(3.0—12.0)	4	0.37(0.277—0.488)	5.0(1.0—11.0)	8	0.467(0.372—0.563)	2.0(1.0—6.0)	19

Table M.2 $\Delta\text{RAP}-\Delta X$ cross-correlation analysis across the resolutions for $0 \leq \text{RAP} \leq 0.4$ state

Parameter pair	Minute-by-minute			5-minute-by-5-minute			10-minute-by-10-minute		
	Maximum correlation	Maximum lag	NA	Maximum correlation	Maximum lag	NA	Maximum correlation	Maximum lag	NA
$\Delta\text{RAP}-\Delta\text{ICP}$	0.117(0.086—0.176)	7.0(2.0—13.0)	3	0.241(0.166—0.352)	7.0(2.0—12.0)	18	0.309(0.226—0.406)	6.0(2.0—12.0)	58
$\Delta\text{RAP}-\Delta\text{AMP}$	0.124(0.086—0.179)	7.0(2.0—13.0)	3	0.245(0.17—0.327)	6.0(2.0—12.0)	18	0.313(0.225—0.42)	5.0(1.0—12.0)	57
$\Delta\text{RAP}-\Delta\text{MAP}$	0.126(0.087—0.186)	9.0(3.0—14.0)	3	0.249(0.176—0.357)	7.0(2.0—13.0)	17	0.313(0.228—0.418)	6.0(2.0—11.0)	56
$\Delta\text{RAP}-\Delta\text{CPP}$	0.127(0.086—0.188)	9.0(4.0—14.0)	3	0.245(0.179—0.341)	6.0(2.0—13.0)	18	0.315(0.234—0.413)	6.0(2.0—11.0)	62
$\Delta\text{RAP}-\Delta\text{PR}_x$	0.139(0.094—0.218)	4.0(0.0—11.75)	3	0.265(0.2—0.364)	5.0(1.0—12.0)	16	0.326(0.242—0.432)	5.0(2.0—11.0)	58
$\Delta\text{RAP}-\Delta\text{PA}_x$	0.152(0.108—0.232)	2.0(0.0—10.0)	3	0.264(0.192—0.379)	5.0(1.0—11.0)	16	0.326(0.236—0.444)	4.0(1.0—9.0)	58
$\Delta\text{RAP}-\Delta\text{RAC}$	0.14(0.097—0.226)	5.0(0.0—12.0)	3	0.262(0.188—0.373)	6.0(1.0—13.0)	16	0.34(0.244—0.454)	4.0(1.0—10.0)	58
$\Delta\text{RAP}-\Delta\text{rSO}_2 \text{ L}$	0.136(0.098—0.227)	8.0(3.0—14.0)	14	0.294(0.216—0.377)	6.0(3.0—13.5)	20	0.332(0.256—0.468)	5.0(2.0—11.0)	28
$\Delta\text{RAP}-\Delta\text{rSO}_2 \text{ R}$	0.141(0.106—0.228)	9.0(3.0—15.0)	13	0.271(0.196—0.356)	6.0(2.0—14.0)	18	0.325(0.255—0.446)	5.0(1.0—11.0)	30
$\Delta\text{RAP}-\Delta\text{CO}_x \text{ L}$	0.142(0.109—0.241)	8.0(4.0—13.0)	11	0.301(0.232—0.416)	7.0(2.0—14.0)	18	0.363(0.297—0.473)	5.0(2.0—11.0)	28
$\Delta\text{RAP}-\Delta\text{CO}_x \text{ R}$	0.16(0.104—0.232)	8.0(4.0—14.0)	10	0.297(0.222—0.402)	6.0(2.0—13.0)	18	0.361(0.288—0.481)	6.0(2.0—12.0)	31
$\Delta\text{RAP}-\Delta\text{CO}_x\text{-a L}$	0.147(0.114—0.26)	8.0(4.0—13.0)	9	0.287(0.226—0.408)	5.0(2.0—11.5)	16	0.364(0.28—0.467)	5.0(2.0—9.0)	26

$\Delta\text{RAP-}\Delta\text{COx-a R}$	0.157(0.103—0.231)	8.0(3.0—14.0)	8	0.295(0.211—0.424)	5.0(2.0—9.0)	16	0.367(0.277—0.45)	5.0(2.0—10.0)	29
$\Delta\text{RAP-}\Delta\text{PbtO}_2$	0.126(0.085—0.182)	6.0(3.0—12.0)	4	0.254(0.178—0.349)	5.0(2.0—12.25)	8	0.32(0.228—0.427)	6.0(2.0—10.0)	19

Table M.3 $\Delta\text{RAP-}\Delta\text{X}$ cross-correlation analysis across the resolutions for $\text{RAP} > 0.4$ state

Parameter pair	Minute-by-minute			5-minute-by-5-minute			10-minute-by-10-minute		
	Maximum correlation	Maximum lag	NA	Maximum correlation	Maximum lag	NA	Maximum correlation	Maximum lag	NA
$\Delta\text{RAP-}\Delta\text{ICP}$	0.07(0.052—0.109)	3.0(0.0—5.0)	0	0.129(0.094—0.185)	1.0(0.0—6.0)	0	0.164(0.117—0.236)	1.0(0.0—9.0)	1
$\Delta\text{RAP-}\Delta\text{AMP}$	0.094(0.069—0.131)	0.0(0.0—4.0)	0	0.145(0.101—0.215)	1.0(0.0—5.0)	0	0.192(0.127—0.271)	1.0(0.0—6.0)	1
$\Delta\text{RAP-}\Delta\text{MAP}$	0.069(0.048—0.11)	2.0(0.0—8.0)	0	0.153(0.108—0.234)	1.0(0.0—6.0)	0	0.196(0.149—0.313)	0.0(0.0—6.0)	0
$\Delta\text{RAP-}\Delta\text{CPP}$	0.069(0.048—0.104)	2.0(0.0—8.0)	0	0.149(0.103—0.216)	1.0(0.0—6.0)	0	0.192(0.142—0.302)	1.0(0.0—6.0)	1
$\Delta\text{RAP-}\Delta\text{PRx}$	0.124(0.075—0.195)	0.0(0.0—1.0)	0	0.17(0.12—0.254)	0.0(0.0—6.0)	0	0.211(0.151—0.308)	1.0(0.0—8.0)	0
$\Delta\text{RAP-}\Delta\text{PAx}$	0.101(0.063—0.158)	0.0(0.0—1.0)	0	0.143(0.1—0.219)	0.0(0.0—7.0)	0	0.179(0.129—0.278)	1.0(0.0—9.0)	0
$\Delta\text{RAP-}\Delta\text{RAC}$	0.184(0.114—0.267)	0.0(0.0—0.0)	0	0.252(0.158—0.349)	0.0(0.0—1.0)	0	0.291(0.206—0.412)	0.0(0.0—2.0)	0
$\Delta\text{RAP-}\Delta\text{rSO}_2\text{ L}$	0.084(0.056—0.121)	5.0(1.0—13.0)	9	0.146(0.106—0.236)	3.0(0.0—11.0)	11	0.193(0.13—0.284)	6.0(1.0—14.0)	11
$\Delta\text{RAP-}\Delta\text{rSO}_2\text{ R}$	0.075(0.05—0.124)	4.0(1.0—11.0)	10	0.14(0.1—0.221)	4.0(1.0—13.5)	12	0.184(0.131—0.264)	6.0(1.0—13.0)	12
$\Delta\text{RAP-}\Delta\text{COx L}$	0.077(0.052—0.11)	3.5(0.0—10.0)	6	0.162(0.101—0.213)	5.5(1.0—13.0)	8	0.212(0.145—0.298)	5.0(0.0—10.0)	8
$\Delta\text{RAP-}\Delta\text{COx R}$	0.071(0.049—0.115)	6.0(1.0—14.0)	7	0.146(0.095—0.231)	5.0(1.0—14.0)	9	0.19(0.15—0.271)	6.0(1.0—16.0)	9
$\Delta\text{RAP-}\Delta\text{COx-a L}$	0.072(0.05—0.114)	3.0(1.0—10.25)	4	0.149(0.097—0.22)	6.0(1.0—12.0)	6	0.2(0.143—0.28)	4.0(1.0—10.0)	6
$\Delta\text{RAP-}\Delta\text{COx-a R}$	0.074(0.044—0.114)	5.0(1.0—11.0)	5	0.14(0.09—0.23)	5.0(1.0—12.0)	7	0.178(0.132—0.278)	5.0(0.0—14.0)	7
$\Delta\text{RAP-}\Delta\text{PbtO}_2$	0.063(0.044—0.092)	5.0(1.0—10.75)	2	0.123(0.088—0.176)	4.0(1.0—13.0)	3	0.159(0.111—0.223)	6.0(1.0—14.0)	3