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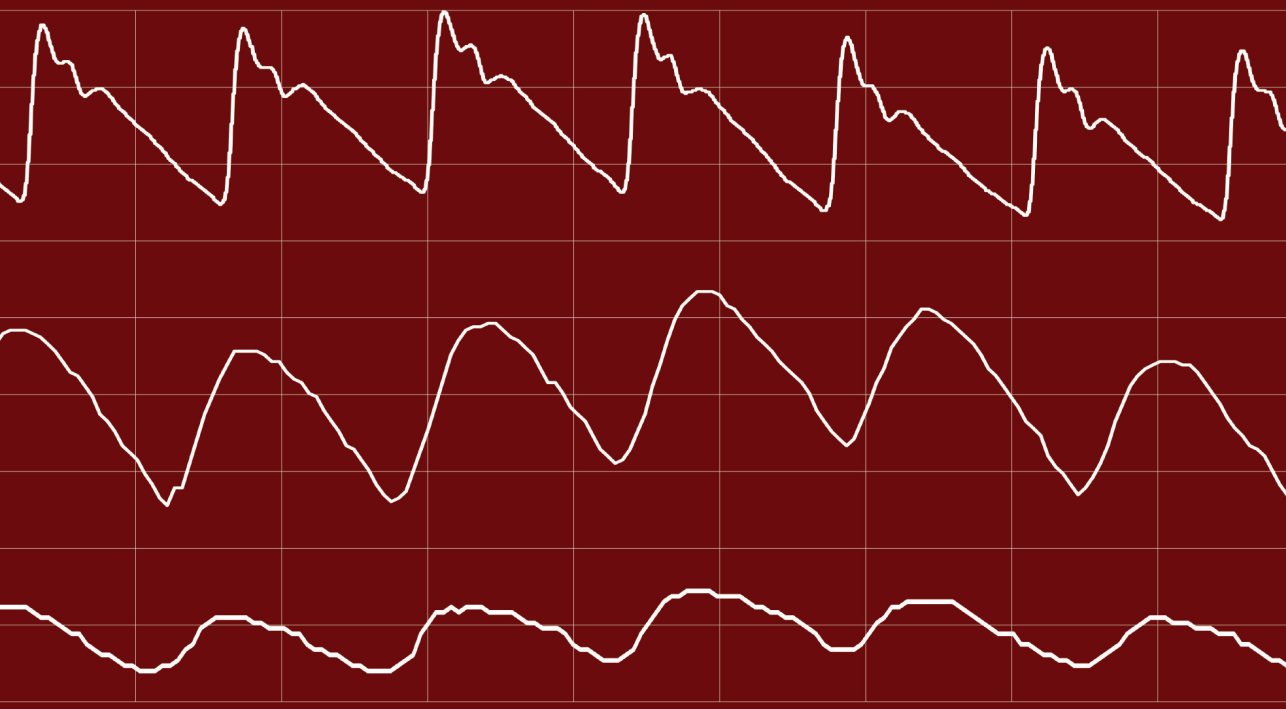
MULTIMODALITY, CEREBRAL AUTOREGULATION AND A REFINED OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY



JEANETTE TAS

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Jeanette Tas

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Next Generation Neuromonitoring

Multimodality, Cerebral Autoregulation and a Refined Outcome in Severe Traumatic Brain Injury

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PART IV – LONG-TERM OUTCOME

PART I
INTRODUCTION

1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

1.1 NEUROCRITICAL CARE TOWARDS PRECISION MEDICINE

Critically ill patients are admitted to the Intensive Care Unit (ICU) for various life-sustaining therapies supported by continuous cardio- and respiratory monitoring. Among those are patients with an acute brain injury that includes traumatic brain injury (TBI), stroke, and hypoxic-ischemic brain injury following cardiac arrest (HIBI) [1,2]. Additional cerebral monitoring is available for a selection of these patients. Recently, there has been an increasing interest in personalized medicine due to advances in therapies, technologies and changing demographics (e.g., advancing age) of the critically ill population. Personalizing medicine is commonly referred to as 'precision or individualized' medicine and was by the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) steering group defined as:

'Targeting a specific treatment to a subset of patients, with a common biological basis of disease, who are most likely to benefit from these approaches [3]'.

Three examples of precision medicine are (I) the integration of signals from multiple neuromonitoring devices (II) individualizing treatment targets using cerebral autoregulation monitoring, and (III) multi-domain clinical outcomes at long-term follow-up. In this thesis, we focus on these aspects in mainly patients with TBI.

1.2 Traumatic brain injury

The worldwide incidence of TBI is about 55 million people yearly, of which 10% are classified as moderate and severe TBI [3]. TBI is a disease affecting both young and older people. However, the main cause of the primary injury in high-income countries is falling due to the advancing age, whereas, in middle and low-income countries, mainly young people are affected by road traffic accidents [3,4]. TBI, in patients admitted to the ICU, is increasingly recognized as a systemic disease with neurological control system impairments and multi-trauma injuries [3]. Therefore, patient care is an integrated neuro-, hemodynamic- and respiratory monitoring approach.

Figure 1 shows the global trajectory from the primary brain injury towards clinical outcome assessment. The primary brain injury often results in a diversity of hemorrhages and/or axonal injuries in the white matter, so-called diffuse axonal injury [5]. It also results in an uncontrolled cascade of pathological pathways [6]. These pathways manifest in secondary injuries such as brain swelling and an increased intracranial pressure (ICP), resulting in diffusion and

perfusion disturbances and brain tissue ischemia when no adequate treatment is initiated [4]. Therefore, the current treatment aim is to prevent the (worsening of) secondary brain injuries.

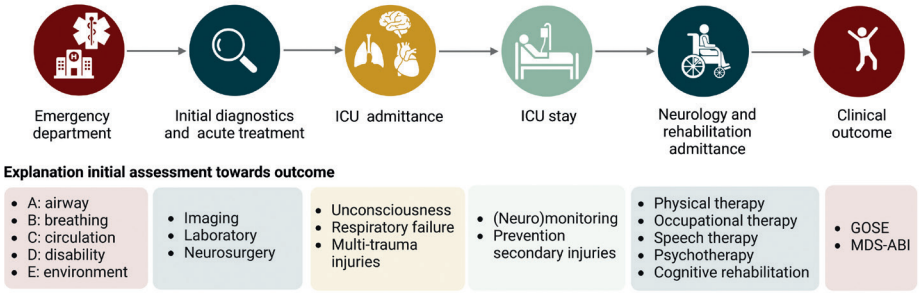


Figure 1 | Traumatic brain injury: from initial assessment towards clinical outcome assessment. The initial assessment and diagnostics determine the severity of the (brain) injury and might result in acute (neurosurgical) interventions. Main determinants of brain injury severity are the level of consciousness assessed by the Glasgow Coma Scale, which is historically classified as mild (GSC 13-15), moderate (GCS 9-12) and severe TBI (GCS 3-8), brain stem function and (repeated) CT-scan results. After that, a patient with severe brain injury and/or multi-trauma injuries is admitted to an ICU to prevent (worsening of) secondary injuries by initiating treatment protocols to control mainly ICP/CPP abnormalities. Several diagnostics and/or interventions might also be applicable in the ICU, but for reasons of readability, they are displayed only once. The rehabilitation of the patient starts during or after ICU admission and includes physical and mental therapies for patients with TBI. CT, computer tomography; GCS, Glasgow coma scale; GOSE, Glasgow outcome scale extended; CPP, cerebral perfusion pressure ICU, intensive care unit; ICP, intracranial pressure; MDS-ABI, Minimal Dataset for Acquired Brain Injury; TBI, traumatic brain injury. Created with BioRender.com

1.2.1 Neuromonitoring management

Box 1 provides an overview of the relevant management guidelines related to neuromonitoring over the years. The first evidence-based management guidelines for severe TBI were introduced in 1995 [7]. Since the introduction of the first guideline, the management of patients with TBI has focused on a single neuromonitoring (ICP/cerebral perfusion pressure (CPP)) modality and management is based on group thresholds. Over the years, it has slowly changed towards individual thresholds. In 2016 cerebral autoregulation (CA) assessment was introduced as an initial step for an individualized cerebral perfusion treatment (**section 1.4**, introduction).

Box 1 | Main changes in neuromonitoring guidelines/consensus for patients with severe traumatic brain injury

1995 [7]	Brain Trauma Foundation. Evidence-based guidelines for managing severe TBI • ICP lower than 20-25 mmHg. • CPP at least 70 mmHg.
2006 [8]	• CPP within the range of 50-70 mmHg. Patients with intact pressure autoregulation tolerate higher CPP values. • Monitoring $SvjO_2$ and $PbtO_2$. Unknown accuracy of measurements. • Recommended studying the interaction between critical ICP values and $SvjO_2$, $PbtO_2$, and rCBF.
2016 [9]	• Critical ICP threshold <22 mmHg. • A CPP within the range of 60-70 mmHg, depending on the CA-status. • Monitor $SvjO_2$ with the critical threshold set at <50%.
2019 [10]	Seattle Severe Traumatic Brain Injury Consensus Conference algorithm. A new ICP-management protocol based on a Delphi consensus meeting. • Critical ICP threshold <22 mmHg. • CPP 60-70 mmHg. • $PbtO_2$ monitoring. No critical threshold provided. • sEEG monitoring for seizure detection • CA assessment monitoring by performing regular MAP challenges.
2022 [3]	Proposal to transfer guidelines into living documents. The use of a consensus management protocol instead of evidence-based guidelines.

CA, cerebral autoregulation; CPP, cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial blood pressure; mmHg, millimeter of mercury; $PbtO_2$, brain tissue oxygenation; sEEG, surface electroencephalography; rCBF, regional cerebral blood flow; $SvjO_2$ = jugular bulb oximetry; TBI = traumatic brain injury.

1.3 Neuromonitoring devices

Neuromonitoring in the ICU aims to inform about changes in intracranial volume, cerebral oxygenation, cerebral blood flow (CBF), cerebral metabolism, cerebral temperature, and cortical electrical activity. One or several (non-) invasive devices can monitor each entity. In addition, combining arterial blood pressure (ABP) and ICP monitoring informs about cerebral autoregulation status (**section 1.4**, Introduction). In this thesis, we give an overview of combining one or several modalities. Detailed research questions are answered for, invasive (ICP/CPP) and non-invasive (near-infrared spectroscopy (NIRS) and transcranial Doppler (TCD)) monitoring.

1.3.1 Cerebral multimodality monitoring

Combining one or several modalities for monitoring brain physiology is called cerebral multimodality monitoring (MMM) or, in case of management, MMM-guided therapy. Le Roux et al. provided in 2014 recommendations regarding cerebral MMM for acute brain injury patients [11]. They envisioned, amongst others, that interfaces would be available, including integrated data streams showing changes in physiology and continuous 'optimal' CPP in five years' time. In this thesis, cerebral MMM studies have been reviewed to outline what has been achieved regarding MMM since 2015 in TBI, stroke (subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH) and acute ischemic stroke (AIS)) and HIBI patients.

1.3.2 Intracranial pressure monitoring (ICP, mmHg)

Invasive ICP monitoring informs the clinician about (continuous) changes in intracranial volume. ICP is influenced by several factors: arterial and venous blood volume, cerebral spinal fluid (CSF) volume, and brain volume (including contusions and hemorrhages). ICP is monitored continuously using either an external fluid-filled pressure transducer in combination with an extra ventricular drain (EVD) or an intraparenchymal microsensor. An intraparenchymal method is based on the strain gauge technology. A small force (applied on a membrane connected to a piezo crystal) changes the resistance of the piezo crystal. This change in resistance is converted into a pressure change [12]. The current thesis uses the intraparenchymal strain gauge technology in clinical studies of TBI patients.

1.3.3 Cerebral perfusion pressure (CPP, mmHg)

CPP is the driving pressure that drives oxygen and nutrients to the brain. The CPP was initially defined as the difference between ABP and the pressure in the cortical or bridging veins [13]. For clinical management, CPP is computed as the difference between mean ABP (MAP) and ICP, with ABP zeroed at the brain level (foramen of Monro).

1.3.4 Near infrared spectroscopy (NIRS, μM, %)

Non-invasive NIRS informs about changes in microvascular CBF and volume. The technique relies on the Lambert Beer's law. Incoming infrared light from different wavelengths travels through tissue layers and is absorbed by oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) in the brain vessels. The returned attenuated light is compared with the incoming light and converted to oxyHb and deoxyHb concentration differences [14]. Changes in CBF are reflected in changes in the tissue saturation index. This index is calculated from the ratio between oxyHb and deoxyHb as in a piglet model, a decline in CBF (measured by radioactive microspheres) correlated with a decline in the

difference between oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) concentrations [15]. Changes in cerebral blood volume are reflected in changes in total hemoglobin concentration differences calculated as the sum of oxyHb and deoxyHb [16–18]. NIRS optodes are applied to the skin and are supposed to collect data mainly from (bi)lateral frontal brain tissue. Several NIRS devices are available for bedside use with different calculation algorithms, sample frequencies, measurement depths, and indices. This thesis focuses on a research NIRS monitor that collects high frequency (50 Hz) oxyHb and deoxyHb concentration differences that allows evaluation of the individual raw signals and relationships.

1.3.5 Transcranial Doppler (TCD, cm/s)

Non-invasive TCD informs about the territorial cerebral blood flow velocity (CBFV, cm/s) in conducting vessels. Changes in CBFV and CBF are similar, assuming that the diameter of the insonated vessel does not change. A probe is placed on the thin temporal (bone) window to provide continuous ultrasound reflections at different depths. The returning ultrasound wave has changed in frequency compared to the incoming frequency. The degree of change in frequency relies on the velocity of red blood cells in a conduit vessel (Doppler shift) [19]. TCD is mainly applied for shorter periods of monitoring due to unstable insonations. Changes in CBFV over time are interpreted as signs of territorial hypo- or hyperperfusion. Additional information about vessel obstruction, vasospasm, or cerebrospinal reserve could be obtained.

1.4 Cerebral autoregulation

The regulation of CBF is a combination of actuators: cerebral autoregulation (CA), chemo regulation, neuronal regulation, and endothelium-dependent regulation [20]. The CA is defined as: 'the response of the cerebral circulation to changes in cerebral perfusion pressure' [20]. The response results from myogenic vessel reactivity, i.e., the vascular tone response to changes in intraluminal pressure. Lassen et al. described the CA conceptually in 1959 as a plateau of CPP values for which CBF minimal fluctuates around a CBF plateau value with an upper and lower limit or breakpoint. CPP values below the lower limit cause hypoperfusion, whereas CPP values above the upper limit cause hyperperfusion [21]. Although this concept is still the basis of CA research, it has been criticized over the years [20,22]. This thesis focuses on individual CA assessment being part of the regulation of global CBF.

1.4.1 Cerebral autoregulation monitoring

Ideally, a CBF monitor is available to study the relationship between CBF and CPP, but currently, no reliable device is available for continuous global CBF monitoring at the bedside [23]. As an alternative surrogate for CA research,

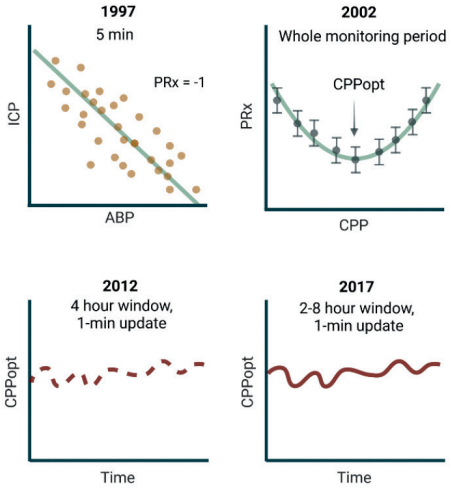
the relationship between ABP and ICP is mostly studied in a time-domain analysis. With an active regulating system, an increase in ABP (pressure) causes intracranial vasoconstriction, a subsequent decrease in volume in the skull and a decreased ICP, without significant changes in CBF [24, 25]. When CA is impaired, the vessel tone cannot adequately respond to changes in ABP; hence, an increased ABP causes an increased volume in the skull which is measured by increasing ICP.

An additional characteristic of the changes in vessel tone is that the vessel response is frequency dependent. To illustrate this characteristic, fast (i.e., heartbeat-to-heartbeat) changes in ABP are not counteracted by adaptations of the vessel tone, whereas slow and potentially harmful (<0.2 Hz) changes in ABP are actively modified. Therefore, intact, or functioning CA acts as a 'high pass filter' [20]. In this thesis, we applied both time- and frequency domain analysis to assess the CA-status.

1.4.2 Invasive monitoring - time-domain analysis

The CA status in the time domain is for TBI patients mostly computed as the Pearson correlation coefficient between slow changes in ABP and ICP signals. This is called the pressure reactivity index (PRx). A negative correlation indicates functioning CA, whereas a positive correlation indicates impaired CA [23,22]. In addition, the relationship between CPP and PRx can be used to study the 'optimal' CPP or CPPopt for an individual patient using longer periods of monitoring periods [26]. CPPopt is the CPP value for which the CA is best preserved. **Box 2** describes the evolution of CPPopt towards a potential individual treatment target. In this thesis, the results of the first prospective CA-guided CPP treatment study are presented.

Box 2 | Evolution of CPPopt



1997 | Czosnyka et al. introduced the PRx. The Pearson correlation between slow waves in 10 sec averaged ABP and ICP signals computed over 5 min [23].

2002 | Steiner et al. showed for individual TBI patients a parabolic curve for the CPP (x-axis), and PRx (y-axis) relationship. The optimum was called the CPPopt, as the PRx value corresponds to the CPP with the best preserved CA (lowest PRx) for the patient [26].

2012 | Aries et al. computed an automated CPPopt over a shorter window of 4 hours that updated every minute [27].

2017 | Liu et al. introduced a multi-window approach to improve the availability of a continuous CPPopt value using a window of six hours [28].

Clinical outcome | Retrospective data showed that a CPP value close to CPPopt resulted in lower mortality and an improved clinical outcome [27,28].

1.4.2.1 Signal averaging and increased signal power

A prerequisite for reliable CA research is that sufficient slow ABP waves are present to trigger the CA system. Several methods to induce slow ABP oscillations are available for mainly awake subjects, such as stand-squat maneuvers or thigh cuffs maneuvers [29, 30]. However, it is challenging to induce slow ABP waves in comatose ICU patients. As an alternative, the signal strength is often relatively increased by averaging the data over seconds/ minute. This reduces the number of 'unwanted' frequencies in the signal [27]. In the current thesis, we increased the signal power using an - adapted from an animal model - innovative methodology for inducing slow ABP waves in ventilated patients with TBI and ICP monitoring.

1.4.2.2 External factors adversely influencing the monitoring signals

As an alternative to increasing the signal power, elimination of external 'noise' could increase the signal quality. Examples of external 'noise' are other devices. In the current thesis, an observation is described in which an external device affects the ICP, ABP signals and consequently the CA estimation.

1.4.3 Non-invasive monitoring - frequency domain CA analysis

Transfer function analysis (TFA) is a well-known methodology to describe the CA using ABP and non-invasive TCD (CBFV) signals. Recommendations for TFA data processing and interpretation are available [31,32,33]. In short, time domain signals are Fourier transformed for TFA. After that, the transfer, gain, phase shift and coherence are derived. The derived TFA measures that inform about the CA-status are gain (damping between the signals), phase shift (time delay between the signals) and the coherence (linearity between the signals, often used as a

quality measure of the signals), but the phase shift in the low-frequency range is an extensively used parameter for CA in the literature [34] (Figure 2). For phase shifts close to zero the CA indicates an impaired CA, whereas phase shifts up to 180 degrees indicates intact functioning CA.

Reinhard et al. showed that NIRS oxyHb and deoxyHb phase shifts are related to the ABP-CBFV phase shift. In other words, although the exact phase shifts differed due to different measurement locations, comparing an intact and impaired CA showed a comparable reduction in phase shift for both oxyHb - deoxyHb and ABP - CBFV TFA results [35]. In the current thesis, a methodology is developed to assess the CA using 'only' oxyHb and deoxyHb signals, and a correction for cerebral microvascular characteristics is applied. The CA estimation is compared with the relationship between TFA using ABP – CBFV signals and evaluated in a critically ill population.

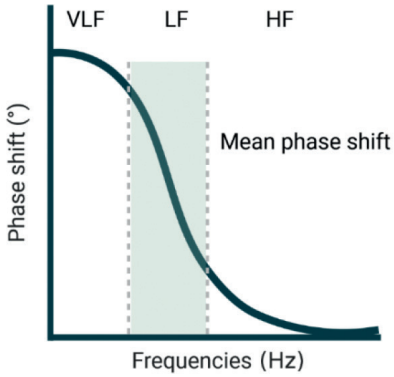


Figure 2 | Transfer function derived high-pass filter that describes the cerebral autoregulation. Schematic illustration of the relationship between ABP and CBFV signals in the frequency domain. In the frequency domain, the frequencies (x-axis) and phase shift between ABP-CBFV (y-axis) show a high-pass filter configuration. The mean phase shift for the VLF or LF-range is a measure off the CA-status (green-shaded for the LF range). HF, high frequency; LF, low frequency; VLF, very low frequency. Created with BioRender.com

1.5 Outcome assessment in patients with traumatic brain injury

The clinical outcome of patients with TBI is, for research purposes, mainly assessed by the Glasgow Outcome Scale Extended (GOSE). The GOSE is an ordinary scale ranging from 1 - 8 (dead – full recovery). Although this is a concise and easy-to-apply scale, recent studies questioned the individual precision [36–38]. Therefore, Domensino et al. introduced the minimal dataset for adults with acquired brain injury (MDS-ABI) to better differentiate clinical outcomes after brain injury [39–41]. The minimal dataset includes twelve outcome domains (demographics, injury characteristics, comorbidity, cognitive functioning,

emotional functioning, energy, mobility, self-care, communication, participation, social support, and quality of life). It also includes data from the informal caregiver, such as caregiver capacity and strain to obtain a global presentation of the patient's outcome for each domain. In the current thesis, the MDS-ABI is applied in former survived ICU patients with TBI in a cross-sectional study.

1.6 Aim and objectives

The research in this thesis **aimed** to investigate the feasibility of invasive and non-invasive neuromonitoring for CA-guided perfusion therapy and continuous CA assessment in adult patients with mainly TBI. In addition, the research in this thesis aimed for the exploration of a refined clinical outcome in patients with TBI. The **first objective** is to review the application of cerebral multimodality monitoring in recent clinical ICU studies in patients with acute brain injury (TBI, SAH, ICH, AIS, HIBI). The **second objective** is to study the feasibility and safety of CA-guided perfusion therapy in patients with TBI and ICP monitoring. The **third objective** is to study a new methodology for non-invasive CA-assessment in healthy subjects with TCD and NIRS monitoring and the evaluation of the model in critically ill and comatose ICU patients with NIRS monitoring. The **fourth** and final objective is to explore the MDS-ABI in former ICU patients with TBI.

1.7 Outline of the thesis

In **Chapter 2**, we summarize the recent application of cerebral multimodality monitoring in ICU patients with acute brain injury (TBI, SAH, ICH, AIS, HIBI). In **Chapter 3**, we describe the first feasibility and safety study towards CPPopt Guided Therapy: Assessment of Target Effectiveness (COGiTATE) study protocol in ICU patients with TBI **(3.1)**, and we provide an update of the COGiTATE enrollment **(3.2)**. In **Chapter 4**, we present the results of the COGiTATE study. In **Chapter 5**, we introduce a – previously described in an animal model - innovative methodology to improve the CA-assessment in patients with TBI. In **Chapter 6**, we report on the observation of the effect of the alternating (in- and deflating) anti-decubitus mattress on the ABP and ICP signals and consequently the PRx calculation in patients with TBI. In **Chapter 7**, we introduce a non-invasive 'NIRS-only' CA-assessment methodology and compare measurement results between NIRS and TCD-derived TFA results in healthy subjects. In **Chapter 8**, we improve the 'NIRS-only' methodology and study the relationship between impaired CA and clinical outcome in critically ill and comatose ICU patients. In **Chapter 9,** we explore the MDS-ABI clinical outcome assessment tool in former ICU patients who survived TBI. Finally, in **Chapter 10**, we summarize and discuss the findings of the chapters and put them into a broader perspective.

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Cerebral Multimodality Monitoring in Adult Neurocritical Care Patients with Acute Brain Injury: a Narrative Review

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ABSTRACT

Cerebral multimodality monitoring (MMM) is, even with a general lack of Class I evidence, increasingly recognized as a tool to support clinical decision-making in the neuroscience intensive care unit (NICU). However, literature and guidelines have focused on unimodal signals in a specific form of acute brain injury. Integrating unimodal signals in multiple signal monitoring is the next step for clinical studies and patient care. As such, we aimed to investigate the recent application of MMM in studies of adult patients with traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), acute ischemic stroke (AIS), and hypoxic ischemic brain injury following cardiac arrest (HIBI). We identified continuous or daily updated monitoring modalities and summarized the monitoring setting, study setting, and clinical characteristics. In addition, we discussed clinical outcome in intervention studies. We identified 112 MMM studies, including 11 modalities, over the last 7 years (2015–2022). Fifty-eight studies (52%) applied only two modalities. Most frequently combined were ICP monitoring (92 studies (82%)) together with $PbtO_2$ (63 studies (56%). Most studies included patients with TBI (59 studies) or SAH (53 studies). The enrollment period of 34 studies (30%) took more than 5 years, whereas the median sample size was only 36 patients (q1- q3, 20–74). We classified studies as either observational (68 studies) or interventional (44 studies). The interventions were subclassified as systemic (24 studies), cerebral (10 studies), and interventions guided by MMM (11 studies). We identified 20 different systemic or cerebral interventions. Nine (9/11, 82%) of the MMM-guided studies included clinical outcome as an endpoint. In 78% (7/9) of these MMM-guided intervention studies, a significant improvement in outcome was demonstrated in favor of interventions guided by MMM. Clinical outcome may be improved with interventions guided by MMM. This strengthens the belief in this application, but further interdisciplinary collaborations are needed to overcome the heterogeneity, as illustrated in the present review. Future research should focus on increasing sample sizes, improved data collection, refining definitions of secondary injuries, and standardized interventions. Only then can we proceed with complex outcome studies with MMM-guided treatment.

1. INTRODUCTION

Neuromonitoring is used to guide treatment in patients with acute brain injuries. Most neuroscience intensive care units (NICU) in high-income countries have intracranial pressure (ICP) and cerebral perfusion pressure (CPP), along with transcranial Doppler (TCD) and surface electroencephalography (sEEG) as brain monitoring tools available in a selection of their acute brain injured patients (Le Roux et al., 2014; Hutchinson et al., 2015; Carney et al., 2017; Cnossen et al., 2017). Partial pressure of brain tissue oxygenation ($PbtO_2$), cerebral temperature (Cerebral T), regional cerebral blood flow (rCBF), jugular bulb venous oximetry ($SvjO_2$), cerebral microdialysis (CMD), nearinfrared spectroscopy (NIRS) and electrocorticography (ECoG; from invasive electrodes on the cerebral surface) and depth electroencephalography (dEEG) are the other frequently applied modalities (Le Roux et al., 2014; Stocchetti et al., 2017). Cerebral multimodality monitoring (MMM) is often mentioned in NICU reviews (Makarenko et al., 2016; Stocchetti et al., 2017; Tasneem et al., 2017; Smith, 2018; Al-Mufti et al., 2019; Veldeman et al., 2020a; Yang, 2020), but reviews and guidelines mainly discuss the results of unimodal signals (Le Roux et al., 2014; Carney et al., 2017). The practical application of “combining modalities” is limited by the high dimensionality of signals and non-standardized methods to present the information at the bedside. Also, clinical context, including imaging results, is not incorporated (Tasneem et al., 2017; Smith, 2018; Al-Mufti et al., 2019; Veldeman et al., 2020a; Yang, 2020). In 2014, Le Roux et al. (2014) formulated five-year expectations and recommendations regarding MMM in acute brain injured patients. They expected patient-specific rather than population-specific thresholds, TCD-based non-invasive measures for ICP monitoring, and advances in the detection of cortical spreading depolarization. Since the projections by Le Roux et al. were put forward, no overview of the application of MMM studies has been published (Le Roux et al., 2014). However, rigorous insight into MMM of recent years could detect benefits, pitfalls, and gaps for improving future clinical study designs. In this narrative review, we, therefore, aim to investigate the recent applications of cerebral MMM in studies for acute brain injured patients (i.e., adult patients with traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), acute ischemic stroke (AIS) or hypoxic ischemic brain injury following cardiac arrest (HIBI). Our objectives are (I) to identify which combinations of monitoring modalities are currently applied, in general, and across the different acute brain injuries, (II) to summarize the monitoring setting, study setting, and clinical characteristics, and (III) to discuss the potential added value of MMM on clinical outcome in intervention studies.

2. METHODS

We identified studies describing combinations of cerebral monitors providing data that updates continuously or on a regular daily basis (i.e. regularly over the day) through a PubMed literature search. We used a stepwise approach for the literature search and identification of eligible studies. Step 1, for each cerebral monitoring modality, a single PubMed query was used (Supplementary Table S1). Step 2, each MMM combination (ICP and NIRS, ICP and sEEG, NIRS and TCD, etc.) was used in the search in combination with the general inclusion criteria. The general inclusion criteria were: clinical study, adult (age, >18 years old) patients, article written in English, and an Epub publication period covering Jan 1, 2015 to Jul 1, 2022. These general criteria were selected in the PubMed filters. Step 3, the abstracts (and, if needed, the full-text studies) were screened for further eligibility: (I) the study had to concern critical care patients with (II) a minimum of five patients and (III) diagnosed with TBI, SAH, ICH, AIS or HIBI. Step 4, all selected full-text studies were read, and their references were screened for additional studies. The abstracts were read when the reference was used in a MMM context in the main text or when in a reference MMM was part of the title. In addition, the citations of the selected studies were screened in the Web of Science Core collection database (August 2022). Step 5, we selected MMM studies for which the study aim or objective(s) were related to MMM. We defined MMM application as (I) the application and reporting results of at least two modalities, i.e., modalities that were part of the research protocol, and (II) without aiming to evaluate superiority/inferiority between modalities (validation studies), as these studies are not designed to integrate multiple signals but aim for the (potential) replacement of a signal. Step 6, we collected the monitoring setting, study setting, and clinical characteristics from each study. In addition, we collected defined secondary injuries from observational and interventional studies. These secondary injuries are the defined cerebral, potential reversible, pathophysiological conditions diagnosed by monitoring, imaging, or other clinical diagnostics. The interventions and the clinical outcome were also collected for the interventional studies. Detailed definitions/descriptions are given in Supplementary Table S2. The collected information resulted in a comprehensive table to support the objectives of our MMM review. For objective I, we described the number and combinations of the different modalities. The number of monitoring combinations was calculated, and their synergy was visualized in a Circos plot (Krzywinski et al., 2009). For objective II, we summarized the monitoring setting, study setting, and clinical characteristics of the selected studies between the diseases and reported the results as frequencies or medians (together with interquartile range, q1-q3). Furthermore, we described the secondary injuries studied in observational and interventional studies. Finally, we summarized the interventions that were applied

in the MMM studies. For objective III, we discussed the added value of MMM on clinical outcome in intervention studies.

3. RESULTS: Study selection

After the abstract, references, and citation identification, 209 full-text studies were read. From these, 97 studies whose aim or objective(s) were not related to MMM were excluded. These excluded studies were predominantly (52 studies) validation (superiority/inferiority) studies comparing non-invasive TCD based ICP with invasive ICP monitoring (25 studies). Supplementary Table S3 lists the modalities used for validation.

The study selection flowchart is shown in Supplementary Figure S1. In addition, the number of included studies by year can be found in Supplementary Figure S2. For the final analysis, 112 MMM studies were available, of which 59 concerned TBI (53%), 53 SAH (47%), 13 ICH (12%), 5 AIS (4.5%), and 9 HIBI (8%).

4. RESULTS objective I and II: Cerebral multimodality monitoring combinations and monitoring setting

We identified 11 monitoring modalities that update continuously or on a regular daily basis. The anatomical locations are graphically presented in Figure 1, showing eight invasive (ICP, $PbtO_2$, Cerebral T, rCBF, $SvjO_2$, CMD, ECoG, dEEG) and three non-invasive (TCD, NIRS, sEEG) modalities. The synergy of the combinations is shown in Figure 2. The individual modalities were integrated into 47 unique combinations (Figure 3). In 58 studies (52%), two modalities were applied, three in 28 studies (25%), and only 26 studies (23%) utilized more than three modalities (Supplementary Figure S3). ICP monitoring was the most frequently combined modality, in 92 studies (82%), with the highest number in TBI patients (53 studies, 90%). The second most applied modality was $PbtO_2$ in 71 studies (63%). $SvjO_2$ monitoring was only applied in six studies (5.4%) and mainly combined with ICP (5 studies) and $PbtO_2$ (5 studies) monitoring. Invasive neuronal activity monitoring (ECoG and dEEG studies, 17 studies) was more common than non-invasive neuronal activity monitoring (sEEG, 10 studies). Regarding non-invasive modalities, TCD was most often studied (25 studies), predominantly in patients with SAH, ICH, and AIS. TCD was not studied in HIBI patients. We studied only modalities that were part of the research protocol. However, 21 SAH studies also mentioned other modalities (mainly ICP, Cerebral T, and TCD), which were only part of the clinical protocol. These modalities were not considered as often only limited, or no continuous information was provided. Supplementary Table S5 lists these modalities for the individual studies. Lastly, only 58% of the studies analyzed more than 24 h of data per patient. A summary of the monitoring settings is given in Table 1 and Supplementary Table S4A.

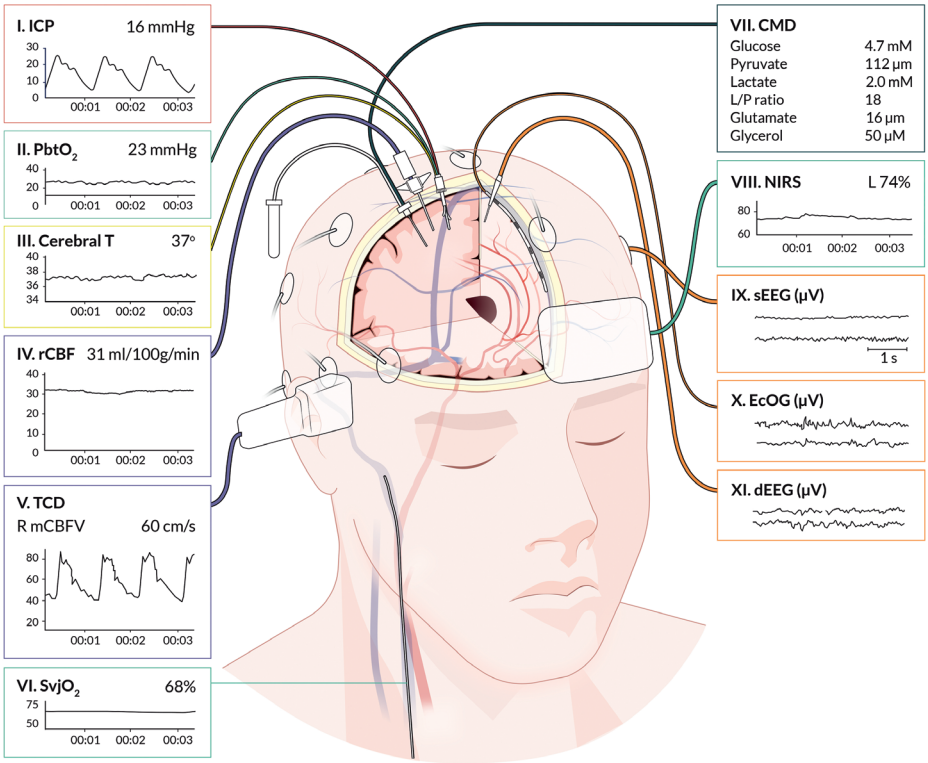

Figure 1 | Graphical representation of cerebral multimodality monitoring modalities. The eleven applied monitoring modalities with numbers and (raw) signals. Each modality presents the standard visualization on the bedside monitoring screen. For the readability of the figure, only two neuronal activity monitoring electrodes are displayed. In common practice, the numbers for sEEG are application of 21 electrodes, for ECoG and dEEG 4-8 electrodes. Cerebral T, cerebral temperature; CMD, cerebral microdialysis; dEEG, depth electroencephalography; ECoG, electrocorticography; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; $PbtO_2$, partial pressure of brain tissue oxygenation; rCBF, regional cerebral blood flow; sEEG, surface electroencephalography; $SvjO_2$, jugular bulb venous oximetry; TCD, transcranial Doppler. Professional illustration by Anna Sieben (Sieben Medical Art).

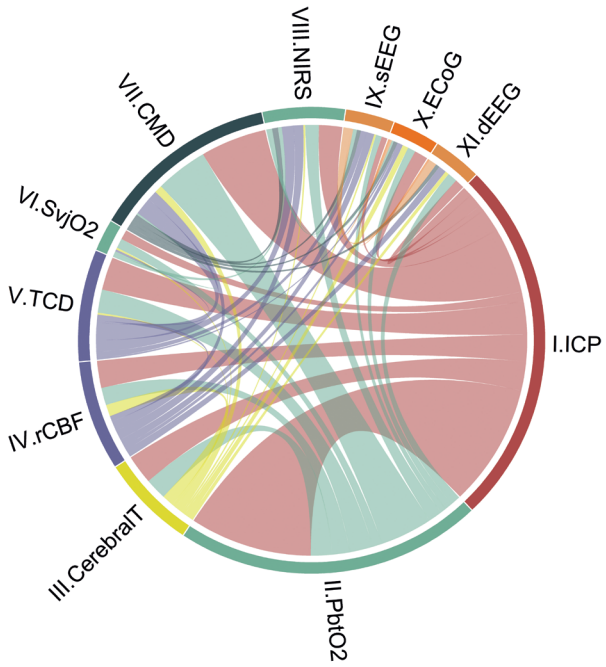

Figure 2 | Combinations of cerebral unimodal monitoring modalities in the literature over the last 7 years (112 studies). Circos-plot visualizing connections between unimodal continuous cerebral monitoring modalities. ICP monitoring is the modality most combined, followed by $PbtO_2$. As an illustration to understand the distribution of each part: ICP monitoring appears in study 1 in combination with modalities II and III, and in study 2, ICP appears with modalities IV and V. ICP monitoring is then displayed on 2/6 of the circle (ICP + ICP + II + III + IV + V, 6 of which 2x ICP). The colors represent intracranial volume (red), cerebral oxygenation (green), regional cerebral blood flow (purple), cerebral metabolism (dark blue), neuronal electrical activity (orange), and cerebral temperature (yellow). Cerebral T, cerebral temperature; CMD, cerebral microdialysis; dEEG, depth electroencephalography; ECoG, electrocorticography; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; $PbtO_2$, partial pressure of brain tissue oxygenation; rCBF, regional cerebral blood flow; sEEG, surface electroencephalography; $SvjO_2$, jugular bulb venous oximetry; TCD, transcranial Doppler.

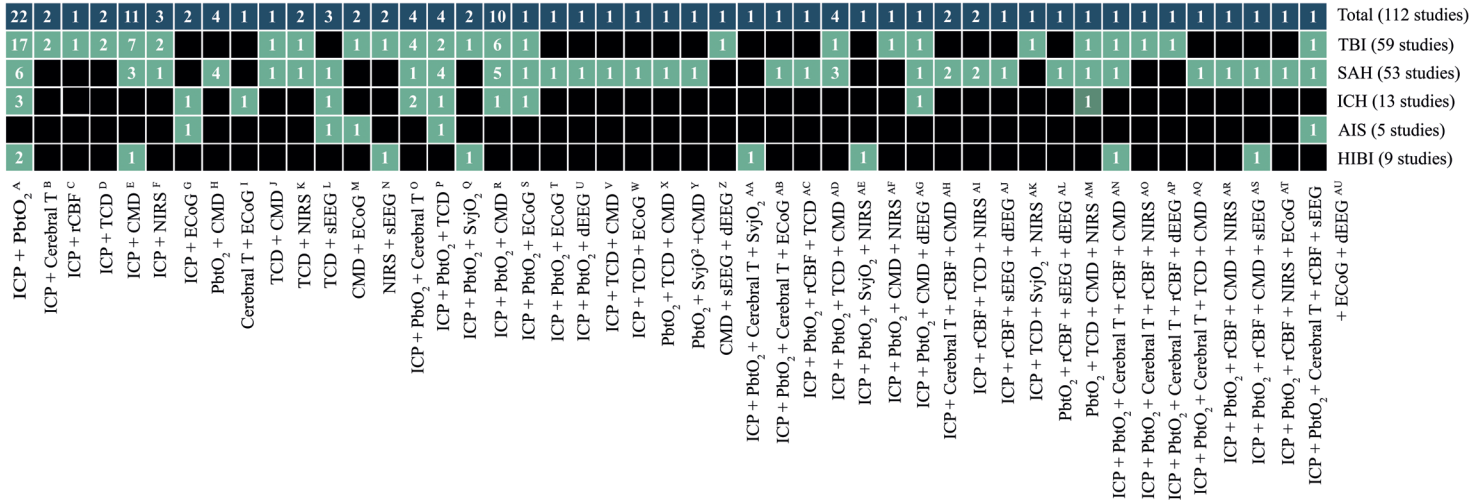

Figure 3 | Unique cerebral multimodality monitoring combinations. The 47 unique combinations of MMM are shown. The first upper row shows the total number of studies per combination. The second to the sixth row shows the number of studies per acute brain injury: TBI, SAH, ICH, AIS, and HIBI. Each box describes the number of studies. The boxes in black do not include a monitoring combination for a particular disease. The references of the studies are added to Supplementary Tables S5A–D. The reference numbers per unique combination are: A (11,14,24,33,43,46,47,48,49,53, 69,71,87,90,91,94,97, 104,105,106,107,110); B (51,55); C (4); D (76,31); E (9,38,45,61,62,63,66,67,77,82, 101); F (32,37,73); G (8,60); H (17,70,95,98); I (21); J (78); K (6,74); L (23,57,58);M(10,20); N (68,79);O(30,40,42,100); p (83,86,93,96);Q(35,44); R (1,3,13,19,34,52,56,59,89,102); S (2); T (27); U (29); V (112); W (64); X (99); Y (5); Z (15); AA (111); AB (16); AC (103); AD (80,92,108,109); AE (81); AF (41); AG (50); AH (12,39); AI (75,88); AJ (18); AK (84); AL (22); AM(72); AN (36); AO (7); AP (26); AQ(85); AR (54); AS (28); AT (65); AU (25). Note: the sum of studies for the individual diseases not count towards the total number of studies because a study can include patients with different diseases. AIS, acute ischemic stroke; Cerebral T, cerebral temperature; CMD, cerebral microdialysis; dEEG, depth electroencephalography; ECoG, electrocorticography; HIBI, hypoxic-ischemic brain injury following cardiac arrest; ICH, intracerebral hemorrhage; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; $PbtO_2$, partial pressure of brain tissue oxygenation; rCBF, regional cerebral blood flow; SAH, subarachnoid hemorrhage; sEEG, surface electroencephalography; $SvjO_2$, jugular bulb venous oximetry; TBI, traumatic brain injury; TCD, transcranial Doppler.

5. RESULTS: Objective II study setting and clinical characteristics

The study setting and clinical characteristics are summarized in Table 2 and Supplementary Table S4B. Most were single center studies (90 studies, 80%) with a median sample size of 36 (q1-q3, 20–74) patients. In 34 studies (30%), patients were enrolled over a period of more than 5 years. TBI studies included more patients compared to SAH studies (TBI 43 (22–100) patients versus SAH 26 (17–69) patients). In addition, TBI studies more often had a multicenter design (TBI, 37% versus SAH, 15%). Eighteen studies (16%) included combinations of acute brain injured patients. Especially, ICH and AIS were combined with other acute brain injuries. There were only four single disease studies of ICH and only three of AIS. Although HIBI is the least contributing group, relatively more single disease studies were included (5 studies) compared to ICH and AIS. Clinical characteristics differed between diseases. TBI studies included relatively younger male patients (71%<50 years, 75% male), whereas SAH studies included older female (70% 50–59 years, 31% male) patients. HIBI studies included middle aged, slightly more male patients (67%, 40–49 years, 61% male). Studies that included ICH patients included a wide range of ages (40–69 years, 53% male). AIS included predominantly patients within the range 50–59 years and female (39% male).

Table 1 | Monitoring setting of cerebral multimodality monitoring studies (112 studies).

	TBI[a] 59 studies	SAH[a] 53 studies	ICH[a] 13 studies	AIS[a] 5 studies	HIBI[a] 9 studies
Unimodal modalities, no. of studies (%)					
I. ICP	53 (90)	42 (79)	10 (77)	3 (60)	8 (89)
II. $PbtO_2$	39 (66)	39 (74)	10 (77)	2 (40)	7 (78)
III. Cerebral T	10 (17)	7 (13)	3 (23)	1 (20)	2 (22)
IV. rCBF	5 (8.5)	12 (23)	0	1 (20)	2 (22)
V. TCD	9 (15)	18 (34)	3 (23)	2 (40)	0
VI. $SvjO_2$	2 (3.4)	1 (1.9)	0	0	3 (33)
VII. CMD	21 (36)	27 (51)	3 (23)	1 (20)	3 (33)
VIII. NIRS	9 (15)	8 (15)	2 (15)	0	2 (22)
IX. sEEG	3 (5.1)	5 (9.4)	1 (7.7)	2 (40)	2 (22)
X. ECoG	2 (3.4)	5 (9.4)	2 (15)	3 (60)	0
XI. dEEG	4 (6.8)	5 (9.4)	1 (7.7)	1 (20)	0
Other neuromonitoring applied (not related to the research protocol), no. of studies (%)					
One modality	9 (15)	21 (40)	3 (23)	1 (20)	1 (11)
Two other modalities	2 (3.4)	4 (7.5)	1 (7.7)	0	0
Duration monitoring used for data analysis, no. of studies (%)					
0–1 hour	8 (14)	4 (7.5)	3 (23)	2 (40)	1 (11)
2–12 hours	8 (14)	8 (15)	2 (15)	0	0
13–23 hours	2 (3.4)	4 (7.5)	0	1 (20)	0
≥24 hours	31 (53)	29 (55)	6 (46)	0	7 (78)
Not reported	10 (17)	8 (15)	2 (15)	2 (40)	1 (11)

Table 1 | Monitoring setting of cerebral multimodality monitoring studies (112 studies). (continued)

	TBI[a] 59 studies	SAH[a] 53 studies	ICH[a] 13 studies	AIS[a] 5 studies	HIBI[a] 9 studies
ABP zeroing (when ICP monitoring was applied), no. of studies (%)	53 (90)	53 (79)	10 (77)	3 (60)	8 (89)
Heart	9 (17)	7 (17)	2 (20)	0	1 (13)
Foramen of Monro	5 (9.4)	3 (7.1)	3 (30)	0	0
Both	1 (1.9)	1 (2.4)	1 (10)	0	0
Not reported	38 (72)	31 (74)	4 (40)	3 (100)	7 (88)

[a]Multiple diseases: several studies report more than one disease. These studies are represented for each diagnosis. The percentages are reported as whole numbers. The percentages not count to 100% due to rounding. Definitions are listed in Supplementary Table S2. ABP, arterial blood pressure; AIS, acute ischemic stroke; HIBI, hypoxic ischemic brain injury; Cerebral T, cerebral temperature; CMD, cerebral microdialysis; dEEG, depth electroencephalography; ECoG, electrocorticography; MMM, multimodality monitoring; ICH, intracerebral hemorrhage; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; No., number; $PbtO_2$, partial pressure of brain tissue oxygenation; rCBF, regional cerebral blood flow; SAH, subarachnoid hemorrhage; sEEG, surface electroencephalography; $SvjO_2$, jugular bulb umatic brain injury; TCD, transcranial Doppler.

Table 2 | Study setting, and clinical characteristics of cerebral multimodality monitoring studies (112 studies).

	TBI[a] 59 studies	SAH[a] 53 studies	ICH[a] 13 studies	AIS[a] 5 studies	HIBI[a] 9 studies
Multicentre studies, no. of studies (%)	22 (37)	8 (15)	3 (23)	3 (60)	3 (33)
Study enrollment period, no. of studies (%)					
0–1 year	11 (19)	9 (17)	3 (23)	1 (20)	2 (22)
2–3 years	13 (22)	9 (17)	4 (31)	1 (20)	6 (67)
4–5 years	7 (12)	10 (19)	1 (7.7)	1 (20)	0
≥6 years	18 (31)	16 (30)	3 (23)	1 (20)	1 (11)
Not reported	10 (17)	9 (17)	2 (15)	1 (20)	0
Sample sizes, median (q1 – q3)	43 (22–100)	26 (17–69)	47 (25–69)	23 (18–59)	18 (11–65)
Sex, male (%), median (q1 – q3)	75 (60–81)	31 (24–50)	53 (49–60)	39 (20–60)	61 (33–70)
Age range, no. of studies (%)					
18–29 years	1 (1.7)	0	0	0	0
30–39 years	20 (34)	4 (7.5)	1 (7.7)	1 (20)	0
40–49 years	21 (36)	7 (13)	3 (23)	0	6 (67)
50–59 years	14 (24)	37 (70)	5 (38)	4 (80)	2 (22)
60–69 years	0	3 (5.7)	4 (31)	0	1 (11)
Not reported	3 (5.1)	2 (3.8)	0	0	0
Multiple pre-defined diseases per study, no. of studies (%)	16 (27)	15 (28)	9 (69)	2 (40)	1 (33)

[a]Multiple diseases: some studies report more than one disease. These studies are represented for each diagnosis. Supplementary Tables S5A–D lists the studies.
The percentages are reported as whole numbers. The percentages not count to 100% due to rounding. Definitions are listed in Supplementary Table S2 AIS, acute ischemic stroke; HIBI, hypoxic-ischemic brain injury following cardiac arrest; ICH, intracerebral hemorrhage; No., number; MMM, multimodality monitoring; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; q1-q3, interquartile range

Table 3 | Study classification of cerebral multimodality monitoring studies (112 studies).

	TBI[a] 59 studies	SAH[a] 53 studies	ICH[a] 13 studies	AIS[a] 5 studies	HIBI[a] 9 studies
No. of studies (%)					
Observational	36 (61)	28 (53)	9 (69)	4 (80)	6 (67)
Systemic intervention	15 (25)	14 (26)	4 (31)	1 (20)	2 (22)
Cerebral intervention	5 (8.5)[b]	5 (9.4)	0	0	0
Interventions guided by MMM	4 (6.8)[b]	6 (11)	0	0	1 (11)
Intervention studies - Clinical outcome endpoint	7 (30)	9 (36)	1 (25)	0	3 (100)
Safety endpoint	8 (14)	10 (19)	2 (15)	1 (20)	2 (22)

[a]Multiple diseases: several studies report more than one disease. These studies are represented for each diagnosis. Supplementary Tables S5A–D lists the studies.
[b]One study was classified as both interventions guided by MMM and cerebral intervention (Khellaf et al., 2022).
The percentages are reported as whole numbers. The percentages not count to 100% due to rounding. Definitions are listed in Supplementary Table S2 AIS, acute ischemic stroke; HIBI, hypoxic-ischemic brain injury following cardiac arrest; ICH, intracerebral hemorrhage; MMM, multimodality monitoring; No., number; SAH, emorrhage; TBI, traumatic brain injury

6. RESULTS objective II: Secondary injuries

Secondary brain injuries are heterogeneous in presentation, with a complex interplay between impairments in diffusion, perfusion, metabolic derangements, and neuronal damage. We studied the different conditions and phenomena defined by the authors of the observational (68 studies) and interventional (44 studies) studies. Authors reported hypo-/hyper perfusion, cerebrovascular autoregulation impairment, ICP plateau waves, spreading depolarization, diffuse cerebral ischemia, vasospasm, and metabolic distress. Due to the inconsistencies in definitions and nomenclature of (single) modalities, no detailed group results across the diseases are presented, but examples are given to explain these inconsistencies. Authors either allocated patients with/without a specific secondary brain injury and compared differences in MMM signals between the groups, or authors selected a whole group of a particular disease. Then, they reported the secondary brain injuries based on the thresholds of each modality. In general, the number of secondary brain injuries is large because each modality has its own threshold for impairment, or a combination of modalities defines an impairment. In other words, the definitions of secondary brain injuries are limited by the number of available modalities. For example, Lindner et al. (2021) defined mitochondrial dysfunction (single modality) as: CMD lactate/pyruvate (L/P)-ratio ≥ 40 + CMD-pyruvate ≥70 µmol/L, whereas Khellaf et al. defined mitochondrial dysfunction (three modalities) as: CMD L/P-ratio>25 for more than 2 h, ICP <20 mmHg; $PbtO_2$ <15 mmHg; PRx <0.3; brain extracellular glucose >1 mmol/L (Khellaf et al., 2022). In addition, there were inconsistencies in nomenclature for impairments using single modalities. For example, Hosmann et al. (2022) define indications for cerebral ischemia as CMD L/P-ratio >40 CMD-glycerol >100 µmol/L, CMDlactate >4 mmol/L, whereas Nyholm et al. (2017) defined cerebral ischemia as CMD-L/P ratio >40 and CMD-pyruvate <50 mol/L). For brain tissue hypoxia monitored by $PbtO_2$ there were in general two definitions used: $PbtO_2$ <15 mmHg (Burnol et al., 2021; Hosmann et al., 2021) or <20 mmHg (Le Roux et al., 2014; Gagnon et al., 2020; Sekhon et al., 2020; Gouvea Bogossian et al., 2021).

7. RESULTS objective III: Interventions, potential therapies

We identified systemic- (24 studies), cerebral (10 studies) interventions, and interventions guided by MMM (11 studies). Table 3 and Supplementary Table S4C summarize the study classifications. In addition, one study was classified as MMM guided and a cerebral intervention. A total number of 20 different systemic- or cerebral interventions were applied. An example of a systemic intervention is the administration of red blood cell (RBC) transfusion (Sekhon et al., 2015; Kurtz et al., 2016; McCredie et al., 2017; Gouvêa Bogossian et al., 2022). An example of a cerebral intervention is the application of prostacyclin with a beneficial effect on neuronal cell membrane destruction (Koskinen et al., 2019). Examples of MMM-guided interventions are the studies of Veldeman et al. They evaluated outcome between periods before and after introducing an invasive MMM-guided protocol to avoid $PbtO_2$ < 10 mmHg and CMD L/P-ratio >40 in severe SAH patients with suspicion of delayed cerebral ischemia (Veldeman et al., 2020a; Veldeman et al., 2020b). Interventions in the MMM studies serve mainly three purposes. Firstly, monitoring the effectiveness of an intervention. Secondly, collecting monitoring data in combination with an intervention for outcome evaluation/prediction. A third purpose is monitoring the need for an intervention. In other words, interventions guided by MMM to investigate the interplay between monitoring and a combination of (in general, systemic) interventions. Figure 4 illustrates the purposes of the interventions across the MMM studies. To give insight into the range of systemic-, cerebral-, and MMM-guided interventions, we classified them into nine categories: ABP management, biomarkers, fluid management, mixed (combination of different) interventions, RBC-transfusion, physical (movement) interventions, vasospasm therapy, ventilation management, and other interventions. The number of studies per group is mostly less than five. The largest groups are the mixed interventions used to guide MMM (11 studies), followed by ventilation management interventions (10 studies). On the other hand, biomarkers and physical (movement) interventions were studied in only three studies. The specific interventions and the corresponding number of studies per category are shown in Table 4.

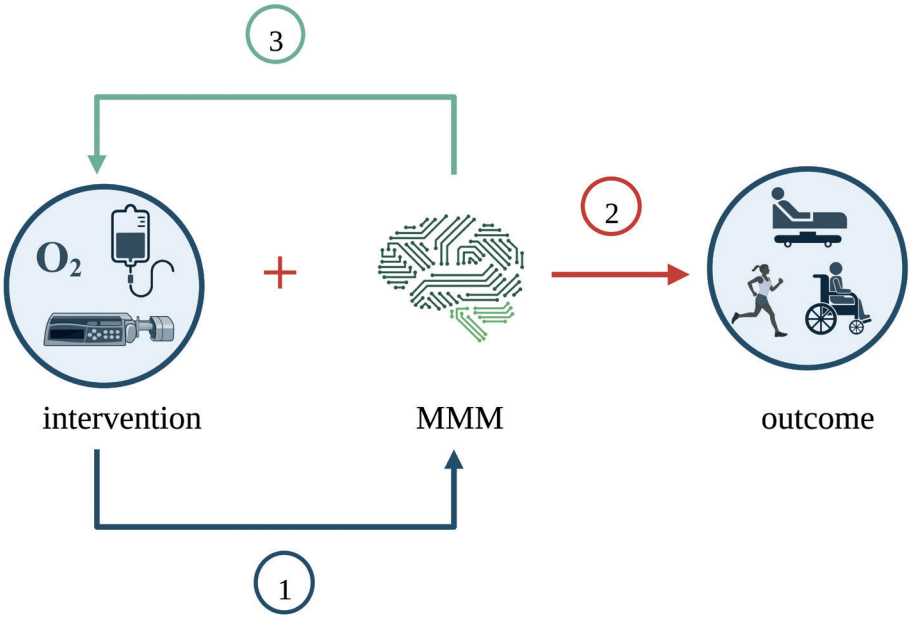

Figure 4 | Purposes of interventions across the MMM studies. MMM was examined in three different ways across the studies. Firstly, MMM was the outcome, and the intervention's effectiveness was studied. Secondly, MMM was considered along with the intervention for its effect on clinical outcome. Thirdly, thresholds of MMM were used to dictate intervention, and the need for intervention was studied. Created with BioRender.com. MMM, multimodality monitoring.

Table 4 | Systemic-, cerebral- interventions, and interventions guided by cerebral multimodality monitoring in 44 studies.

Intervention group	Interventions	No. of studies	References
ABP-management	Arterial blood pressure-management	4	(Jakkula et al., 2018; Calviello et al., 2019; Sekhon et al., 2019; Kovacs et al., 2021)[b]
Biomarkers	Neuroglobin, prostacyclin, succinate	3	(Ding et al., 2019; Koskinen et al., 2019; Khellaf et al., 2022)[a].
Fluid management	CSF drainage, hypertonic saline, and/or fluid management	5	Akbik et al., 2017; Carteron et al., 2018; Hoiland et al., 2021; Rasset al., 2021; Bernini et al., 2022)
Mixed interventions	Nimodipine, ICP/CPP management (vasopressors, sedation, etc.), hyperoxia, glucose, head elevation/flat position	11	(Bele et al., 2015; Lin et al., 2015; Okonkwo et al., 2017; Sekhon et al., 2017; Rass et al., 2019; Veldeman et al., 2020a; Veldeman et al., 2020b; Fergusson et al., 2021; Gouvea Bogossian et al., 2021; Khellaf et al., 2022; Winberg et al., 2022)[a]
RBC transfusion	Red blood cell transfusion	4	(Sekhon et al., 2015; Kurtz et al., 2016; McCredie et al., 2017; Gouvêa Bogossian et al., 2022)
Physical (movement) interventions	Intrahospital transport, head elevation/flat position	3	(Burnol et al., 2021; Dagod et al., 2021; Hosmann et al., 2021)
Vasospasm therapy	Nimodipine, endovascular therapy, papaverine-hydrochloride	4	(Hockel et al., 2016; Albanna et al., 2017; Hockel et al., 2017; Hosmann et al., 2020)
Ventilation management	Hyperoxia, hypercapnia, hypocapnia	10	(Westermaier et al., 2016; Zhang et al., 2016; Ghosh et al., 2017; Sahoo et al., 2017; Brandi et al., 2019; Calviello et al., 2019; Svedung Wettervik et al., 2020b; Stetter et al., 2021; Gargadennec et al., 2022; Hosmann et al., 2022)[b]
Other therapies	Analgesia, hypothermia, enteral nutrition, decompressive craniectomy	4	(Flynn et al., 2015; Kofler et al., 2018; Kovac et al., 2018; Ianosi et al., 2020)

[a]One study included both cerebral intervention and MMM-guided treatment (mixed interventions). [b]One study included two study groups studying two interventions. ABP, arterial blood pressure; CSF, cerebral spinal fluid; RBC, red blood cell; No., number; ICP, intracranial pressure; CPP, cerebral perfusion pressure; MMM, multimodality monitoring.

8. RESULTS objective III: Clinical outcome in interventional studies

Clinical outcome is a study endpoint in 18 (41%) of the 44 interventional studies. Systemic- and cerebral interventions evaluated MMM for either outcome prediction (1 study) (Lubillo et al., 2018) or monitoring the effectiveness of an intervention in both the MMM signals and clinical outcome (8 studies) (Hockel et al., 2016; Jakkula et al., 2018; Ding et al., 2019; Sekhon et al., 2019; SvedungWettervik et al., 2020b; Dagod et al., 2021; Kovacs et al., 2021). For MMM-guided intervention studies, clinical outcome resulted from the interplay between MMM and interventions. Nine (9/11, 82%) of the MMM-guided included clinical outcome as an endpoint, of which seven showed an improved outcome in favor of the MMM-guided group (78%, 7/9 studies). Five (45%) studied an ICP and $PbtO_2$-guided treatment in either TBI (Lin et al., 2015; Okonkwo et al., 2017; Sekhon et al., 2017) or SAH (Rass et al., 2019; Gouvea Bogossian et al., 2021) patients. Two of these compared pre-/post implementation of an MMM-guided protocol. Okonkwo et al. (2017) studied the feasibility and safety of an ICP and $PbtO_2$ protocol in a randomized controlled trial (RCT). Their study showed lower mortality and improved outcome, but the effects did not reach statistical significance. This was attributed to the small sample size. In addition, Rass et al. (2019) studied the brain hypoxia burden in two centers and found no difference in $PbtO_2$-levels and clinical outcome. The remaining four MMM-guided studies that showed an improved clinical outcome included the following modalities: (I) CMD in combination with ICP, $PbtO_2$, TCD (Veldeman et al., 2020a; Veldeman et al., 2020b) (II) ICP, $PbtO_2$, Cerebral T, and $SvjO_2$ (Fergusson et al., 2021), and (III) ICP, $PbtO_2$, rCBF, and TCD (Bele et al., 2015).

9. DISCUSSION

The principal insights gained from our analysis of the MMM literature are that: (Insight I) most reports of MMM involve just two monitoring modalities, one of which is typically ICP monitoring; (Insight II) we found relatively often 10 (8.9%) ECoG and 7 (6.3%) dEEG studies, of which 8 (50%) investigated cortical spreading depolarization; (Insight III) our results show that MMM is primarily used in TBI and SAH patients. In addition, ICH and AIS are sparsely studied as a single study population but mainly combined with other acute brain injuries. One of the reasons could be that (non) invasive cerebral monitoring was not part of HIBI, AIS, and ICH (international) treatment guidelines and protocols compared to TBI and SAH patients; (Insight IV) most MMM studies had an observational design without direct clinical and therapeutic implications at the bedside; (Insight V) The sample sizes are in general small with long inclusion periods; (Insight VI) a large variety of interventions were studied in limited numbers of studies; (Insight

VII) seven of the nine MMM-guided intervention studies showed a significant improved clinical outcome in favor of treatment guided by MMM.

9.1 Strengths and weaknesses of MMM (studies)

9.1.1 Acceptance of MMM in clinical practice

Almost 10% of the studies were MMM-guided, of which only one was an RCT. The remaining MMM-guided studies investigated a clinical intervention protocol guided by MMM (e.g., comparing the pre-/post implementation of a protocol). This reflects the acceptance of MMM in current clinical practice, even with general lack of Class I evidence. The recent Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC) included in their tier-based protocol not only ICP but also $PbtO_2$ for monitoring (Hawryluk et al., 2019). While no (phase-III) clinical outcome benefits of MMM-guided treatment exist yet, there are three large phase-III trials currently underway. All study in TBI patients whether a combined ICP and $PbtO_2$-guided tiered management protocol is associated with a beneficial outcome (ClinicalTrials.gov, 2021a; ClinicalTrials.gov, 2021b; Udy, 2021). ICP and $PbtO_2$ monitoring were also mostly applied in the MMM studies. This is not surprising as ICP/CPP monitoring is the cornerstone of TBI monitoring and treatment guidelines (Carney et al., 2017; Hawryluk et al.,2019). sEEG has infrequently been used, which is surprising as non-convulsive status epilepticus has been reported in 10–20% of NICU patients (Laccheo et al., 2015). Epileptic activity is not only related to cortical damage and poor outcome but might also confound the interpretation of MMM results (Nolan et al., 2021). The least studied modality is $SvjO_2$. Although $SvjO_2$ has a lengthy history of use, the availability of non-invasive alternatives like NIRS or the increasing use of $PbtO_2$ may explain this (Bhatia and Gupta, 2007).

9.1.2 Multiple research questions per study cohort

Our results showed that limited (20%) multicenter studies were included, of which more than ten concerned COSBID (Co-Operative studies on Brain Injury Depolarizations) or CENTERTBI (Collaborative European Neuro Trauma Effectiveness Research in TBI) study cohorts. Both cohorts are collaborations between different international centers studying a diversity of research questions. In addition, single-center studies also reuse their cohort by publishing different research questions, for example, the series from Svedung Wettervik et al. (Svedung Wettervik et al., 2019; Svedung Wettervik et al., 2020b; Svedung Wettervik et al., 2020a). The strength of a recycled study cohort is that it saves time and money; and could result in a broad understanding of the neuromonitoring signals. Also, the different studies were performed under the same conditions, which improves the ability to compare the studies. On the other hand, the

weakness is that reusing study cohorts overestimate the feasibility of MMM for clinical use.

9.1.3 Data quality

We found that 30% of the studies enrolled patients over a period of more than 5 years. The long inclusion period, in combination with the low number of patients, might be explained because several studies use large (observational) databases to select patients with a particular condition (e.g., ICP plateau waves). In addition, insufficient data quality might contribute. A number of studies excluded patients due to poor data quality of both invasive and non-invasive monitoring modalities. For example, rCBF monitoring (Hemedex Inc.; Cambridge, MA) requires regular calibrations, which causes a regular artifact in the data, whereby Foreman et al. could use only 62% of the rCBF monitoring time (Foreman et al., 2018). Other examples are the exclusion of five (21%) NIRS data recordings (McCredie et al., 2017); the exclusion of five (4.8%) $PbtO_2$ recordings due to malfunctioning $PbtO_2$ probes (Rass et al., 2019); the exclusion of 17 (10%) recordings because of poor ECoG data quality (Hartings et al., 2020); and exclusion of 8.8% (637/7223) of the hourly analyzed CMD samples because of insufficient quality (Winberg et al., 2022). Finally, 30% (100–2435/3483 h) of the ICP and Cerebral T data was excluded due to artifacts (Birg et al., 2021). Misplaced probes were less often reported (Gagnon et al., 2020; Winberg et al., 2022) but also contributed to the removal of patient data. A weakness of MMM (studies) is that although most studies were performed in NICU, collecting continuous, high-quality data from multiple monitors seems complex as several studies report artifacts or poor data quality, limiting its feasibility in clinical practice. Moreover, post-hoc manual removal of a large number of artifacts lead to a false clinical conclusion.

9.1.4 Data duration and the start of monitoring

The data covered for analysis for more than 24 h of monitoring was only 58%. The short analysis periods contrast with continuous or regularly daily updated monitoring data. Important to realize is that we used the data analysis period for comparisons instead of the total monitoring period (of which data were limited reported). The short analysis periods are related to, firstly, the type of monitoring. For example, 79% (15/19 studies) of the TCD studies reported time periods <24 h of monitoring. Recent technological advances in automated stable TCD insonations will probably allow longer recordings (Zeiler et al., 2019). Secondly, the study design. For example, studies selected monitoring epochs around specific interventions or physiological changes (such as pre-/post-hypocapnia intervention) (Brandi et al., 2019) or pathophysiological insults (such as delayed cerebral ischemia) (Patet et al., 2017). Thirdly, the timing of the applied monitoring (if reported) after the estimated time of ictus. The strength of MMM would be to have continuous monitoring available, informing about different aspects of the

brain and evaluate changes over time. However, since limited studies analyze whole signal recordings and very few studies reported the delay between the estimated time of ictus and the start of study monitoring, it is a weakness of the current MMM studies that it is often unknown which pathophysiological condition the patients were studied in time. Therefore, we recommend to report the disease time course for multimodality studies. In this way, we will gain insight into time-specific monitoring patterns related to pathophysiological changes.

9.1.5 Signal integration

We defined MMM as "the application and reporting results of at least two modalities (i.e., modalities were part of the research protocol) without aiming for superiority/inferiority between modalities". However, almost 30% of the studies monitored patients with additional neuromonitoring modalities for other (clinical) purposes. Therefore, the results included these additional modalities as "other modalities". For example, ICP monitoring is standard of care in TBI patients and has been reported only in the methods of the study as part of their "clinical management". However, when the aim or objective(s) of the study was to study the relationship between CMD and $PbtO_2$, ICP was not classified as part of their study modalities. The strength of MMM would be to integrate multiple monitoring signals. However, we observed that the analysis was mainly group comparisons, correlations, and uni- or multivariate (regression) analysis. Hemphill et al. proposed advanced analysis in NICU in 2011. They discussed that advanced analysis can be divided into unsupervised data driven (e.g., hierarchical clustering), supervised data-driven (e.g., decision trees, neural networks), or model-based methods (e.g., dynamic system models Dynamic Bayesian networks). Regression analysis is also part of data-driven methods, but these are only appropriate for linear predictions (Hemphill et al., 2011; Volovici et al., 2022), whereas time series of different modalities include multiple features (dimensions) and interactions. For these complex interactions, model-based methods are more appropriate (Hemphill et al., 2011; Acosta et al., 2022). We included an explorative study using hierarchical clustering (Rajagopalan et al., 2022). They successfully classified four clusters, each corresponding with a specific (patho)-physiological state (cerebral ischemia, intracranial hypertension without ischemia, hyper-glycolysis, and normal cerebral physiology) from cerebral MMM data. In addition, Åkerlund et al. (2022) applied an unsupervised statistical clustering model on clinical variables in a TBI population. They concluded that this approach might contribute to a refinement in disease classification and a better understanding of pathological processes and their relation with clinical outcome. For future studies, it might be interesting to integrate different domains such as neuromonitoring data, clinical variables, medication (e.g., sedatives, analgesia, vasopressor medication), ventilation, or advanced cardiac monitoring signals for a further understanding of complex disease entities. However, for

successful models, a large number of patients with complete and annotated data sets are required (Acosta et al., 2022).

9.2 Limitations

Our current MMM overview is based on a stepwise search covering a 7 years period. However, we should acknowledge that this approach has limitations. Firstly, we studied the literature starting from the projections of Le Roux et al. to give an overview of the literature, knowing it limits conclusions about MMM advances over time. In addition, only adult patients were included, while reviewing pediatric studies would be of interest too. Secondly, although the review outline and interpretation of the review results were discussed within the coauthors' group, the studies were screened and classified by a single author. In addition, we did not use a formal (PRISMA guided) systematic review and meta-analysis, given the heterogeneity in study design, patient population, and monitoring devices applied. However, we performed a reproducible and extensive literature search with pre-defined inclusion criteria covering the past 7 years.

9.3 Future perspectives

For the upcoming years, it would be recommended to focus on, firstly, data quality, collection of both MMM signals and other continuous trends (medication, ventilation, advanced cardiac monitoring), and advanced analytics. Interdisciplinary collaborations can achieve this. Secondly, increasing sample sizes, homogeneity of studied diseases, and shortening inclusion periods. This can be achieved by increasing the number of multicenter studies. Thirdly, introducing new refined definitions of secondary injuries to improve the comparison between studies. Fourthly, one of the stated near future MMM reflections was the increased validation of direct current EEG methodology (i.e., the ability to detect a wide range of EEG frequencies) (Kovac et al., 2018) to detect cortical spreading depolarization. The included explorative studies showed promising results regarding the pathophysiology of cortical spreading depolarization. Therefore, future exploration could indicate a potential new treatment target for acute brain injury patients (Winkler et al., 2017; Hartings et al., 2020); and, finally, the start of new phase-III MMM studies that might result in new outcome benefits and therapies for acute brain injured patients.

10. CONCLUSION

Cerebral MMM in neurocritical care patients with acute brain injury focuses predominantly on bimodal monitoring, studied mainly in TBI and SAH patients. Definitions of secondary injuries are limited by the number of modalities and differ in entity due to different thresholds. In addition, the applied interventions are large in variety, but they are limited in the number of studies. Although the improved clinical outcome in MMM-guided intervention studies strengthens the belief in this application, further interdisciplinary collaborations are needed to overcome the heterogeneity. Future research should focus on improved data collection, sample sizes, refining definitions of secondary injuries, and standardized interventions. Only then can we proceed with complex outcome studies with MMM-guided treatment.

Author contributions

JT performed the literature search, reviewed the studies for eligibility, and interpreted the individual study results. Concept and design were done by JT, MA, IH, CH, and FZ. Figures: JT, MA, IH, and SP. Next, all authors critically reviewed the results of the manuscript. Finally, all authors reviewed and approved the final manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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SUPPLEMENTARY MATERIAL

Supplementary Table S1 | PubMed search terms

Supplementary Table S2 | Definitions for classification of cerebral multimodality monitoring studies

Supplementary Table S3 | Cerebral monitoring modalities of superiority / inferiority studies

Supplementary Figure S1 | Flowchart study search and identification

Supplementary Figure S2 | Number of cerebral multimodality monitoring studies per year

Supplementary Figure S3 | Number of cerebral monitoring modalities

Supplementary Table S4a | Monitoring setting of 112 cerebral multimodality monitoring studies

Supplementary Table S4b | Study setting and clinical characteristics of 112 cerebral multimodality monitoring studies

Supplementary Table S4c | Study classification of 112 cerebral multimodality monitoring studies

Supplementary Table S1 | PubMed search terms. Each modality includes a query. MeSH Terms were included when available.

ICP	((“intracranial pressure” [MeSH Terms]) OR intracranial pressure OR ICP OR ((“cerebral perfusion pressure” [MeSH Terms]) OR “cerebral perfusion pressure” OR CPP)
$PbtO_2$	Partial brain tissue oxygen OR PbtO2
Cerebral T	Cerebral temperature” OR “Brain temperature” OR “cerebral T” OR “Temperature
rCBF	(“Regional cerebral blood flow” OR Regional cerebral blood flow [MeSH Terms]) OR rCBF)
TCD	(Transcranial Doppler [MeSH Terms]) OR Transcranial Doppler OR TCD
$SvjO_2$	Jugular bulb venous oximetry OR Sjvo2 OR SvjO2
CMD	(microdialysis [MeSH Terms]) OR Cerebral microdialysis OR CMD
NIRS	(Near infrared spectroscopy [MeSH Terms]) OR Near infrared spectroscopy OR NIRS
sEEG	(Surface Electroencephalography [MeSH Terms]) OR Surface Electroencephalography; OR EEG OR qEEG
EcOG	(Electrocorticography [MeSH Terms]) OR Electrocorticography; EcOG
dEEG	Depth Electroencephalography OR dEEG

Cerebral T = cerebral temperature; CMD = cerebral microdialysis; dEEG = depth electroencephalography; ECoG = electrocorticography; ICP = intracranial pressure; NIRS = near-infrared spectroscopy; $PbtO_2$ = partial pressure of brain tissue oxygenation; rCBF = regional cerebral blood flow; sEEG = surface electroencephalography; $SvjO_2$ = jugular bulb venous oximetry; TCD = transcranial Doppler

Supplementary Table S2 | Definitions for classification of cerebral multimodal monitoring studies

Parameter	Description
MMM study	The aim or objective(s) were related to MMM. MMM is defined as the application and reporting of results of at least two modalities without aiming for superiority/inferiority between modalities. Note. An included modality could also be a covariate in a multivariable model or a modality used for the detection of a secondary injury that was primarily studied (e.g., TCD for detection of vasospasm).
Unimodal modalities	The applied modalities for studying the aim/objective(s). TCD also includes transcranial color doppler sonography (TCCD). CBF includes only invasive regional CBF monitoring. NIRS only includes non-invasive monitoring.
Other neuromonitoring modalities	Modalities described in the study but not part of the study aim or objective(s). These modalities were either used for clinical management (e.g., ICP monitoring not part of the study aim/objective(s)) or not part of our included modalities, but continuously or daily updated monitoring (e.g., a non-invasive CBF monitor).
Duration monitoring for data analysis	The period (hr) used for data analysis as described in the studies. This means that the recording time may differ from the analysis period for specific interventions. For example, when only the pre-and post-periods are used for data analysis.
ABP zeroing	The location where the ABP transducer was zeroed when ICP monitoring was available.
Multicentre study	More than one study site included patients for data collection. For example, the Collaborative European Neuro Trauma Effectiveness Research in TBI (CENTER-TBI) and Co-Operative Studies on Brain Injury Depolarizations (COSBID) cohorts.
Study enrollment period	The duration of the study as reported by the authors.
Sample size	The sample size is reported per study, albeit some studies included a combination of diseases. Therefore, studies can appear more than once in the results.
Sex	Percentage of the sample with males.
Multiple pre-defined diseases	More than one acute brain injury, as defined in this review, was described in the study design (TBI, SAH, ICH, AIS, HIBI).

Supplementary Table S2 | Definitions for classification of cerebral multimodal monitoring studies (continued)

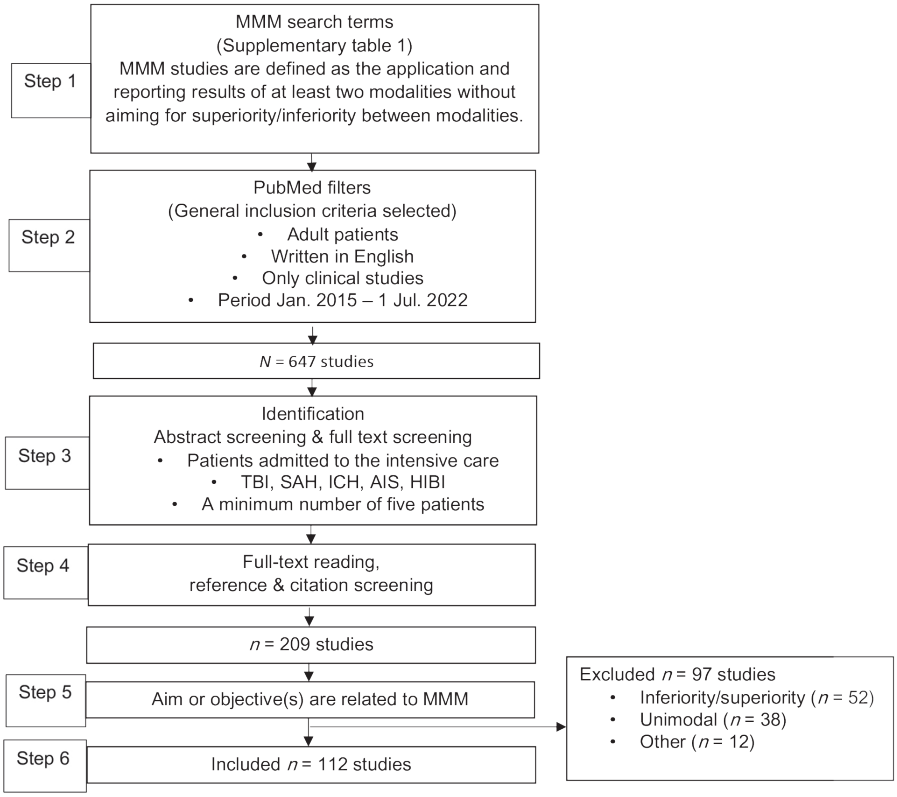
Parameter	Description
Study classification	*Observations.* The study aim or objective(s) of the study is related to studying a secondary injury by using at least a combination of two modalities. Results are reported as, e.g., clinical outcome comparison between groups or changes within patients (with/without the condition). *Interventions.* The study aim or objective(s) of the study is related to external manipulation. This can be either a clinical event (e.g., studying the periods with changes in ventilator settings) or a pre-defined intervention protocol. *Intervention, systemic*. Interventions applied with a direct systemic effect (like studying the effect of packed cell red blood transfusion). *Intervention, cerebral.* Interventions applied with a direct local cerebral effect (like studying the effect of cerebral spinal fluid drainage on MMM signals). *Interventions guided by MMM.* The study aims to compare groups applying a pre-defined management protocol guided by MMM results. This subtype includes randomized controlled trials, pre-/post- introduction of a (clinical) management protocol, or the evaluation of an MMM-guided clinical management protocol. *Safety.* The study aim or objective(s) is to test a new MMM modality, method, or intervention with a safety endpoint. *Clinical outcome*. The study compares the results of monitoring modalities in patient groups with different clinical outcome (either mortality or functional outcome).
Other diseases/healthy controls	Other than our pre-defined diseases or healthy controls were included in the study. These diseases are only reported per study (Supplementary table 5a-d).

ABP = arterial blood pressure; AIS = acute ischemic stroke; CBF = cerebral blood flow; HIBI = hypoxic-ischemic brain injury following cardiac arrest; ICH = intracerebral hemorrhage; ICP = intracranial pressure; MMM = multimodality monitoring; NIRS = near infrared spectroscopy; SAH = subarachnoid hemorrhage; TBI = traumatic brain injury; TCD = transcranial Doppler

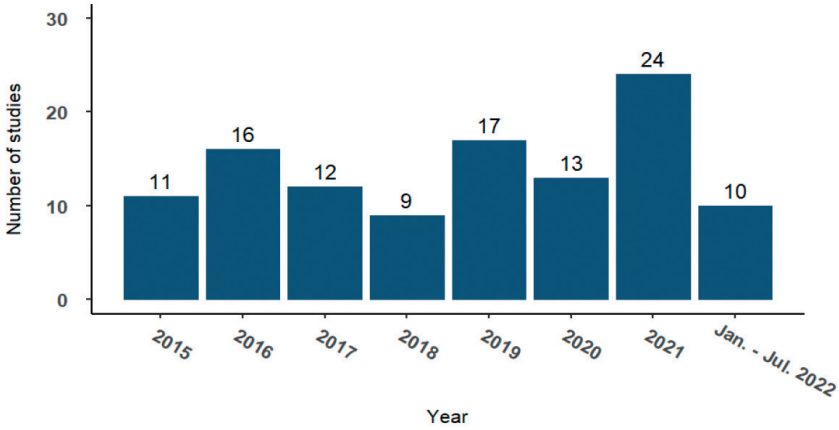
Supplementary Table S3 | Cerebral monitoring modalities of superiority/ inferiority studies

No. of studies (%)	Total 52 studies	TBI[a] 38 studies	SAH[a] 16 studies	ICH[a] 10 studies	AIS[a] 4 studies	HIBI[a] 6 studies
Unimodal modalities						
I. ICP	40 (77)	32 (84)	11(69)	8 (80)	2 (50)	0
II. $PbtO_2$	13 (25)	8 (21)	6 (38)	2 (20)	0	2 (33)
III. Cerebral T	2 (3.8)	1 (2.6)	1 (6.3)	0	0	0
IV. rCBF	4 (7.7)	4 (11)	0	1 (10)	0	1 (17)
V. TCD	33 (63)	26 (68)	9 (56)	8 (80)	3 (75)	3 (50)
VI. $SvjO_2$	1 (1.9)	1 (2.6)	0	1 (10)	1 (25)	0
VII. CMD	4 (7.7)	1 (2.6)	3 (19)	1 (10)	0	1 (17)
VIII. NIRS	8 (15)	7 (18)	2 (13)	3 (30)	0	3 (50)
IX. sEEG	4 (7.7)	3 (7.9)	2 (13)	1 (10)	1 (25)	0
Invasive neural activity						
X. ECoG	2 (3.8)	2 (5.3)	1 (6.3)	0	1 (25)	0
XI. dEEG	1 (1.9)	1 (2.6)	1 (6.3)	0	0	0

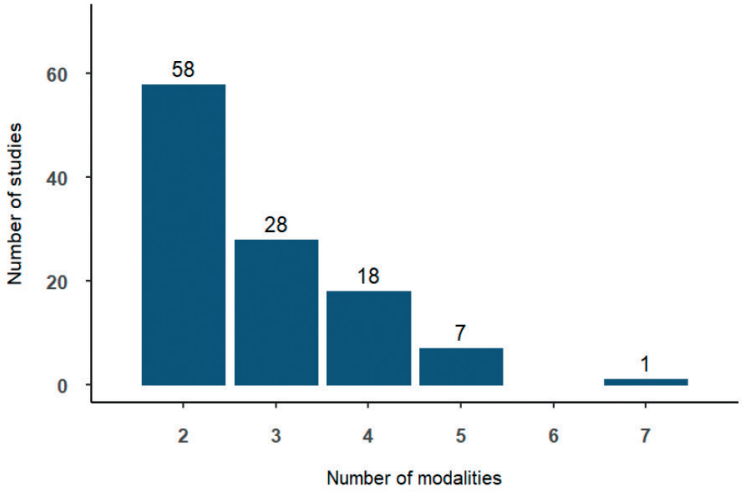
The percentages are reported as whole numbers. The percentages may not count to 100% due to rounding.
[a]Multiple diseases: several studies report more than one disease. These studies are represented for each diagnosis.
AIS = acute ischemic stroke; Cerebral T = cerebral temperature; CMD = cerebral microdialysis; dEEG = depth electroencephalography; ECoG = electrocorticography; MMM = multimodality monitoring; HIBI = hypoxic-ischemic brain injury following cardiac arrest; ICH = intracerebral hemorrhage; ICP = intracranial pressure; NIRS = near-infrared spectroscopy; No. = number; $PbtO_2$ = partial pressure of brain tissue oxygenation; rCBF = regional cerebral blood flow; SAH = subarachnoid hemorrhage; sEEG = surface electroencephalography; $SvjO_2$ = jugular bulb venous oximetry; TBI = traumatic brain injury; TCD = transcranial Doppler.



Supplementary Figure S1 legend | Study search and identification flowchart. We used a stepwise approach to select MMM studies described in the methods. The number of excluded studies does not count to 97, as more than one reason could have excluded the study. The excluded group 'unimodal' included studies for which a unimodal aim/objective was described, albeit other modalities were available for, e.g., clinical purposes. Details about the excluded inferiority/superiority studies are given in Supplementary Table S3. The group 'other' included: studies not reporting monitoring results (*n* = 10) (e.g., study protocols); one (exceptional) study was excluded because the authors aimed to evaluate an artifact in ECoG data using $PbtO_2$ monitoring to detect the trigger of the artifact (1), one double publication was excluded (2,3). AIS = acute ischemic stroke; ECoG = electrocorticography; HIBI = hypoxic-ischemic brain injury following cardiac arrest; ICH = intracerebral hemorrhage; MMM = multimodality monitoring; SAH = subarachnoid hemorrhage; $PbtO_2$ = partial pressure of brain tissue oxygenation; TBI = traumatic brain injury.



Supplementary Figure S2 | Number of included cerebral multimodality monitoring studies per year. The number of cerebral multimodality monitoring studies per year since 2015.



Supplementary Figure | S3 Number of cerebral monitoring modalities.

The number of cerebral monitoring modalities combined within a study. Each bar represents the number of studies with the corresponding number of combined modalities on the x-axis. On the y-axis, the number of studies is shown. Dreier et al. applied seven modalities, but not in each patient similar combinations (5).

Supplementary Table S4a | Monitoring setting of 112 cerebral multimodality monitoring studies

No. of studies (%)	Total 112 studies
Unimodal modalities	
I. ICP	92 (82)
II. $PbtO_2$	71 (63)
III. Cerebral T	16 (14)
IV. rCBF	15 (13)
V. TCD	25 (22)
VI. $SvjO_2$	6 (5.4)
VII. CMD	45 (40)
VIII. NIRS	17 (15)
IX. sEEG	10 (8.9)
Invasive neural activity	
X. ECoG	10 (8.9)
XI. dEEG	7 (6.3)
Other neuromonitoring modalities (not related to the research protocol)	
One modality	29 (26)
Two other modalities	5 (4.5)
Duration monitoring used for data analysis (hr)	
0-1	11 (9.8)
2-12	13 (12)
13-23	7 (6.3)
≥ 24	65 (58)
Not reported	16 (14)
ABP zeroing (when ICP monitoring was applied)	
Heart	13 (12)
Foramen of Monro	9 (8)
Both	1 (1)
Not reported	54 (48)

ABP = arterial blood pressure; Cerebral T = cerebral temperature; CMD = cerebral microdialysis; dEEG = depth electroencephalography; ECoG = electrocorticography; ICP = intracranial pressure; NIRS = near-infrared spectroscopy; No. = number; $PbtO_2$ = partial pressure of brain tissue oxygenation; rCBF = regional cerebral blood flow; sEEG = surface electroencephalography; $SvjO_2$ = jugular bulb venous oximetry; TCD = transcranial Doppler.

Supplementary Table S4b | Study setting and clinical characteristics of 112 cerebral multimodality monitoring studies

No. of studies (%)	**Total 112 studies**
Multicentre studies	22 (20)
Study inclusion period	
0-1 year	23 (21)
2-3 year	26 (23)
4-5 year	13 (12)
≥ 6 year	34 (30)
Not reported	16 (14)
Sample sizes (median, q1 - q3)	36 (20 - 74)
Clinical characteristics	
Sex, male (%), median (q1-q3)	60 (30 - 75)
Age range	
18 - 29 year	1 (0.9)
30 - 39 year	21 (19)
40 - 49 year	29 (26)
50 - 61 year	48 (43)
60 - 69 year	8 (7.1)
Not reported	5 (4.5)
Multiple pre-defined diseases [a]	18 (16)

The percentages are reported as whole numbers. The percentages may not count to 100% due to rounding. Definitions are listed in Supplementary Table S2.
[a]Multiple diseases: some studies report more than one disease. These studies are represented for each diagnosis. Supplementary Table S5a-d lists the studies.
MMM = multimodality monitoring; No. = number; q1-q3 = interquartile range.

Supplementary Table S4c | Study classification of 112 cerebral multimodality monitoring studies

No. of studies (%)	**Total 112 studies**
Study classification	
Observations	68 (61)
Cerebral intervention	10[a] (8.9)
Systemic intervention	24 (18)
Intervention guided by MMM	11[a] (9.8)
Intervention studies - Clinical outcome endpoint	18 (41)
Safety endpoint	17 (15)

[a]One study was classified as both intervention guided by MMM and cerebral intervention (4). MMM = multimodality monitoring; No. = number

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SUPPLEMENTARY MATERIAL

Details of the individual cerebral multimodality (MMM) studies, including title, disease, main objective, sample size, enrollment period, monitoring modalities, and interventions.

Supplementary Table S5a | Observations - cerebral multimodality monitoring studies

Supplementary Table S5b | Systemic intervention - cerebral multimodality monitoring studies

Supplementary Table S5b | Cerebral intervention - cerebral multimodality monitoring studies

Supplementary Table S5d | Management guided - cerebral multimodality monitoring studies

Overview of individual cerebral multimodality monitoring studie
Supplementary Tables S5a, b, c, and d summarize the individual cerebral multimodality monitoring (MMM) studies (112 studies). The order of the studies is by year of publication and alphabetically by author name. Supplementary Table S5a describes the observational studies (68 studies), Supplementary Table S5b the systemic interventional studies (24 studies), Supplementary Table S5c Cerebral interventional studies* (10 studies), and Supplementary Table S5d Management guided by cerebral multimodality studies* (11 studies).

*One study was classified as both cerebral interventional and management guided by MMM.

Supplementary Table S5a | Observational cerebral multimodality monitoring studies

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Bouzat et al., 2015 (1)	TBI	Detect cerebral hypoperfusion using multimodality monitoring compared to unimodal (ICP) monitoring.	27	May 2010 - Nov 2013	• ICP • $PbtO_2$ • CMD
Esnault et al., 2015 (2)	TBI (*n*=5) SAH (*n*=1) ICA dissection (*n*=1) ICH (*n*=1)	Correlate NIRS (rSO_2) with a third-generation NIRS monitor and an invasive measure of $PbtO_2$.	8	Nov 2011 - Jan 2012	• ICP • $PbtO_2$ • NIRS
Helbok et al., 2015 (3)	aSAH	Relate pathophysiological events involved in the development of early brain injury in poor-grade aneurysmal SAH patients over time and relate these findings to clinical course and outcome.	26	2010 - 2012	• ICP • $PbtO_2$ • TCD[a] • CMD
Tackla et al., 2015 (4)	TBI	Discussing the experience in calculating a new rCBF index (correlation rCBF and CPP).	7	-	• ICP • rCBF
Tholance et al., 2015 (5)	aSAH	Describe the changes in cerebral energy metabolism observed with eight hourly updated retrograde jugular vein catheter, continuous $PbtO_2$, and hourly CMD to compare these two approaches and to evaluate whether they could be complementary to predict the outcome of poor-grade aneurysmal SAH patients.	18	2006 - 2010	• $PbtO_2$ • TCD[a] • $SvjO_2$ (update 8 hours) • CMD

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Budohoski et al., 2016 (6)	aSAH	Analyze the relationship between various methods of testing cerebral autoregulation and their predictive value for clinical outcome (DCI). Including combining CA-measures (TCD and NIRS).	98	Jun 2010 - Jan 2012	• TCD • NIRS
Dias et al., 2016 (7)	TBI	Describe the characteristics of plateau waves with MMM results.	18	-	• ICP • Cerebral T • $PbtO_2$ • rCBF • NIRS
Helbok et al., 2016 (8)	ICH	Describe the incidence of SDs in a cohort of poor-grade ICH patients in whom hematoma evacuation was performed; describe the timing of ECoG SDs relative to the bleeding and perihematomal edema, and compare the ECoG curve characteristics to those patients with other etiologies of acute brain injury.	27	Jan 2013 - Jul 2015	• ICP • ECoG
Hifumi et al., 2016 (9)	HIBI	Associate CMD with blood lactate and glucose levels in relation to neurological outcomes after cardiac arrest, and associate ICP with the CMD-L/P-ratio in relation to clinical outcome.	10	1 Jul 2005 - 30 Apr 2009	• ICP • CMD
Hinzman et al., 2016 (10)	TBI	Examine the association of SD with changes in cerebral neurochemistry by placing a CMD probe alongside a subdural electrode strip (ECoG) in peri-lesional cortex in TBI patients requiring neurosurgery.	16	-	• ICP[a] • CMD • ECoG

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Myers et al., 2016 (11)	TBI	Evaluate an ICP and brain tissue oxygenation prediction model and compare this model with the clinical outcome.	817	1989 - 2000 and 2006 - 2013	• ICP • $PbtO_2$
Papadopoulos et al., 2016 (12)	SAH	Correlate rCBF with CMD parameters in SAH patients; study the relationship with clinical outcome.	21	2009 - 2013	• ICP • Cerebral T • rCBF • CMD
Patet et al., 2016 (13)	aSAH	Evaluate the predictive value of CMD abnormalities for the diagnosis of delayed cerebral hypoperfusion diagnosed with static brain CT-perfusion.	20	-	• ICP • $PbtO_2$ • CMD
Vanga et al., 2016 (14)	TBI (*n* =65) SAH ICH Other (not specified)	Examine whether $PbtO_2$, ICP, and heart rate correlated with the incidence and type of acute arrhythmias in patients with acute brain injury.	106	-	• ICP • Cerebral T[a] • $PbtO_2$
Vespa et al., 2016 (15)	TBI	Determine the incidence of electrographic seizures and interictal epileptiform activity on sEEG and dEEG and associate metabolic changes in CMD during interictal and ictal epileptiform discharges.	34	2009 - 2013	• ICP[a] • $SvjO_2$[a] • CMD • sEEG • dEEG

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Winkler et al., 2016 (16)	aSAH	Associate different MMM modalities with clinical outcome.	33	Sep 2009 - Aug 2013	• ICP • $PbtO_2$ • Cerebral T • TCD[a] • ECoG
Carteron et al., 2017 (17)	aSAH	Study the relationship between CMD, $PbtO_2$, and static CBF using CT-perfusion.	18	Mar 2013 - Apr 2015	• ICP[a] • $PbtO_2$ • CMD
Foreman et al., 2017 (18)	aSAH	Describe the relationship between rCBF and EEG (dEEG or sEEG) in both patients with and without DCI.	20	Jun 2006 - Mar 2012	• ICP • $PbtO_2$ [a] • rCBF • sEEG • dEEG
Nyholm et al., 2017 (19)	TBI	Evaluate the relationship between hyperthermia and ICP and the influence of intracranial compliance and CBF pressure autoregulation; study the relationship between hyperthermia and $PbtO_2$ and CMD.	87	Jan 2008 - Dec 2010	• ICP • $PbtO_2$ • Cerebral T[a] • CMD
Pinczolits et al., 2017 (20)	AIS	Investigate whether SDs in patients with AIS are associated with altered CMD of glutamate, lactate, pyruvate, or L/P-ratio.	18	May 2009 – Apr 2011	• CMD • EcoG

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Schiefecker et al., 2017 (21)	ICH	Investigate the dynamics of Cerebral T relative to the occurrence of SDs and core temperature in patients with ICH.	20	Jan 2013 – Jan 2016	• ICP [a] • Cerebral T • EcoG
Witsch et al., 2017 (22)	SAH	Relate periodic discharges (using a change-point analysis to characterize electrophysiological changes) on sEEG with other MMM ($PbtO_2$ and rCBF) variables.	90	Jun 2006 – Sep 2014	• ICP [a] • $PbtO_2$ • rCBF • sEEG • dEEG
Chen et al., 2018 (23)	ICH	Comprehensively evaluate brain function by administering TCD combined with qEEG in patients with severe acute supratentorial-ICH; assess outcome at the 90-day follow-up; explore a new basis for pathophysiological changes in severe ICH.	47	Jun 2015 – Dec 2016	• TCD • sEEG
Dellazizzo et al., 2018 (24)	TBI	Describe the association between PaO_2 and $PbtO_2$ to determine the minimal PaO_2 required to maintain $PbtO_2$; investigate the relationship with clinical outcome.	38	2013 - 2016	• ICP • $PbtO_2$

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Dreier et al., 2018 (25)	TBI (*n*=5) aSAH (*n*=3) AIS (*n*=1)	Analyze pathological events in patients during abrupt hypoxia-ischemia after withdrawal from life-sustaining treatments.	9	-	• ICP (*n*=9) • $PbtO_2$ (*n*=6) • rCBF (LDF) (*n*=2) • Cerebral T (*n*= 4) • ECoG (*n*=4) • dEEG (*n*=5) • sEEG (*n*=1)
Foreman et al., 2018 (26)	TBI	Describe the safety and the reliability of a single burr hole access for invasive MMM monitoring application.	43	Mar 2015 - Mar 2017	• ICP • $PbtO_2$ • Cerebral T • rCBF • dEEG
Lückl et al., 2018 (27)	aSAH	Characterize negative ultraslow potential (NUP). First party of the study is an animal study. Second part was a clinical study using simultaneous DC/AC-ECoG, $PbtO_2$, rCBF, ICP, and ABP recordings; serial neuroimaging scans were used to determine whether electrodes displaying the NUP are more likely to overlie a newly developing ischaemic lesion than electrodes not displaying the NUP.	11	-	• ICP (*n*=1) • $PbtO_2$ (*n*=8) • Cerebral T[a] • rCBF [a] (LDF) (*n*=4) • ECoG (*n*=1)

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Morris et al., 2018 (28)	aSAH + HIBI (*n*=31) aSAH (*n*=146)	Describe the differences in MMM results between SAH with and without additional cerebral hypoxia at presentation. Three hypotheses were tested: (1) clinical phenotypes between the groups differ and may suggest the cause of arrest, (2) brain physiology measures would demonstrate cerebrovascular decompensation in the HIBI patients despite identical CPP and management targets, (3) outcomes of aggressively treated HIBI patients should not significantly differ from those of non-HIBI patients.	177	Jul 1996 - Jun 2016	• ICP • $PbtO_2$ • rCBF • CMD • sEEG
Alkhachroum et al., 2019 (29)	SAH	Evaluate the relationship between CPP, CPPopt, deltaCPP (calculated as CPP-CPPopt), and PRx during seizures and ictal-interictal continuum.	73	Jun 2006 - Jun 2013	• ICP • $PbtO_2$ • dEEG
Bailey et al., 2019 (30)	• TBI (*n*=286) • SAH (*n*=133) • ICH (*n*=25) • Penetrating TBI (*n*=20) • Other (*n*=37)[b]	Describe the safety of a triple-lumen bolt placement by reporting the number of placed devices and the post-insertion complications.	501	8 year	• ICP • $PbtO_2$ • Cerebral T

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Calviello et al., 2019 (31)	TBI	Study the feasibility of methods most suitable for describing patient cerebral hemodynamics; build a function to monitor changes in intracranial compliance, compare invasive and non-invasive calculations, and compare data-driven trend charts.	52	1992 – 2012	• ICP • TCD
Davie et al., 2019 (32)	TBI	Determine the incidence and severity of rSO_2 desaturation in patients with TBI and determine the feasibility of monitoring rSO_2 in the ICU; examine the correlation between rSO_2 and ICP and rSO_2 and MAP.	20	Jul 2016 – Sep 2017	• ICP • NIRS
Donnelly et al., 2019 (33)	TBI	Describe cerebral oxygenation and cerebral autoregulation indices PRx, and relate AMP (ICP amplitude) response to severe and sustained intracranial hypertension.	33	1992 – 2017	• ICP • $PbtO_2$
Forsse et al., 2019 (34)	aSAH	Describe the association between CMD and jugular bulb microdialysis (JBMD); correlate CMD abnormalities with clinical outcome.	12	Sep 2017 – Mar 2018	• ICP • $PbtO_2$ • CMD • JBMD [a]

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Launey et al., 2019 (35)	TBI (*n*=68) Healthy control (*n*=27)	Characterize cerebrovascular physiology within brain regions that initially appear structurally normal; describing temporal changes in physiology, changes in flow-metabolism, local microvascular flow-volume association, disentangle ischemia from coupled hypoperfusion and assess the contribution of vascular engorgement to ICP elevation.	68	Feb 1998 - 2014	• ICP • $PbtO_2$ • $SvjO_2$
Rajagopalan et al., 2019 (36)	HIBI (*n*=6) TBI (*n*=3) SAH (*n*=2)	Identify and describe trends in ICP, CPP, PRx, $PbtO_2$, rCBF, Cerebral T, and CMD that occur during progression to and at the time of brain death.	11	Oct 2015 - Jun 2018	• ICP • $PbtO_2$ • Cerebral T • rCBF • CMD
Silverman et al., 2019 (37)	aSAH	Describe the feasibility of invasive (ICP, PRx, CPPopt) and non-invasive (NIRS, TOx, ABPopt) CA measures; correlate invasive and non-invasive results, including the autoregulation limits; relate deviation from CPPopt/ABPopt with radiographic and clinical outcome.	31	-	• ICP • TCD [a] • NIRS
Wettervik et al., 2019 (38)	TBI	Investigate the association between arterial glucose, PRx, and CMD	120	2008 - 2018	• ICP • CMD

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Addis et al., 2020 (39)	aSAH	Describe the relationship between delta T (cerebral T – T systemic) and (preserved) brain metabolic activity; describe the relationship between delta T and clinical outcome.	46	2010 - 2016	• ICP • Cerebral T • rCBF • CMD
Gagnon et al., 2020 (40)	TBI (*n*=20) ICH (*n*=5)	Describe the frequency of hypoxic episodes and their characteristics.	25	Jun 2017 - Aug 2018	• ICP • $PbtO_2$ • Cerebral T
Marini et al., 2020 (41)	TBI	Evaluate the relationship between CPP and estimates of cerebral oxygenation (NIRS, $PbtO_2$) and CMD.	20	-	• ICP • $PbtO_2$ • CMD • NIRS
Rass et al., 2020 (42)	TBI	Quantify changes in $PbtO_2$ during temperature increases in severe TBI to explore simultaneous changes of hemodynamic parameters and the CA state; compare periods of temperature increases identified through visual plot analysis and by algorithm-supported detection.	33	Jan 2015 - Dec 2017	• ICP • $PbtO_2$ •CerebralT (*n*=16)

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Robba et al., 2020 (43)	TBI	Indicating the threshold of cerebral hypoxia and parameters that are determinants of cerebral hypoxia; assess whether any of these indices ($PbtO_2$, PaO_2, $PbtO_2/PaO_2$, ratio of $PbtO_2$ to FiO_2, and PaO_2/FiO_2) based on the relationship between cerebral tissue oxygenation and systemic arterial oxygenation and the fraction of inspired oxygen, can be helpful for prognostication of mortality in TBI patients.	70	Nov 2014 – Oct 2018	• ICP • $PbtO_2$
Sekhon et al., 2020 (44)	HIBI	Characterizes the difference in the diffusion gradient (Pvo_2 – $PbtO_2$) of cellular oxygen delivery and the presence of diffusion limitation physiology (the relationship between the Pvo_2 – $Pbto_2$ gradient and CPP) in hypoxic-ischemic brain injury patients with brain hypoxia ($PbtO_2$ < 20 mm Hg) versus normoxia ($PbtO_2$ > 20 mm Hg).	14	Nov 2016 – Jan 2019	• ICP • $PbtO_2$ • $SvjO_2$
Wettervik et al., 2020 (45)	TBI	Clarify the association on endogenous arterial lactate in relation to intracranial pressure dynamics, pressure CBF autoregulation, cerebral energy metabolism, systemic injuries, and clinical outcome following severe TBI.	115	2008 – 2018	• ICP • CMD

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Zeiler et al., 2020 (46)	TBI	Explore the relationship between insults in ICP, $PbtO_2$, and PRx and investigate preliminary associations with outcome. Insults in the variables were studied by: (1) % of time with ICP > 20 mmHg (2) % of time with $PbtO_2$ < 20 mmHg (3) % of time with ICP PRx > threshold (0.25, 0.35 were used) (4) % of time with normal or abnormal ICP PRx and normal or abnormal $PbtO_2$ (<20 or >20 mmHg).	43	Jan 2015 - Dec 2017	• ICP • $PbtO_2$
Zeiler et al., 2020 (47)	TBI	Study the physiological consequences of high versus normal ICP periods by comparing % of time (and dose) above or below thresholds for ICP, $PbtO_2$, and CA index PRx.	185	Jan. 2015 - Dec 2017	• ICP • $PbtO_2$
Zeiler et al., 2020 (48)	TBI	Explore the relationship between slow-wave fluctuations in ICP, MAP, and $PbtO_2$ over time.	47	Jan 2015 - Dec 2017	• ICP • $PbtO_2$
Balu et al., 2021 (49)	HIBI Other (hypoxic injury without cardiac arrest)	Describe the clinical characteristics of monitored patients; evaluate the feasibility and complication rate of invasive neuromonitoring; assess the association of intracranial neuromonitoring parameters with neurological outcome.	36	Oct 2015 - Jun 2018	• ICP • $PbtO_2$

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Barajraji et al., 2021 (50)	SAH (*n*=56) TBI (*n*=35) ICH (*n*=200) Medical, not specified (*n*=2)	Evaluate a single-center experience of an intracranial multimodal monitoring bolt system regarding surgical placement and related complications, management, technical malfunctions, and adverse events.	113	Jul 2016 - Jan 2020	• ICP • $PbtO_2$ • CMD • dEEG
Birg et al., 2021 (51)	TBI	Describe Cerebral T, ICP, and CPP; clarify the relationship between Cerebral T, ICP, and CPP during Cerebral T changes.	21	Jan 2015 - Dec 2017	• ICP • Cerebral T • $PbtO_2$ [a]
Guilfoyle et al., 2021 (52)	TBI	Quantify the independent effect of L/P-ratio and cerebral glucose on neurological outcome; characterize the temporal course of these parameters following TBI; assess the functional relationship between energy metabolism and other monitoring variables to inform an outline clinical protocol for managing traumatic, metabolic function.	619	1997 - 2016	• ICP • $PbtO_2$ • CMD
Hoiland et al., 2021 (53)	HIBI (*n*=18) Healthy (*n*=14)	Assess brain hypoxia ($PbtO_2$<20) versus no brain hypoxia ($PbtO_2$>20) regarding elevated biomarkers (neuronal, astroglial, endothelial injury) and inflammation; assess if brain hypoxia is related to a diffusion limitation of O_2 and that hyperosmolar therapy reduces brain hypoxia.	18	2016 - 2019	• ICP • $PbtO_2$ • JVP [a]
Kieninger et al., 2021 (54)	aSAH (*n*=22) Carotid artery aneurysm (*n*=4)	Describe complications related to MMM; describe therapeutic measures derived in cases of pathological values in MMM.	26	Jan 2012 - Dec 2017	• ICP • $PbtO_2$ • rCBF • TCD [a] • CMD • NIRS

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Kuo et al., 2021 (55)	TBI	Characterize the cerebral T rhythm and investigate its prognostic value in terms of postoperative mortality and functional outcome in patients with moderate to severe TBI.	108	May 2011 - Dec 2017	• ICP • Cerebral T
Lindner et al., 2021 (56)	ICH	Define ABP targets in poor-grade ICH patients during postoperative care after hematoma evacuation based on the lowest prevalence of brain tissue hypoxia and metabolic distress.	40	2011 - 2018	• ICP • $PbtO_2$ • CMD
Mueller et al., 2021 (57)	SAH	Compare the ability of qEEG and TCD/TCCS to provide early identification of cerebral infarction on imaging.	34	Nov 2011 - Feb 2013 and Nov 2014 - May 2016	• TCD or TCCS • sEEG
Qi et al., 2021 (58)	AIS	Explore the possibility of obtaining more accurate and comprehensive prognostic predictors for patients with large hemispheric infarction by TCD-qEEG.	59	Jul 2018 - Dec 2019	• TCD • sEEG
Rajagopalan et al., 2021 (59)	TBI (*n*=6) aSAH (*n*=14)	Explore a data-driven approach to group invasive MMM measurements to identify distinct physiological states that inform brain injury mechanisms and outcome prediction.	20	Mar 2005 - Sep 2009	• ICP • $PbtO_2$ • CMD

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Schumm et al., 2021 (60)	AIS	Investigate the effect of physiological variables (body temperature, MAP, CPP, and ICP) on the incidence and features of SD in the postoperative monitoring period following hemicraniectomy.	60	Aug 2008 - Mar 2017	• ICP • ECoG
Wettervik et al., 2021 (61)	TBI	Investigate the impact of CPP insults (according to CPPopt thresholds and Brain Trauma Foundation thresholds) on CMD results and clinical outcome.	98	2008 – 2018	• ICP • CMD
Wettervik et al., 2021 (62)	TBI	Elucidate the role of arterial oxygenation, the incidence of hypoxia, hyperoxia, and the relation to cerebral metabolism, cerebrovascular reactivity, and clinical outcome.	115	2008 – 2018	• ICP • CMD
Wettervik et al., 2021 (63)	TBI	Determine the incidence and temporal course of hyperthermia after TBI and its relation to ICP dynamics and cerebral energy metabolism; determine whether hyperthermia was associated with clinical outcomes following TBI.	115	2008 - 2018	• ICP • CMD

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Dreier et al., 2022 (64)	aSAH	Investigate whether the peak total SD-induced depression duration of a recording day during delayed neuromonitoring (delayed SD duration) indicates delayed ipsilateral infarction. Secondary outcome measures: occurrence of delayed neurological deficit in clinically assessable, non-sedated patients; manually segmented volumes of ipsilateral damage due to ICH, ECI, and DCI alone or in combination; MRI segmentation analysis; clinical outcome analysis; multivariate analysis including neuromonitoring data and digital subtraction angiography.	180	Sep 2009 - Apr 2018	• ICP (*n*=150) • $PbtO_2$ (*n*=71) [a] • rCBF (LDF) (*n*=22) [a] • TCD (*n*=157) • ECoG
Owen et al., 2022 (65)	aSAH	Elucidate the relationship between various CA measures and assess how they relate to both clinical outcomes and SD incidence.	19	-	• ICP • $PbtO_2$ • rCBF • NIRS • ECoG
Wettervik et al., 2022 (66)	aSAH	Investigate the association among the arterial metabolic content variables PaO_2, $PaCO_2$, glucose, and lactate with the PRx and energy metabolism; study the relationship between delayed ischemic neurological deficits (DIND) and clinical outcome.	60	Nov 2016 - May 2021	• ICP • CMD

Supplementary Table S5a | Observational cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Modalities
Wettervik et al., 2022 (67)	aSAH	Determine the association between ICP- and CPP threshold insults and cerebral energy metabolism; determine the association of these insults with clinical outcome.	75	2008 - 2018	• ICP • CMD
Yang et al., 2022 (68)	TBI (*n* =102) Healthy (*n*=55)	Evaluate the effect of the apolipoprotein E (*APOE*) *ε4* allele on rSO_2 and qEEG at the early stage of TBI and explore the relationship between APOE and cerebral oxygen saturation and brain electrical activity.	102	Sep 2018 - Sep 2020	• sEEG • NIRS

[a]Other modalities. Modalities described in the study but not part of the study aim or objective(s). These modalities were either used for clinical management or not part of our included modalities, but continuous or daily updated monitoring.
[b]Other diseases included: cerebral arteriovenous malformation, intracranial infections, hepatic encephalopathy, and cerebral edema from ornithine transcarbamylase deficiency.
ABP = arterial blood pressure; ABPopt = optimal arterial blood pressure; AIS = acute ischemic stroke; CA = cerebral autoregulation; Cerebral T = cerebral temperature; CMD = cerebral microdialysis; CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; CT = computer tomography; DC/AC = Direct current /alternate current (AC)-electrocorticography; DCI = diffuse cerebral ischemia; dEEG = depth electroencephalography; DIND = delayed ischemic neurological deficits; ECI = early cerebral ischaemia;
ECoG = electrocorticography; FiO_2 = fraction of inspired oxygen; HIBI: hypoxic ischemic brain injury following cardiac arrest; ICA = internal carotid artery; ICH = intracerebral hemorrhage; ICP = intracranial pressure; ICU = intensive care unit; JBMD = jugular bulb microdialysis; JVP = jugular venous pressure; L/P-ratio = lactate/pyruvate ratio; LDF = Laser Doppler flowmetry; MAP = mean arterial blood pressure; MRI = magnetic Resonance Imaging; NIRS = near-infrared spectroscopy; No. = number; PaO_2 = partial arterial oxygenation pressure; PaO_2 = partial pressure of oxygen; $PbtO_2$ = partial pressure of brain tissue oxygenation; PRx = pressure reactivity index; rCBF = regional cerebral blood flow; (a) SAH = (aneurysmal)subarachnoid hemorrhage; SD = spreading depolarisation; sEEG = surface electroencephalography; $SvjO_2$ = jugular bulb venous oximetry; TBI = traumatic brain injury; TCCS = transcranial colour doppler sonography; TCD = transcranial Doppler; TOx = tissue oxygenation index.

Supplementary Table S5b | Systemic interventions - cerebral multimodality monitoring studies

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Intervention	Modalities
Flynn et al. 2015 (69)	TBI	Examine the effect of induction of therapeutic hypothermia on ICP and $PbtO_2$.	17	-	Hypothermia	• ICP • $PbtO_2$ • Cerebral T[a]
Kurtz et al. 2015 (70)	aSAH	Investigate the effect of packed red blood cell (RBC) transfusion on cerebral oxygenation and metabolism.	15	Jan 2008 - Jun 2009	RBC transfusion	• ICP [a] • $PbtO_2$ • CMD
Sekhon et al. 2015 (71)	TBI	Study the effect of packed RBC-transfusion on the CA index PRx. Primary outcome was the change in CA, as measured by PRx, after RBC transfusion. Secondary outcomes: the change in hemoglobin concentration and $PbtO_2$ after RBC transfusion.	28	Jan 2007 - 30 Jun 2014	RBC transfusion	• ICP • $PbtO_2$
Ghosh et al. 2016 (72)	TBI (*n*=7) SAH (*n*=8) ICH (*n*=1)	Investigate the oxygen dependence (NIRS, $PbtO_2$, TCD) of mitochondrial metabolism (CMD L/P-ratio) in vivo following acute brain injury.	16	-	Hyperoxia	• $PbtO_2$ • TCD • CMD • NIRS

Supplementary Table S5b | Systemic interventions - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Intervention	Modalities
McCredie et al. 2016 (73)	TBI	Study the effect of packed RBC transfusion on NIRS rSO_2; correlate rSO_2 changes to other systemic- and cerebral variables; study the dependence of rSO_2 on baseline hemoglobin level; study the effect on fractional tissue oxygen extraction.	19	Nov 2012 - Mar 2014	RBC transfusion	• ICP • NIRS
Sahoo et al. 2016 (74)	TBI	Evaluate the effect of normobaric hyperoxia on CBF velocity (TCD) and NIRS in operated TBI patients. In addition, study the effect on CA status.	50	-	Hyperoxia	• TCD • NIRS
Westermaier et al. 2016 (75)	SAH	Investigate changes in rCBF during hypercapnia, and compare rCBF with TCD mean CBFV and NIRS rSO_2 results.	12	Jan 2013 - Feb 2014	Hypercapnia	• ICP • Cerebral T [a] • rCBF • NIRS • TCD
Zhang et al. 2016 (76)	TBI	Correlate cerebral autoregulation indices (TCD-based) ARI and Mx with carbon dioxide reactivity during transient mild hypocapnia (hyperventilation period of 60 min).	31	-	Hypocapnia	• ICP • TCD
Kofler et al. 2017 (77)	SAH	Investigate the effect of enteral nutrition on CMD and ICP.	17	2010 - 2012	Enteral nutrition	• ICP • Cerebral T[a] • CMD

Supplementary Table S5b | Systemic interventions - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Intervention	Modalities
Carteron et al. 2018 (78)	TBI (*n*=13) aSAH (*n*=10)	Analyze changes - compared with baseline TCD-derived indexes of cerebral perfusion and brain extracellular concentrations of energy metabolites (CMD lactate and glucose) during a 3-hour intravenous infusion of hypertonic lactate, administered as a resuscitation fluid during the early post-injury phase + clinical outcome.	23	Mar 2012 - Dec 2017	Hypertonic lactate	• ICP[a] • TCD • CMD
Jakkula et al. 2018 (79)	HIBI	Compare results between patients treated with low (65-75 mmHg) or high (80-100 mmHg) MAP values: evaluate serum biomarkers (like NSE) at 48 hr after cardiac arrest to study the regional differences in frontal NIRS-based rSO2% and compare sEEG findings.	120	22 Mar 2016 - 3 Nov 2017	ABP-management	• NIRS • sEEG
Brandi et al. 2019 (80)	TBI	Study the (adverse) effects of moderate short-term hyperventilation during the acute phase on cerebral hemodynamics (ICP/CPP), oxygenation ($PbtO_2$), and metabolism (CMD).	11	May 2014 - May 2017	Hyperventilation	• ICP • $PbtO_2$ • TCD (TCCD) • CMD
Sekhon et al. 2019 (81)	HIBI	Describe the relationship between $PbtO_2$ and MAP over time using a tier-based clinical protocol to manage increased ICP in combination with low $PbtO_2$. Other endpoints included the observed PRx, $SvjO_2$, and rSO_2 values over time.	10	Nov 2016 - Jan 2018	ABP-management	• ICP • $PbtO_2$ • $SvjO_2$ • NIRS

Supplementary Table S5b | Systemic interventions - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Intervention	Modalities
Wettervik et al. 2020 (82)	TBI	Evaluate the safety and treatment effect of mild hyperventilation (4.0 - 4.5 kPa/30-34 mm Hg) in TBI; evaluate mild hyperventilation and its effect on ICP and CMD, pressure autoregulation, and clinical outcome.	120	2008 - 2018	Hyperventilation	• ICP • CMD
Burnol et al. 2021 (83)	TBI (*n*=16) SAH (*n*=3) AIS (*n*=3) Other, not specified (*n*=1)	Study the effect of a 30° upright posture versus 15° versus 0° on brain oxygenation and circulation; sub-analysis of patients who underwent a decompressive craniectomy to investigate whether changes in brain compliance could affect these potential effects.	23	Feb 2012 - Sep 2015	Head-bed posture	• ICP • $PbtO_2$ • TCD
Dagod et al. 2021 (84)	TBI	Assess the impact of the temporary changeover from the half-seated position to the lying position on CPP and oxygenation parameters during the first week of management of patients admitted for severe TBI.	24	Sep 2014 - Oct 2016	Head-bed posture	• ICP • TCD • $SvJO_2$ • NIRS
Hosmann et al. 2021 (85)	aSAH	Study the impact of intrahospital transport to the CT-scanner on MMM in patients suffering SAH, with a particular focus on cerebral metabolism.	20	-	Intrahospital transport	• ICP • $PbtO_2$ • Cerebral T • TCD • CMD

Supplementary Table S5b | Systemic interventions - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Intervention	Modalities
Kovacs et al. 2021 (86)	TBI (*n*=20) SAH (*n*=29) ICH (*n*=4)	Evaluate which level of CPP corresponds to an adequate $PbtO_2$ in a heterogeneous population of brain-injured patients; assess whether this level of CPP changes over time and characterize patients requiring higher than recommended CPP targets to have optimal brain oxygenation values.	53	Jan 2016 - Dec 2020	ABP- management	• ICP • $PbtO_2$ • TCD • NeurOptics [a] (neurological pupil index)
Rass et al. 2021 (87)	SAH	Investigate the effect of fluid management and cardiac function on $PbtO_2$ by integrating advanced hemodynamic and invasive neuromonitoring tools.	60	2010 - 2019	Fluid management	• ICP • $PbtO_2$
Stetter et al. 2021 (88)	aSAH	Investigate the course of rCBF (primary) and rSO_2 (secondary) during longer-term hypercapnia and determine the time point at which physiologic adaptation mechanisms start to mitigate the CBF-increasing effect in order to locate the optimum duration of controlled hypercapnia in poor-grade SAH patients.	12	Jan 2015 - Jun 2017	Hypercapnia	• ICP • rCBF • TCD • NIRS
Bernini et al. 2022 (89)	TBI (*n*=13) SAH (*n*=4)	Study patients who received sequential osmotherapy with hypertonic saline (HS) followed by hypertonic lactate (HL) and compare HL with HS by studying the effect on ICP, $PbtO_2$ and CMD, ABP, pH, and chloride.	17	Nov 2016 - Dec 2019	Hypertonic saline and hypertonic lactate	• ICP • $PbtO_2$ • CMD
Bogossian et al. 2022 (90)	TBI (*n*=21) SAH (*n*=42) ICH (*n*=6)	Identify factors associated with $PbtO_2$ changes after RBC transfusion in a heterogeneous population of brain-injured patients.	69	2012 - 2020	RBC transfusion	• ICP • $PbtO_2$

Supplementary Table S5b | Systemic interventions - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (*N*)	Enrollment period	Intervention	Modalities
Gargadennec et al. 2022 (91)	TBI (*n*= 17) SAH (*n* = 29) ICH (*n*= 7)	Compare the accuracy of ICP, $PbtO_2$ or oxygen ratio (OxR) and their combinations to detect cerebral hypoperfusion in brain-injured patients; the accuracy to detect cerebral hypoperfusion of all these variables according to the underlying brain disease.	53	Jan 2016 - Aug 2019	Hyperoxia	• ICP • $PbtO_2$ • CMD • dEEG
Hosmann et al. 2022 (92)	SAH	Evaluate whether a quick and easy-to-perform hyperoxic challenge of 3-minutes can identify patients at risk for cerebral ischemia detected by CMD.	20	Feb 2016 - Jan 2019	Hyperoxia	• ICP • $PbtO_2$ • TCD • CMD

[a] Other modalities. Modalities described in the study but not part of the study aim/objective(s). These modalities were either used for clinical management or not part of our included modalities, but continuous or daily updated monitoring.
ABP = arterial blood pressure; ABPopt = optimal arterial blood pressure; AIS = acute ischemic stroke; ARI = autoregulation index; CA = cerebral autoregulation; CBFV = cerebral blood flow velocity; Cerebral T = cerebral temperature; CMD = cerebral microdialysis; CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; CSF = cerebral spinal fluid; CT = computer tomography; DCI = diffuse cerebral ischemia; dEEG = depth electroencephalography; ECoG = electrocorticography; FiO_2 = fraction of inspired oxygen; HL = hypertonic lactate; HS = hypertonic saline; HIBI: hypoxic ischemic brain injury following cardiac arrest; ICH = intracerebral hemorrhage; ICP = intracranial pressure; L/P-ratio = lactate/pyruvate ratio; MAP = mean arterial blood pressure; Mx = correlation between CPP and cerebral blood flow velocity; NIRS = near-infrared spectroscopy; No. = number; OxR = oxygen ratio; PaO_2 = partial arterial oxygenation pressure; PaO_2 = partial pressure of oxygen; $PbtO_2$ = partial pressure of brain tissue oxygenation; PRx = pressure reactivity index; RBC = red blood cell; rCBF = regional cerebral blood flow; (a)SAH = (aneurysmal) subarachnoid hemorrhage; SD = spreading depolarization; sEEG = surface electroencephalography; $SvjO_2$ = jugular bulb venous oximetry; TBI = traumatic brain injury; TCD = transcranial Doppler.

Supplementary Table S5c | Cerebral intervention - cerebral multimodality monitoring studies

Ref.	Dx.	Aim or objective(s)	No. of patients (N)	Enrollment period	Intervention	Modalities
Hockel et al., 2015 (93)	aSAH	Evaluate the feasibility and safety of long-term continuous intra-arterial nimodipine (CIAN) therapy; test the effects on macrovascular vasospasm, $PbtO_2$, and cerebrovascular autoregulation indices, including PRx and ORx; evaluate 3-months clinical outcome.	13	10 months	Nimodipine	• ICP • $PbtO_2$ • Cerebral T[a] • TCD
Akbik et al., 2017 (94)	TBI	Study the effect of CSF drainage on $PbtO_2$ and parenchymal ICP.	40	2014 - 2016	CSF drainage	• ICP • $PbtO_2$
Albanna et al., 2017 (95)	aSAH	Investigate the effect of endovascular rescue therapy (angioplasty /intraarterial lysis) for refractory vasospasm by $PbtO_2$ and CMD results.	13	Dec 2014 - 2015	Endovascular rescue therapies	• $PbtO_2$ • CMD • TCD [a]
Hockel et al., 2017 (96)	aSAH	Determine the effect of different modes of nimodipine application on vasoreactivity as assessed by PRx, with particular focus on the temporal profile after intra-arterial bolus application and continuous infusion and concomitant changes in cerebral oxygen pressure as a surrogate marker of CBF.	105	2009 - Jul 2015	Nimodipine	• ICP • $PbtO_2$ • Cerebral T [a] • TCD

Supplementary Table S5c | Cerebral intervention - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (N)	Enrollment period	Intervention	Modalities
Lubillo et al., 2018 (97)	TBI	Investigate changes in $PbtO_2$ both before- and after decompressive craniectomy; and determine whether these changes could be used as an independent prognostic factor in patients with severe TBI and refractory ICH without an indication for intracranial mass lesion evacuation.	42	2002 - 2014	Decompressive craniectomy	• ICP • $PbtO_2$
Ding et al., 2019 (98)	aSAH	Study the relationship between neuroglobin on CMD and $PbtO_2$ and clinical outcome at 12 months.	36	Jan 2017 - 2018	Neuroglobin	• ICP [a] • $PbtO_2$ • TCD [a] • CMD
Hosmann et al., 2019 (99)	aSAH	Investigate whether papaverine-hydrochloride mediated resolution of angiographic vasospasm translates into improved measures of CMD and oxygenations.	10	-	Papaverine-Hydrochloride	• ICP [a] • $PbtO_2$ • TCD • CMD
Ianosi et al., 2019 (100)	aSAH	Describe the effects of intravenous paracetamol, metamizole, and diclofenac during febrile and nonfebrile episodes on brain and systemic temperature and hemodynamics.	77	Apr 2010 - Jul 2017	Analgesia	• ICP • $PbtO_2$ • Cerebral T
Koskinen et al., 2019 (101)	TBI	Study the effect of prostacyclin or placebo treatment on the cerebrovascular pressure reactivity and CMD glycerol marker; study the relationship between glycerol and the cerebrovascular pressure reactivity.	45	Jan 2002 - Dec 2005	Prostacyclin	• ICP • CMD-glycerol

Supplementary Table S5c | Cerebral intervention - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (N)	Enrollment period	Intervention	Modalities
Khellaf et al., 2021 (102)	TBI	Assess the feasibility and utility of a systematic protocol to identify, characterize and treat derangements of cerebral microdialysis-derived L/P-ratio >25 within MMM; target a novel focally administered intervention, succinate in patients identified as having mitochondrial derangement based on MMM parameters.	33	Sep 2017 - Jun 2019	Succinate	• ICP • $PbtO_2$ • CMD

[a] Other modalities. Modalities described in the study but not part of the study aim/objective(s). These modalities were either used for clinical management or not part of our included modalities, but continuous or daily updated monitor.
ABP = arterial blood pressure; ABPopt = optimal arterial blood pressure; AIS = acute ischemic stroke; CA = cerebral autoregulation; CBFV = cerebral blood flow velocity; Cerebral T = cerebral temperature; CIAN = Continuous intra-arterial nimodipine; CMD = cerebral microdialysis; CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; CSF = cerebral spinal fluid; CT = computer tomography; DCI = diffuse cerebral ischemia; dEEG = depth electroencephalography; ECoG = electrocorticography; FiO_2 = fraction of inspired oxygen; HIBI: hypoxic ischemic brain injury following cardiac arrest; ICH = intracerebral hemorrhage; ICP = intracranial pressure; L/P-ratio = lactate/pyruvate ratio; MAP = mean arterial blood pressure; NIRS = near-infrared spectroscopy; NSE = Neuron-Specific Enolase; No. = number; OxR = oxygen ratio; PaO_2 = partial arterial oxygenation pressure; PaO_2 = partial pressure of oxygen; $PbtO_2$ = partial pressure of brain tissue oxygenation; PRx = pressure reactivity index; RBC = red blood cell; rCBF = regional cerebral blood flow; (a) SAH = (aneurysmal) subarachnoid hemorrhage; SD = spreading depolarization; sEEG = surface electroencephalography; $SvjO_2$ = jugular bulb venous oximetry; TBI = traumatic brain injury; TCD = transcranial Doppler.

Supplementary Table S5d | Management-guided - cerebral multimodality monitoring studies

Ref.	Dx.	Aim or objective(s)	No. of patients (N)	Enrollment period	Modalities
Bele et al., 2015 (103)	aSAH	Feasibility, patient selection, and overall outcome by applying a treatment protocol for CIAN in patients with refractory cerebral vasospasm.	41	Jan 2008 - Aug 2014	• ICP • $PbtO_2$ • rCBF • TCD
Min Lin et al., 2015 (104)	TBI	Study the effect of $PbtO_2$-guided therapy compared to ICP-guided therapy on the management of cerebral variables, therapeutic interventions, survival rates, and neurological outcome.	50	Jan 2009 - Dec 2010	• ICP • $PbtO_2$
Okonkwo et al., 2017 (105)	TBI	Study the efficacy and safety of an ICP + $PbtO_2$ treatment protocol. Differences in outcome between ICP+$PbtO_2$ protocol compared to the ICP-only treatment protocol.	119	Oct 2009 - Mar 2014	• ICP • $PbtO_2$
Rass et al., 2019 (106)	SAH	Describe the incidence of brain tissue hypoxia burden (% of the time with $PbtO_2$ < 20 mmHg) when a strict $PbtO_2$-guided protocol is applied and describe which factors are related to brain tissue hypoxia.	100	2010 - 2017	• ICP • $PbtO_2$ • CMD [a]

Supplementary Table S5d | Management-guided - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (N)	Enrollment period	Modalities
Sekhon et al., 2017 (107)	TBI	Examine the impact of implementing a dedicated NICU program, consisting of a collaborative model of care amongst the consulting neurosurgeon and neurointensivist with a primary care attending intensivist in a general mixed medical-surgical ICU on the long-term outcome; assessing the effect of NICU on the process of care metrics, i.e., neurophysiological and temperature management.	113	Feb 2010 - May 2016	• ICP • $PbtO_2$ • $SvjO_2$ [a]
Veldeman et al., 2020 (108)	aSAH	Assess the impact of invasive neuromonitoring on the clinical course and clinical outcome of good-grade SAH patients who experience secondary deterioration.	54	2010 - 2018	• ICP • $PbtO_2$ • TCD • CMD
Veldeman et al., 2020 (109)	aSAH	Assess the impact of invasive neuromonitoring on the detection rate of DCI and its influence on patient outcome.	190	2010 - 2018	• ICP • $PbtO_2$ • TCD • CMD
Bogossian et al., 2021 (110)	SAH	Assessed the impact of ICP/$PbtO_2$-guided therapy on neurological outcome in SAH patients; a subgroup analysis including only patients receiving therapies driven by neuromonitoring (ICP-guided vs. ICP/$PbtO_2$ -guided); the impact of ICP/ $PbtO_2$-guided therapy on hospital mortality; subgroup analysis of aneurysmal SAH patients.	163	Jun 2014 - Mar 2020	• ICP • $PbtO_2$

Supplementary Table S5d | Management-guided - cerebral multimodality monitoring studies (continued)

Ref.	Dx.	Aim or objective(s)	No. of patients (N)	Enrollment period	Modalities
Fergusson et al., 2021 (111)	HIBI	Evaluating whether goal-directed therapy using invasive neuromonitoring is associated with improved neurological outcome in hypoxic ischemic brain injury patients after cardiac arrest.	65	Jul 2016 - Nov 2019	• ICP • Cerebral T • $PbtO_2$ • $SvjO_2$ • sEEG [a]
Khellaf et al., 2021 (102)	TBI	Assess the feasibility and utility of a systematic protocol to identify, characterize and treat derangements of CMD-derived L/P-ratio>25 within MMM; target a novel focally administered intervention, succinate in patients identified as having mitochondrial derangement based on MMM parameters.	33	Sep 2017 - Jun 2019	• ICP • $PbtO_2$ • CMD
Winberg et al., 2022 (112)	aSAH	Evaluate the use and clinical efficacy of CMD-based interventions in the NICU of patients with SAH and to assess the prevalence of DCI-related infarction.	49	Jan 2018 - Dec 2020	• ICP • CMD • TCD

[a] Other modalities. Modalities described in the study but not part of the study aim/objective(s). These modalities were either used for clinical management or not part of our included modalities, but continuous or daily updated monitor.
ABP = arterial blood pressure; AIS = acute ischemic stroke; CA = cerebral autoregulation; Cerebral T = cerebral temperature; CIAN = Continuous intra-arterial nimodipine; CMD = cerebral microdialysis; CPP = cerebral perfusion pressure; CT = computer tomography; DCI = diffuse cerebral ischemia; dEEG = depth electroencephalography; ECoG = electrocorticography; FiO_2 = fraction of inspired oxygen; HIBI: hypoxic ischemic brain injury following cardiac arrest; ICH = intracerebral hemorrhage; ICP = intracranial pressure; ICU = intensive care unit; L/P-ratio = lactate/pyruvate ratio; MRI = magnetic Resonance Imaging; NICU = neuroscience intensive care unit; NIRS = near-infrared spectroscopy; No. = number; PaO_2 = partial arterial oxygenation pressure; PaO_2 = partial pressure of oxygen; $PbtO_2$ = partial pressure of brain tissue oxygenation; PRx = pressure reactivity index; rCBF = regional cerebral blood flow; (a)SAH = (aneurysmal) subarachnoid hemorrhage; sEEG = surface electroencephalography; $SvjO_2$ = jugular bulb venous oximetry; TBI = traumatic brain injury; TCD = transcranial Doppler.

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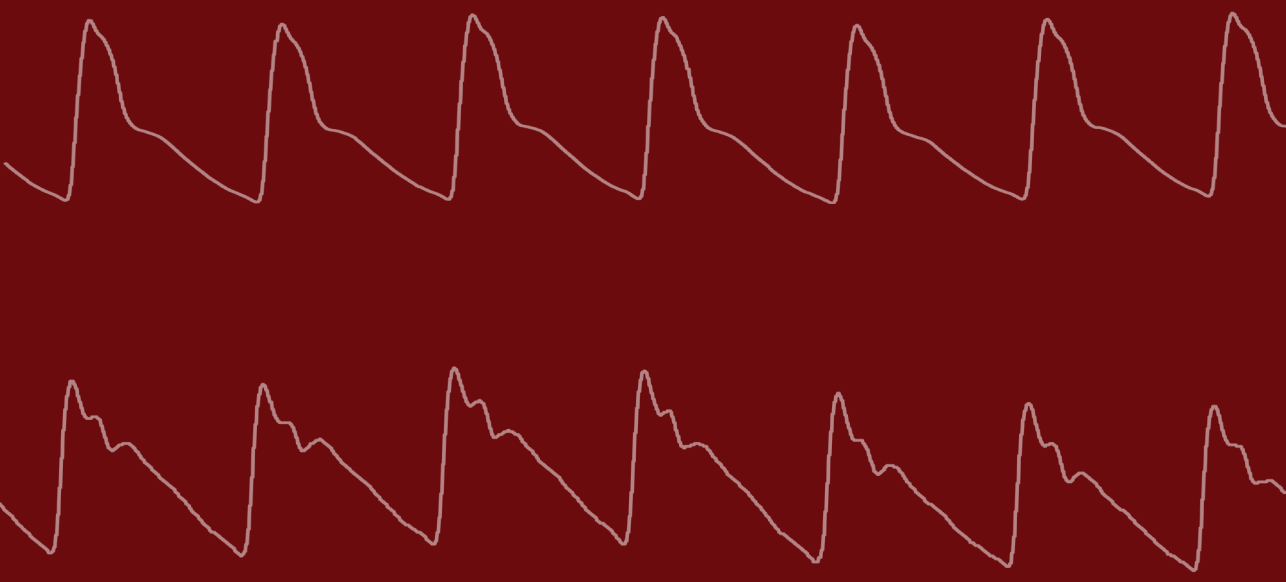
PART II
INVASIVE NEUROMONITORING



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3.1

Feasibility of Individualised Severe Traumatic Brain Injury Management Using an Automated Assessment of Optimal Cerebral Perfusion Pressure: the COGiTATE Phase II Study Protocol

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ABSTRACT

Introduction

Individualising therapy is an important challenge for intensive care of patients with severe traumatic brain injury (TBI). Targeting a cerebral perfusion pressure (CPP) tailored to optimise cerebrovascular autoregulation has been suggested as an attractive strategy on the basis of a large body of retrospective observational data. The objective of this study is to prospectively assess the feasibility and safety of such a strategy compared with fixed thresholds which is the current standard of care from international consensus guidelines.

Methods and analysis

CPPOpt Guided Therapy: Assessment of Target Effectiveness (COGiTATE) is a prospective, multicentre, non-blinded randomised, controlled trial coordinated from Maastricht University Medical Center, Maastricht (The Netherlands). The other original participating centres are Cambridge University NHS Foundation Trust, Cambridge (UK), and University Hospitals Leuven, Leuven (Belgium). Adult severe TBI patients requiring intracranial pressure monitoring are randomised within the first 24 hours of admission in neurocritical care unit. For the control arm, the CPP target is the Brain Trauma Foundation guidelines target (60–70 mm Hg); for the intervention group an automated CPP target is provided as the CPP at which the patient's cerebrovascular reactivity is best preserved (CPPopt). For a maximum of 5 days, attending clinicians review the CPP target 4-hourly. The main hypothesis of COGiTATE are: (1) in the intervention group the percentage of the monitored time with measured CPP within a range of 5 mm Hg above or below CPPopt will reach 36%; (2) the difference in between groups in daily therapy intensity level score will be lower or equal to 3.

Ethics and dissemination

Ethical approval has been obtained for each participating centre. The results will be presented at international scientific conferences and in peer-reviewed journals.

Trial registration number NCT02982122

INTRODUCTION

The main aim of the intensive care management of severe traumatic brain injury (TBI) patients is to prevent secondary injury. Central to this is the control of intracranial pressure (ICP) and maintaining an adequate cerebral perfusion pressure (CPP).[1] Various international guidelines have recommended a variety of CPP targets over the years with the current iteration of Brain Trauma Foundation (BTF) 2016 guidelines recommending a CPP tightly controlled between 60 and 70 mm Hg.[2]

However, it is unlikely that such a fixed therapeutic CPP target will be optimal for all individual TBI patients. Indeed, a failure to individualise therapies has been suggested as a reason for the difficulty to translate plausible therapies into outcome benefit.[1] With the demographics of TBI changing to an older patient group with more comorbidity, the patient group is likely to become more heterogeneous.[3] Furthermore, TBI pathobiology evolves[4] and so, even within the same individual, optimal targets may vary over time. Potentially, individualising therapies and tailoring medical treatment to dynamic pathophysiology could offer a precision medicine approach with advantages over the current 'one size fits all' strategy.

In health, cerebral autoregulation (CA) maintains a constant and adequate cerebral blood flow, thereby protecting the brain from both ischaemia and hyperperfusion in the face of inevitable changes in CPP. CA can frequently be impaired after TBI and this is related to poor outcome.[5–7] Czosnyka *et al* [5] first demonstrated that the moving correlation coefficient (pressure reactivity index, PRx) between slow changes in arterial blood pressure (ABP) and ICP offers a surrogate method for the continuous bedside estimation of global CA.[8]

This concept has gained interest in the last decade with the observation that PRx and CPP often exhibit a U-shaped relationship over time with a minimum PRx occurring at a CPP for which cerebrovascular pressure reactivity is best preserved (or least impaired).[9] Such observations suggest that targeting a CPP such that global CA is best maintained ('optimal' CPP—CPPopt) is a potentially attractive strategy for individualising care.

In recent years, there has been a great deal of work in trying to translate the concept CPPopt into an automated clinical application at the bedside.[9–12] Such technological improvements have been accompanied by a growing body of retrospective evidence (mostly single centre) of a robust association between poor outcome and deviation from calculated CPPopt in severe TBI patients.[9, 10] Prospective evaluation has, however, been lacking to date. Two prospective

pilot studies evaluating autoregulation/CPPopt tailored therapy in different settings demonstrated an improvement in patient outcome.[13,14] However, neither was a randomised study with a published intervention protocol. Prospective evaluation is therefore urgently needed.

A phase II study is needed to resolve a number of outstanding issues before a properly powered and designed phase III trial can be conducted. In particular, it is not known whether it is feasible to track a dynamically changing physiological target in practice. Furthermore, retrospective studies have demonstrated that CPPopt tends to be higher than the 60–70 mm Hg fixed target from international guidelines.[10,12] The physiological effects of this are difficult to assess from retrospective data. Targeting higher CPP values may require a higher therapeutic intensity (eg, greater use of vasopressors and fluids) and lead to extracranial complications (eg, pulmonary, myocardial or renal injury). In addition, the very intervention of targeting CPPopt may itself affect the ICP behaviour, in terms both of mean values and presence of transient hypertensive episodes, and in general on brain compensatory reserve and compliance.

In summary, a prospective evaluation of the feasibility, safety and the physiological implications of CPPopt-guided management is now timely to inform the design of any future phase III study in severe TBI patients with ICP monitoring. In this paper we describe the protocol for such a phase II study: 'CPPOpt Guided Therapy: Assessment of Target Effectiveness (COGiTATE)'.

METHODS AND ANALYSIS

Design

COGiTATE is a prospective, multicentre, non-blinded, randomised, controlled trial in patients with severe TBI. Three tertiary centres are involved at the start of the study: Maastricht University Medical Center, Maastricht (The Netherlands), Cambridge University Hospitals NHS Foundation Trust, Cambridge (UK), and University Hospitals Leuven, Leuven (Belgium).

The patients are recruited in the first 24 hours of admission in the intensive care unit (ICU) and randomised into two treatment arms: the control group (CPP target given by the BTF guidelines—60–70 mm Hg) and the intervention group (CPP target given by the autoregulation status—CPPopt). The duration of the study is 5 days. Other interventions (such as measures to control ICP) are unaltered from local protocols.

The first patient was enrolled on 16 February 2018.

Objectives

The main objective of the study is to demonstrate that targeting CPP at CPPopt is feasible in TBI patients. The secondary objective is to demonstrate that targeting CPP at CPPopt is safe in TBI patients. The primary endpoints are (1) feasibility: the percentage of monitored time with measured CPP within a range of 5 mm Hg above or below CPPopt; (2) safety: daily therapy intensity level (TIL) score. The secondary endpoints are safety and physiology variables listed in box 1.

Box 1 | Prespecified secondary outcomes

Safety variables

- ICP/CPP variability (representing adequacy/consistency of ICP control).
- Frequency and average duration of ICP spikes >20 mm Hg (associated with a dose-dependent harm).
- Frequency and average duration of CPP outside preset safety ranges (50–100 mm Hg).
- Mean daily RAP (correlation between ICP amplitude and ICP) index (as measure of brain compensatory reserve).
- Analysis of routine CT head scans for evidence of differences in contusion, cerebral oedema and haemorrhage.
- Mean daily vasopressor dose; necessity and dose of inotropic support.
- Incidence of troponin rise and ECG changes stratified by day (as measure of cardiac complications).
- Incidence of serum creatinine rise (as measure of renal complications).
- Mean daily fluid balance.
- Mean daily oxygen arterial pressure/oxygen inspired fraction (PaO_2/FiO_2) ratio + oxygenation index (as measure of pulmonary complications).
- Intensive care survival, and Glasgow Coma Score at ICU discharge.

Physiology variables

- Mean daily MAP.
- Mean PRx.
- Mean daily PRx at CPPopt.
- Mean daily cerebral microdialysis lactate/pyruvate ratio.
- Brain tissue glucose as well as brain tissue oxygen tension ($PbtO_2$ and $PbtO_2/PaO_2$ ratio).
- Near infrared spectroscopy.

CPP, cerebral perfusion pressure; CPPopt, optimal cerebral perfusion pressure; ICP, intracranial pressure; MAP, mean arterial blood pressure; PRx, pressure reactivity index; RAP, compensatory reserve index.

METHODS AND MEASUREMENTS

Data collection and online processing

In this study, ICP and ABP will be monitored as per normal clinical practice in the units: ICP will be recorded by a parenchymal ICP probe; ABP will be monitored by invasive arterial cannulation in the radial artery and zeroed at the level of the foramen of Monroe. The data will be collected at a frequency >100 Hz (waveform resolution), and processed by means of ICM+ ® software (http://icmplus.neurosurg.cam.ac.uk) at the bedside.

COGiTATE CPPopt algorithm

PRx is calculated as a moving correlation coefficient between 10 s averages of ICP and ABP waveforms in a window of 5 min. CPPopt is calculated using a multiwindow approach inspired by Depreitere *et al*,[15] subsequently implemented in ICM+ and investigated in a retrospective TBI data set by Liu *et al*.[12] The algorithm has been further adapted to make it more suitable for prospective bed-side use.

At each time point, 36 PRx-CPP plots are generated from past data windows of increasing duration ranging from 2 to 8 hours, using incremental steps of 10 min. Prior to that, CPP time series are preprocessed with a 5 min duration median filter and PRx data are Fisher transformed.[16] Subsequently, all the data points are divided into groups corresponding to CPP bins of 5 mm Hg length, within 40–120 mm Hg range of CPP values. For each bin, mean PRx and CPP values are used to fit a second order polynomial describing the theoretical U-shape, with its nadir determining CPPopt. This process is repeated for each progressively longer data window. Individual results undergo certain quality control criteria and the accepted values are combined using weighted average operation, as detailed below. The calculations are repeated every minute and the resulting time series is finally subjected to an exponentially weighted average (EWA) filter of 2 hours of duration (details below), forming the CPPopt time trend and giving the current CPPopt target recommendation.

The curve fitting process for each time window follows the algorithm described by Aries *et al* [10] with additional criteria as follows:

1. Each CPP bin must represent at least 3% of the total data count. In this way, CPP values that are very scarcely represented, likely due to short spikes or drops, but not to the physiological trend, will be disregarded.
2. At least 50% of the data in the time window must be included in the curve fit.

3. A PRx variation of at least 0.2 is mandated (thus rejecting flatter PRx-CPP curves).
4. The PRx range of interest is enforced to be between −0.3 and 0.6: the algorithm will not return any CPPopt value when PRx is always very high (indicating a complete loss of pressure reactivity) or always very low (pressure reactivity preserved at each CPP value).
5. The coefficient of determination of the fitted curve R^2_{full} (calculated also for the bins excluded from the curve fitting process) must be at least 0.2.

The weights for combining the CPPopt calculations are given by the following formula:

$$weight = R^2_{full} * \begin{cases} 1, & shape = P \\ 0, & shape = NP \end{cases}$$

where P and NP stand for parabolic (U-shape curve) and non-parabolic (non-U shape curve), respectively. In this way, in the COGiTATE study only parabolic curves are taken into account.

The EWA weight is calculated as $(1-\alpha)^k$ where k is the distance, in number of samples, from the current sample and α is set at 0.1. In this way, more recent CPPopt values contribute more to the final calculation.

The curve fit and the weighting heuristics were chosen based on their performance in our retrospective data set, with regards to the resulting CPPopt time series lowest short term variability, ability to reject non-physiological values, and greatest discrimination from values generated from randomised, surrogate, signals (unpublished data).

The missing data limit of the calculation is set at 50%, therefore at least 4 hours of continuously acquired data are necessary to generate the first CPPopt value.

Assessment of compliance

Compliance with the protocol will be assessed at 4 hourly CPP treatment reviews and by investigators from the research team three times per day. The 4-hour interval is a pragmatic choice and reflects results from visualisation studies which suggested that CPPopt changes over a time frame of 4–8 hours, making the 4 hours an appropriate choice.[17] To facilitate the compliance assessment, a custom module has been added to the ICM+ software that implements the alert and review system designed specifically for this trial. During the review time points, a CPP target is suggested by the software according to the protocol and depending on the arm. The treating clinicians

may deviate from protocol but must provide their proposed target and clinical rationale for deviation in a structured short questionnaire presented by the software (see online supplementary files 1 and 2).

OUTCOME MEASURES

Feasibility

Percentage of monitored time with measured CPP within a range of 5 mm Hg above or below CPPopt. The primary objective of the study is to demonstrate that it is clinically feasible to individualise CPP at CPPopt in TBI patients continuously over time, and demonstrate that we could achieve acceptable concordance with CPPopt. We also wish to explore whether a CPPopt-guided strategy resulted in a significant difference in CPP compared with the controls. Specifically, we aim to assess whether the application of a CPPopt oriented protocol provides a greater percentage of time during which CPP is within 5 mm Hg above or below the calculated CPPopt during the first 5 days of admission. Analysis of retrospective dataset in patients not managed according to the CPPopt concept showed that on average 30% of the monitored time CPP fell within 5 mm Hg margin of CPPopt (unpublished data). This study was powered to target an increase of the monitored time by 20% (relative increase), meaning increase from 30% to 36% of the monitored time within the 5 mm Hg margin of CPPopt, in the intervention group.

Safety: daily TIL score

The main secondary objective of the study is to demonstrate that targeting CPPopt is safe. Safety is defined in two domains. First, COGiTATE aims to assess whether a dynamic target is associated with excess haemodynamic support or organ failure. Second, the study will assess whether such a therapy leads to either worse or more difficult ICP control by driving cerebral oedema. This will be assessed by looking for an excess of (potentially burdensome) treatments to control ICP in the treatment arm as assessed by the use of the daily TIL score.[18] A change in TIL score of >3 is representative of a significant escalation of TBI treatment from basic ICP management involving rescue therapies which are known to carry a clinically significant risk of harm. An increase of TIL score >3 is therefore expected to represent a clinically significant potentially harmful effect of CPPopt-guided treatment and the assessment of this will be the main secondary endpoint.

Safety: safety and physiology variables

Finally, we want to evaluate differences in physiological parameters between interventional and control arms (box 1). In particular, it is aimed to assess whether CPPopt-guided therapy itself affects autoregulation indexes compared

with the control group. Brain oxygenation and tissue chemistry will be assessed in those patients for which additional monitoring was considered clinically justifiable.

Study population

The study population consists of unconscious adult patients with severe TBI admitted to the ICU of three academic hospitals in whom invasive ICP monitoring is clinically indicated.

Inclusion criteria: (1) any adult severe TBI patient (age >18 years) requiring multimodality monitoring and ICP-directed therapy for at least 24 hours on the assessment of the recruiting team; (2) randomisation occurred within 24 hours after ICU admission; (3) informed consent/agreement obtained by a legally authorised representative before inclusion, accordingly to the local legislations.

Exclusion criteria: (1) patients <18 years old; (2) known pregnancy; (3) moribund at presentation (eg, bilaterally absent pupillary responses); (4) patients with primary decompressive craniectomy (DC); (5) patients already enrolled in one other intervention study.

If patients are treated with a secondary DC, they will end the study as it is unknown how brain physiology changes after a DC and the calculation of CPPopt is poorly validated in such patients. Data up to the time of the DC will be retained for analysis. Once the study is terminated, the patients' CPP will be managed according to the BTF guidelines.

Study arms and randomisation

Patients are randomised to either standard CPP protocol therapy (control group) or to CPPopt-guided management of CPP (intervention group). Block randomisation by centre are used to ensure a uniform distribution of patients. Randomisation is done electronically on recruitment using a purpose built electronic Case Report Form (eCRF) hosted by the Clinical Trial Center Maastricht in Maastricht with a secure web interface.

Patient allocated to the control group are managed according to the most recent BTF guidelines[2] which recommend maintaining CPP between 60 and 70 mm Hg. In this group, online autoregulation information is hidden from the treating team although available to the study team for analysis.

Patients allocated to the intervention group are managed according so as to target CPPopt, when there is sufficient data for it to be available. If at the fixed review time points the CPPopt value is not available (eg, due to noisy or

missing data) or it is outside of the safety limits (50–100 mm Hg), the protocol advises to follow a CPP target at the discretion of the clinician: this may be either the BTF guideline target or a previous target. As a safety precaution, the maximum difference in CPP target value suggested by the software at the new review time from the current target value has been limited to ±10 mm Hg to avoid potentially harmful jumps in CPP.

A flowchart of the patients' inclusion, randomisation and study procedures in the COGiTATE trial is presented in figure 1.

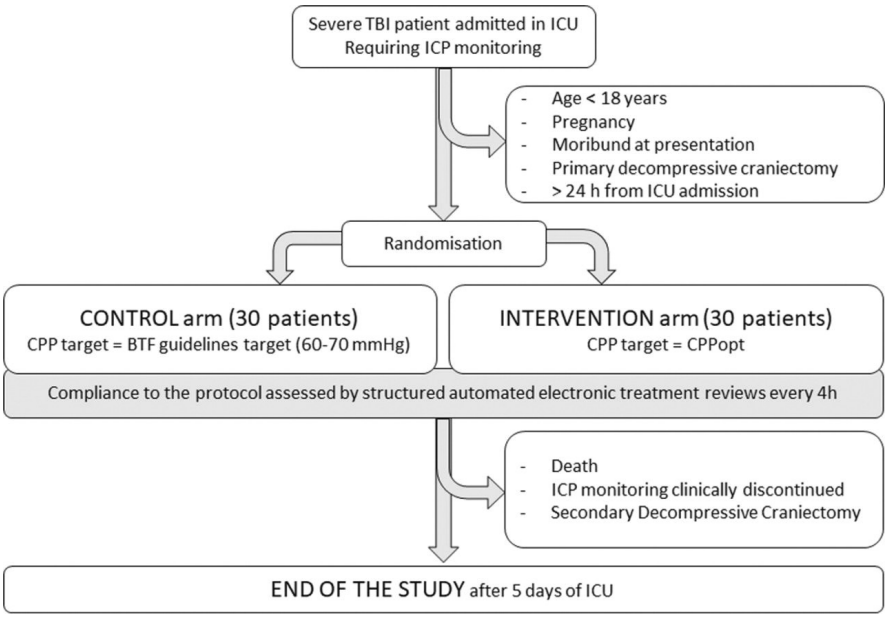

Figure 1 | Flowchart of the patients' inclusion, randomisation and study procedures in the COGiTATE trial. BTF, Brain Trauma Foundation; CPP, cerebral perfusionpressure; CPPopt, optimal cerebral perfusion pressure; ICP, intracranial pressure; ICU, intensive care unit; TBI, traumatic brain injury.

Sample size

The sample size justification is based on the primary endpoint for the feasibility objective. The analyses will be conducted according to the intention-to-treat principle, therefore all the enrolled and randomised patients will be included in the analysis, regardless of their compliance with the protocol. Sample sizes were determined using the R statistical language[19] and the PWR package.[20] A significance of 5% and power of 80% were assumed.

As described in the outcome measures paragraph, the primary endpoint for the main objective, feasibility, is the percentage of monitored time with measured

CPP within a range of 5 mm Hg above or below CPPopt. Retrospective analysis in unpublished data showed that on average patients spent a mean (+SD) of 30% (+8%) of their monitored time with measured CPP within 5 mm Hg of CPPopt. In the absence of prospective data, we powered COGiTATE study to target a relative increase in CPPopt target adherence by 20% (a pragmatic choice but justifiable on typical differences seen between good/poor outcome in the retrospective data), that is, from 30% to 36% of monitored time within the CPPopt target margin, while keeping the SD at 8%. This produced a desired sample size of 56, which was increased to 60 patients, to allow for dropout, technical problems or need for a non-parametric analysis.

The primary endpoint for the safety secondary objective is to assess whether there is an increase of the daily TIL score of >3 in the CPPopt treatment arm. We regard an increase of daily TIL of 3 as a significant effect as it represents a difference comparable to one treatment tier and in comparison with typical TIL variability from pilot data. Conversely, a TIL score increase of 2 can be expected in the intervention group because two points are counted for CPP-related therapy (vasopressor therapy/fluids), so this could be not interpreted as a significant worsening of TBI therapy. We estimate, for 80% power and 5% significance an averaged change in daily TIL score of 3 would require an n=25 in each arm (although this is a secondary endpoint and this estimation does not correct for multiple comparisons).

Data storage

High frequency ICP and ABP signals are recorded continuously and processed to obtain CPP and CPPopt. The values are subsequently transferred to secure local servers for offline analysis. Only the local study teams have access to the server.

Additional clinical and biochemical data (severity of injury and hospital course) use the patient's medical record as source data and are subsequently transcribed to the eCRFs with access limited to members of the study team only.

Imaging data and radiological reports obtained from the CT scans, are collected and stored on a secure local server.

The patients enrolled in the study and randomised, are assigned a study deidentification number that will be used in the data collection forms. An enrolment log is used in each centre to keep the link between the participants' identity and the study number. This log is secured in password-protected local servers to which only the local study coordinator and the members of the

research team have access. The data transmitted to the data coordinating centre in Maastricht will be entirely deidentified.

Paper copies of the data, consent forms and protocols will be stored locally. Personal data will be destroyed after 1 year. Fifteen years after the completion of the study, all the paper study files and all the stored electronic files will be destroyed.

Statistical analysis

The data will be analysed on an intention-to-treat basis with all randomised patients included in the analysis. For the primary endpoint, the total time (in minutes) each patient had CPP values close (±5 mm Hg) to CPPopt will be calculated and analysed in a blinded manner by the study team. The fraction of time that CPP will be within 5 mm Hg of CPPopt, will represent the primary analysis for this outcome. For secondary analysis, different deviation thresholds (7.5 and 10 mm Hg) will also be assessed. The two groups will be compared with an unpaired t-test (or a non-parametric equivalent in the event of a significant departure the normal distribution). Multivariable linear models will be used to control for the covariates centre, age, Glasgow Coma Score after resuscitation, pupil reactivity, presence of extracranial injury and primary craniotomy.

For the secondary safety endpoint, a t-test (or non-parametric equivalent) will be used for the statistical comparison of the TIL score, vasopressor and fluid use and organ dysfunction summary measures between the two groups. If necessary, multivariable linear regression analysis will be used to adjust for imbalances in main prognostic variables between the two groups. For the other secondary safety and physiology endpoints, the results will be presented as mean (SD) for continuous variables and as frequencies (%) for categorical variables. Intervention and control group will be compared using a t-test or non-parametric equivalent for continuous variables and χ^2/Fisher test for categorical variables.

Patient and public involvement

Improving outcomes from TBI is a known area of societal importance.[3] Patients and public were not involved in the study design and, as patients in this study were unconscious, they could not be otherwise involved. The results will be disseminated through peer-reviewed publications and presentation at international conferences as well as by social media and the study website (www.cppopt.org) which also contains information for the public.

Ethics and dissemination

Ethical considerations

The trial is conducted according to the Declaration of Helsinki and the respective participating countries laws governing clinical research, and the principles of Good Clinical Practice.

Enrolled subjects, by definition, lack capacity to consent due to their level of consciousness at presentation. The informed consent procedure involves identifying a legally authorised representative of the patient, whose opinion is sought about the participant's wishes and feelings in relation to the project, and whether he/she would want to take part to the study. When available, a legally authorised representative (accordingly to the local laws) is then approached by a member of the clinical team, to inform them of the research study. If he/she agrees, a member of the research team will then provide further verbal and written explanation of the research study. If the family member/legal representative advises that the patient would want to take part in the study, the patient will be enrolled.

For this study, it was deemed physiologically important to begin CPPopt therapy as early as possible following the injury since pathobiological determinants of inflammation and oedema are likely to be determined in the first 24–48 hours after injury. Therefore, if a legally authorised representative is not identified within the first 12 hours after ICU admission, depending on the local country laws, the patient may be included via agreement with one of the treating clinicians not involved in the study (in UK), or using a deferred consent procedure (in Netherlands and Belgium). Following enrolment via deferred consent, if a legal representative does not agree for the patient to continue their participation in the study within 24 hours the patient will be withdrawn. If the patient regains consciousness and capacity during their admission (ICU or hospital admission according to the local protocols), the patient will be approached to provide consent for their participation in the study. If the patient declines, they will be given the option to have data collected retained for analysis or destroyed completely.

Safety considerations

Safety of this study is independently monitored by an external clinical trials agency (Clinical Trial Center Maastricht, Oxfordlaan 70, 6229 EV Maastricht (NL)) who will also have oversight of data quality. For this cohort of patients, a mortality rate of 25% and a severe disability rate of 30% is expected at baseline. However, it is unknown whether targeting CPPopt, which may typically be higher than a fixed range of 60–70 mm Hg could drive further

oedema or contusion expansion over the next days or lead to respiratory, renal or myocardial injury due to greater vasopressor requirements. Therefore, the followings are reported: increases in oedema or haemorrhages on repeated brain CT, troponin rise and/or ECG changes, NT-proBNP rise, significant serum creatinine rise and PaO_2/FiO_2 ratio <300. Severe adverse events and predefined adverse events that are commonly expected in TBI patients will also be recorded and reported. Glasgow Outcome Scale Extended at 6 months will also be collected as part of institutional practice or other observational studies.

Dissemination

The results of this study will be presented at international scientific conferences and in peer-reviewed journals, regardless of the trial outcome.

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3.2

An Update on the COGiTATE Phase II Study: Feasibility and Safety of Targeting an Optimal Cerebral Perfusion Pressure As a Patient - Tailored Therapy in Severe Traumatic Brain Injury

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INTRODUCTION

A raised intracranial pressure (ICP) and a reduced cerebral perfusion pressure (CPP) are long-established and important causes of secondary brain injury and are associated with worsened clinical outcomes after traumatic brain injury (TBI) [1]. Monitoring and management of ICP/CPP has become a cornerstone of severe TBI management. The 2016 Brain Trauma Foundation (BTF) guidelines recommend keeping ICP at <22 mmHg and CPP strictly between 60 and 70 mmHg [2]. Whether a fixed therapeutic CPP target range is suitable for all individual TBI patients is the subject of scientific debate. Potentially, individualizing therapies and tailoring medical treatment to dynamic pathophysiology could offer a precision medicine approach with advantages over the current 'one size fits all' strategy. The authors of the recently published SIBICC [Seattle International Severe Traumatic Brain Injury Consensus Conference] algorithm have presented expert recommendations for treatment of adult patients with ICP management [3]. In addition to formalizing what is already known, the SIBCC consensus includes new content. The authors recommend a mean arterial pressure (MAP) challenge to assess the state of cerebral autoregulation (CA). If MAP augmentation results in a reduction in ICP (confirming some degree of working CA), an increase in MAP can be used as a method to reduce ICP in an individual patient. This concept is not completely new; it was previously proposed some decades ago, with very mixed results. In an editorial accompanying the publication of the SIBICC algorithm, Smith and Maas consider the 'one size fits all' and escalating 'staircase' approaches to ICP/CPP management undesirable and strongly support future development of recommendations for targeted individual approaches [4]. Autoregulation-guided CPP treatment could be one of the more personalized approaches to ICP management based on current understanding of the underlying pathophysiology of TBI. In healthy individuals, CA maintains constant and adequate cerebral blood flow (CBF),thereby protecting the brain from both ischaemia and hyperperfusion in the face of inevitable changes in CPP [5]. However, after TBI, CA can frequently be impaired, and this impairment is statistically related to poor outcomes [1]. This chapter describes the progress of the first randomized trial in four European centres of cerebral autoregulation-orientated management of TBI patients, with results expected to be presented early 2021.

METHODS

The CPPopt Concept and COGiTATE

Czosnyka et al. first proposed use of a moving correlation coefficient (the pressure reactivity index (PRx)) between slow changes in MAP and ICP as a surrogate method for continuous bedside estimation of global CA. This concept has attracted interest in the last decade, with the observation that PRx and CPP often exhibit a U-shaped relationship over time, with a minimum PRx value occurring at a CPP value at which cerebrovascular pressure reactivity is best preserved (or least impaired) [6,7]. These observations provide the rationale for the hypothesis that targeting a CPP value such that global CA is best could be a potential strategy for individualizing CPP targets. Indeed, deviations from this 'optimal' CPP (CPPopt) value have been associated with worse outcomes in retrospective studies [7]. However, this concept has never been studied prospectively. In this chapter, we describe the current status of the COGiTATE [CPPopt Guided Therapy: Assessment of Target Effectiveness] study (www.cppopt.org)[8]. This is a prospective, multicentre, non-blinded, randomized, controlled trial in patients with severe TBI. Unconscious adult patients with severe TBI with an indication for ICP monitoring are recruited in the first 24 h of admission to the intensive care unit (ICU) and randomized into one of two treatment arms: the control group (with a CPP target of 60–70 mmHg in accordance with the BTF guidelines) and the intervention group (with an 'optimal' CPP target (CPPopt) based on the CA status). The duration of the intervention is maximum 5 days. Other therapies (such as measures to control ICP) are unaltered from local protocols. In this study, ICP and arterial blood pressure (ABP) are monitored as per normal clinical practice in the ICU: ICP is recorded by a parenchymal ICP probe, and ABP is monitored by invasive arterial cannulation in the radial or femoral artery and zeroed at the level of the foramen of Monro. The data are collected at a frequency ≥100 Hz (waveform resolution) and processed by means of ICM+® software (Cambridge Enterprise, Cambridge, UK; http://icmplus.neurosurg.cam.ac.uk) at the bedside. Compliance with the protocol is assessed at 4-hourly CPP treatment reviews. The 4-h interval is a pragmatic choice [9]. To facilitate the compliance assessment, a custom module has been implemented in the ICM+ software, with a system of alert and review forms designed specifically for this trial. At the review time points, a CPP target is suggested by the software, according to the randomisation group. The treating clinicians may deviate from the suggested target but must provide their proposed target and clinical rationale for deviation in a structured short questionnaire presented by the software. CPPopt is calculated using a multi-window weighted approach, inspired by Depreitere et al. [10], which was subsequently implemented in the ICM+ software and investigated in a retrospective TBI data set by

Liu et al. [11]. The algorithm has been further adapted by Beqiri et al. [8] to make it more suitable for prospective bedside use. The primary end points are (1) feasibility: the percentage of monitored time with measured CPP within a range of 5 mmHg above or below the dynamic CPP target; and (2) safety: the daily (intracranial hypertension) therapy intensity level (TIL) score [12]. The secondary end points are markers that suggest differences in organ dysfunction. The study is powered to accomplish a relative increase of 20% in monitored time with CPP close to the individual CPP target. The study is not designed to assess differences in clinical outcomes. Our protocol does not allow us to perform and report any interim analysis; in this report, we provide a qualitative description of our study experiences.

RESULTS

Three tertiary centres have been involved since the start of the study: Maastricht University Medical Centre (coordinating centre, Maastricht, the Netherlands), Cambridge University Hospitals NHS Foundation Trust (Cambridge, UK), and Catholic University Hospitals Leuven (Leuven, Belgium). The first patient was randomized in February 2018. In March 2019, a fourth study centre was added: Radboud University Medical Centre (Nijmegen, the Netherlands). Figures 1 and 2 provide examples of recordings from two randomized patients. The first example (Fig. 1) shows a recording from a patient who was randomized into the intervention group. Besides data on basic monitoring variables, data on trends in CPPopt and PRx are available to the treating clinicians. The patient in the second example (Fig. 2) was randomized into the control group, with a target CPP of 60–70 mmHg. On the overview screen, time trends in CPP, ABP and ICP are displayed. CA information is hidden from the treating clinicians. The study enrolment rate is 2.4 patients per month (Fig. 3). As of October 2019, 51 patients were randomized (85% of the intended total). At the same randomization rate, we expect enrolment to be finished around February 2020.

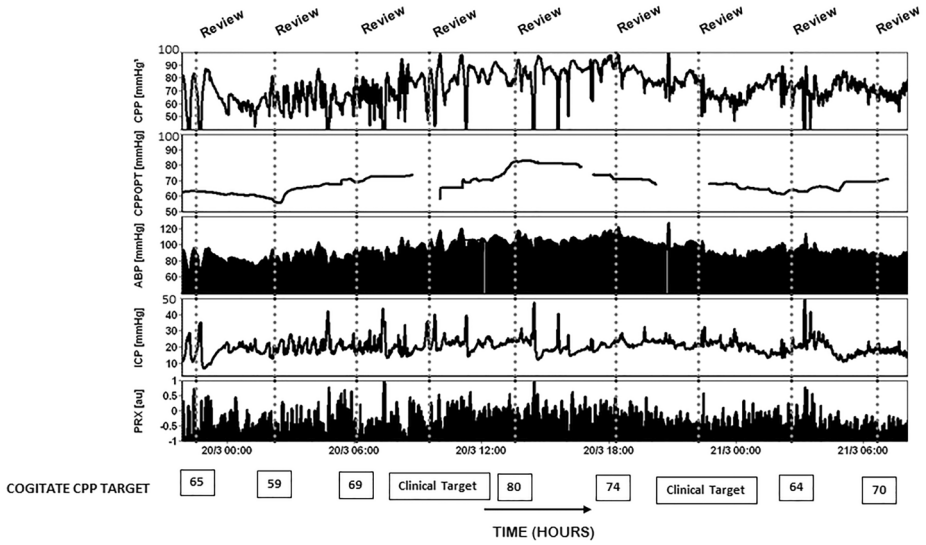

Figure 1 | Example of a (retrospective) l.5-day recording from a patient randomized into the intervention group of the COGiTATE [CPPopt Guided Therapy: Assessment of Target Effectiveness] study. Six times daily, a CPP review is requested at the *dotted vertical line* time stamps. Physiological trends that are available to the clinical team for the cere bral perfusion pressure (CPP) target reviews are the CPP, 'optima!' CPP (CPPopt), arterial blood pressure (ABP), intracranial pressure (ICP).

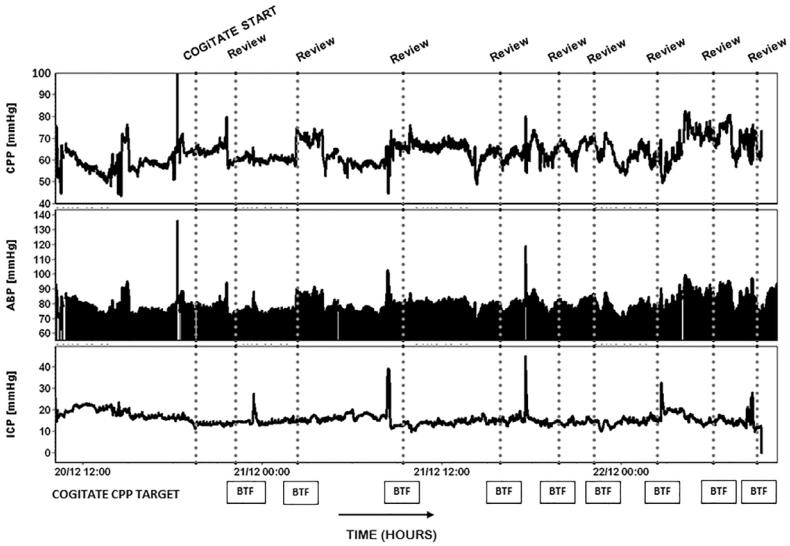

Figure 2 | Example of a 1.5-day recording from a patient randomized into the control group of the COGiTATE [CPPopt Guided Therapy: Assessment of Target Effectiveness] study. Six times daily, a review is filled in, shown by the *dotted vertical lines. Trend lines* for cerebral perfusion pressure (CPP), arterial blood pressure (ABP) and intracranial pressure (ICP) are shown. The CPP targets suggested during the reviews are displayed at the bottom of the figure. In the conu·ol group, the suggested targets are those recommended by the Brain Trauma Foundation (BTF) guidelines (60-70 mmHg) [2].

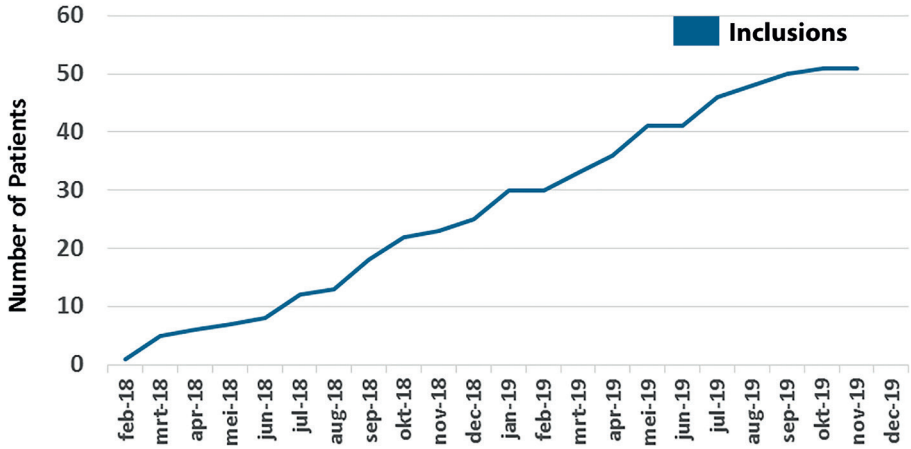

Figure 3 | The total number of study inclusions over time are presented in *blue.* The first enrolment occurred on 16 February 2018. The fourth study centre (Nijmegen, the Netherlands) started enrolling patients in March 2019. The study aims to enrol a total of 60 patients. An actual update of study inclusions can be found on www.cppopt.org. The first study results are expected early 2021.

DISCUSSION

In this chapter, we provide an update of the phase II COGiTATE study in severe TBI patients with ICP monitoring. This prospective evaluation of the feasibility, safety and physiological implications of autoregulation-guided management is providing evidence that will be useful in the design of a phase III outcome study. Several homeostatic processes contribute to the adequate delivery of oxygen- and nutrient-rich arterial blood to the brain to match metabolic demands. These processes operate at distinct frequencies to precisely regulate CBF. There is a long-standing belief that the lower limit of cerebral autoregulation (LLA) is 50 mmHg and that the upper limit of autoregulation (ULA) is 150 mmHg, based on a seminal report published by Lassen in 1964 [13]. However, the acceptance of these limits of autoregulation as a 'simple' guiding principle for haemodynamic management has been challenged by many studies [14]. The data support the notion that the upper and lower limits should be defined individually and cannot be determined accurately on the basis of population data. Many clinical methods of CA monitoring involve assessment of cerebrovascular reactivity (PRx) to continuously evaluate the correlation between spontaneously occurring slow-wave changes in MAP and ICP. In this way, they avoid the need to lower or raise ABP significantly in order to assess the limits of autoregulation, especially in patients who have compromised organ perfusion or brain swelling. The

CPPopt concept relies on this latter methodology, with the compromise that often only parts of the autoregulation curve are available. However, with long-term and continuous monitoring— which is currently limited to invasive and robust monitoring signals such as ICP—the CPP value at which autoregulation is best preserved (CPPopt) can be identified. At the moment, the benefit of autoregulation-guided perfusion therapy is being tested in different patient groups. To evaluate the importance of autoregulation-guided therapy to patient outcome after cardiac surgery, a recent prospective, randomized, single-blinded study was completed. This study assessed use of a MAP target greater than the LLA (using transcranial Doppler ultrasound measurements) during cardiopulmonary bypass versus usual institutional care in which MAP targets were chosen empirically [15]. In a subset of 199 patients (in whom postoperative delirium testing was performed), the odds of delirium were reduced by 45% in the group whose MAP targets were determined by CA monitoring (odds ratio 0.55, 95% confidence interval 0.31–0.97, $P = 0.04$). Petersen et al. conducted a singlecentre, prospective (observational) cohort study of patients undergoing endovascular therapy (ET) after a large-vessel occlusion ischaemic stroke [16]. Autoregulatory function was measured continuously for 24 h following thrombectomy by interrogating changes in tissue oxygenation (measured by near-infrared spectroscopy) in response to changes in MAP, using time correlation analysis (TOx). The data showed that exceeding individualized thresholds of CA was associated with haemorrhagic transformation and worse functional outcomes even after adjustment for prognostic covariates.

CONCLUSION

ICU clinicians now have a potential tool for individualizing an ‘optimal’ CPP target based on continuous cerebral blood volume (autoregulation) monitoring. This intervention protocol is currently being tested in the COGiTATE feasibility and safety study, which is close to reporting its first results. Current (retrospective) data point to the limitations of using a fixed CPP range for a heterogenic TBI population because the individual’s LLA or ULA may or may not be within this arbitrary range.

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4

Targeting Autoregulation-Guided Cerebral Perfusion Pressure after Traumatic Brain Injury (COGiTATE): A Feasibility Randomized Controlled Clinical Trial

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ABSTRACT

Managing traumatic brain injury (TBI) patients with a cerebral perfusion pressure (CPP) near to the cerebral autoregulation (CA)-guided “optimal” CPP (CPPopt) value is associated with improved outcome and might be useful to individualize care, but has never been prospectively evaluated. This study evaluated the feasibility and safety of CA-guided CPP management in TBI patients requiring intracranial pressure monitoring and therapy (TBIicp patients). The CPPopt Guided Therapy: Assessment of Target Effectiveness (COGiTATE) parallel two-arm feasibility trial took place in four tertiary centers. TBIicp patients were randomized to either the Brain Trauma Foundation (BTF) guideline CPP target range (control group) or to the individualized CA-guided CPP targets (intervention group). CPP targets were guided by six times daily software-based alerts for up to 5 days. The primary feasibility end-point was the percentage of time with CPP concordant (±5 mm Hg) with the set CPP targets. The main secondary safety end-point was an increase in therapeutic intensity level (TIL) between the control and intervention group. Twenty-eight patients were randomized to the control and 32 patients to the intervention group. CPP in the intervention group was in the target range for 46.5% (interquartile range, 41.2–58) of the monitored time, significantly higher than the feasibility target specified in the published protocol (36%; $p < 0.001$). There were no significant differences between groups for TIL or for other safety end-points. Conclusively, targeting an individual and dynamic CA-guided CPP is feasible and safe in TBIicp patients. This encourages a prospective trial powered for clinical outcomes.

INTRODUCTION

It is increasingly recognized that patients with traumatic brain injury (TBI) may benefit from individualized clinical management.[1,2] Cerebral autoregulation (CA) may allow for maintaining cerebral blood flow for adequate energetic requirements in response to changes in mean arterial pressure (MAP), by means of vasoconstriction and vasodilation.[3,4] In TBI patients, CA is frequently affected, and impaired CA is associated with poor clinical outcome.[5] Given that dynamic slow variations in cerebral blood volume produced by CA are transmitted into changes in intracranial pressure (ICP), the relationship between slow changes in MAP and ICP (named the pressure reactivity index [PRx]) can be considered a surrogate method for the assessment of CA.[6]

The Brain Trauma Foundation (BTF) guideline recommends a target cerebral perfusion pressure (CPP) value between 60 and 70 mm Hg. The "optimal" CPP target within this range is, however, uncertain and may depend upon the patient's autoregulatory status.[7] In 2019, a consensus ICP management algorithm was published that incorporated the assessment of CA using a discrete MAP challenge to define individual CPP goals in TBI patients.[8] However, given the well-recognized temporal evolution of physiology after TBI, a continuous assessment of CA status and range might allow for improved dynamic and precise MAP/CPP titration over the disease narrative. In this regard, a continuously updated PRx and its derived "optimal" CPP (CPPopt) value could be advantageous. CPPopt is the CPP value where patients' CA is best preserved and is derived automatically from the U-shaped (parabolic) CPP-PRx relationship typically observed.[9,10] Retrospective data demonstrated an association between improved outcome in patients who had a CPP value concordant with the CPPopt value.[9,10]

Accordingly, we performed the first randomized controlled clinical trial—the CPPopt Guided Therapy: Assessment of Target Effectiveness (COGiTATE)—to assess feasibility as the percentage of monitoring time with CPP concordant with CPPopt in the intervention group and whether this leads to a potentially harmful need for higher therapeutic intensity levels (TILs) in TBI patients with ICP monitoring (TBIicp).

METHODS

Trial design

The protocol has been published previously.[11] An extended summary of the methodology and (statistical) analysis can be found in Supplementary Appendix S1. COGiTATE was a multi-center, international, non-blinded, randomized controlled parallel phase II trial (RCT). Four tertiary hospitals that provide acute neurocritical care for TBI patients were involved. Ethical approval was obtained at all participating institutions.

Participants

Eligible participants were patients with TBIicp meeting the following inclusion criteria: 1) adults (age ≥18 years) indicated for ICP-directed therapy for at least 24 h; 2) randomization within 24 h after intensive care unit (ICU) admission; and 3) signed proxy informed consent. Exclusion criteria were: 1) primary decompressive craniectomy; 2) injury deemed to be unsurvivable at presentation; and 3) known pregnancy. Block randomization, with stratification according to trial site, was used to ensure a uniform patient distribution. Randomization was performed electronically using a centralized electronic case report form (eCRF) by a researcher. The study was powered to achieve a 20% increase in percentage of monitored time with CPP concordant ±5 mm Hg of the CPPopt values; from 30% (historical cohort) to 36% in the intervention group, resulting in a sample size of 60 patients.[11]

Data collections

Baseline and daily patient characteristics were collected. The daily characteristics included the TIL score,[12,13] laboratory and diagnostic organ function parameters, measures of hemodynamic and ventilatory support intensity, and pre-defined adverse events (AEs) and serious adverse events (SAEs). The aim of the summary (daily) TIL score is to provide a quantitative estimate of the ICP lowering interventions used in a given period (recommended 24 h) by assigning numerical scores to each therapy intensity level of each intervention and summating these (0–38).[12,13] The 6-month neurological outcome was assessed using the Glasgow Outcome Scale (GOS).[11] In addition, the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT) score was calculated.[14] High-frequency monitoring data were collected using the research software, ICM+® (Cambridge Enterprise, Cambridge, UK), at the bedside. MAP was monitored by invasive arterial cannulation in the radial or femoral artery and zeroed at the tragus. ICP was recorded by a parenchymal microsensor.

Interventions

Patients were randomized to either the BTF CPP range (60–70 mm Hg)[7] or targeting a "dynamic" CPP value (defined as the CPPopt). According to the randomization group, the software displayed the appropriate physiological targets and CPP review information (Supplementary Fig. S1) at the bedside.[11] CA information, including PRx, CPP-PRx curve, and the updated 1-min trend of CPPopt (further referred to as "CPPopt trendline"), was displayed for the intervention group only (Fig. 1).[11,15] In the intervention group, patients were managed according to the calculated CPPopt, that is, the CPP value extracted from the CPPopt trendline at the regular review time points (further referred to as the "CPP target"). How to achieve the CPP target was left to the discretion of the attending clinical team. The protocol ended after a maximum of 5 study days or after reaching pre-defined end-points (Supplementary Appendix S1).[11]

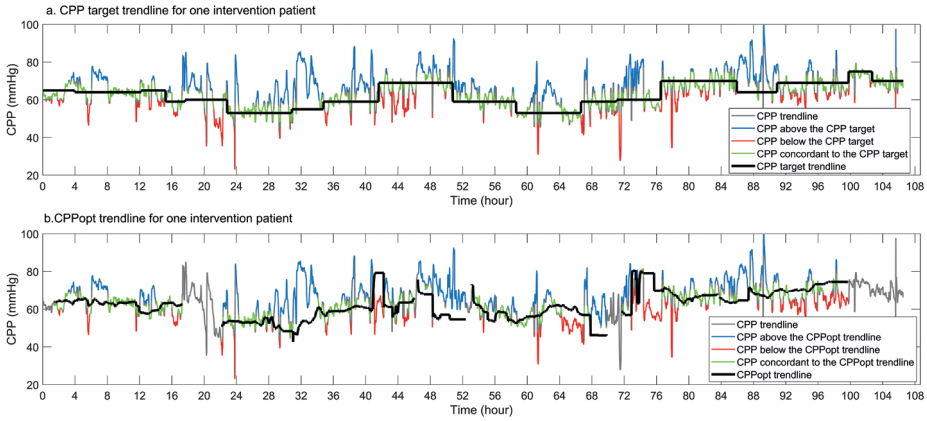

Figure 1 | Illustrative example of a recording from a patient in the intervention group. Time $t = 0$ is the start of the intervention protocol, which is the time that a CPP target can be provided. (**A**) Serial CPP target trendline and the corresponding percentage of time the patients' CPP is concordant (±5 mm Hg) with the chosen CPP target (the primary end-point, for the intervention group only). In addition, categories of the percentage of time with patients' CPP above and below (±5 mm Hg) the chosen target is depicted in different colors. The CPP target trendline yield was always 100% given that a CPP target had to always be there. (**B**) Illustrates for the same individual the CPPopt trendline (retrospective available for both groups) and the corresponding categories of percentages of time patients' CPP was concordant with, above, and below (±5 mm Hg) the CPPopt in different colors. The gray line (referred to as the CPP trendline) indicates the period when the software algorithm was not able to provide a CPPopt. The CPPopt trendline yield was 85%. Each minute that patients' CPP was concordant with the (±5 mm Hg) CPP target trendline or CPPopt trendline was summed and divided by the total time (in minutes). CPP was available during the intervention period (%). For this example patient, the percentage of time the patients' CPP was concordant with (±5 mm Hg) the CPP target trendline was 52%, and the percentage of time concordant with (±5 mm Hg) the CPPopt trendline was 43%. Figure 1 was constructed in MATLAB (Release 2019b; The MathWorks, Inc., Natick, MA). CPP, cerebral perfusion pressure; CPPopt, "optimal" CPP.

Cerebral perfusion pressure reviews

The clinical team reviewed the CPP targets according to visual alerts generated by the software six times daily. Until the first review alert, the protocol recommended to keep CPP between 60 and 70 mm Hg in both groups (the period up to the first review alert was not used for data analysis). For the intervention group, a CPP was recommended at each review, which was either 1) the calculated CPPopt trendline value or 2) a "clinical" CPP value. The latter was suggested when the CPPopt calculation was not available, and the clinical team were to choose an appropriate target themselves.[11] In both groups, the clinical team was allowed to deviate from the software recommendation, but requested to record their rationale and the chosen CPP target value in real time.

Outcome measures

To assess the feasibility of the study protocol, we aimed to increase the percentage of the monitored time with measured CPP within a range of 5 mm Hg above or below the CPP target to values above the pre-defined 36% in the intervention group (primary end-point).[11] To examine safety, we identified a clinically relevant difference in daily TIL score as an averaged daily TIL score difference ≥3 between the groups (main secondary end-point). Between-group differences of physiological, diagnostic, treatment, and AE/SAEs were assessed for additional evidence for safety. Finally, clinical outcome parameters were assessed.

DATA ANALYSIS

Data preparation

High-frequency monitoring data, including the 1-min average physiological data (including ICP, MAP, CPP, PRx, CPPopt) and the six times daily review results, were anonymized and packaged into HDF5 files,[16] using ICM+, and imported into MATLAB (Release 2019b; The MathWorks, Inc., Natick, MA) for further calculations. Patients' total mean (covering the study protocol period) and 1-h mean physiological values were calculated after automated removal of non-physiological values in MATLAB. The eCRF and averaged physiological data were imported in R (version 4.0.3; R-Core Team).[17]

Statistical analysis

Data are presented as mean ± standard deviation (SD) or median and interquartile range (IQR) for continuous variables. We used frequencies (%) for categorical variables. The primary feasibility end-point was evaluated using a one-sample *t*-test. All other between-group comparisons were based on the two-sample *t*-test/Mann-Whitney *U* test for continuous variables, and analyses

of categorical variables were based on the chi-squared/Fisher's exact test. Levene's test was used to test equality of variances between groups. A *p* value <0.05 was considered statistically significant. All statistical analyses were performed in R.

Data availability
Not applicable.

RESULTS

The enrollment flowchart and study timeline are summarized in Supplementary Figures S2 and S3. From February 2018 until January 2020, 28 patients were randomized to the control group and 32 patients to the intervention group. Admission patient characteristics were slightly imbalanced between the groups (Table 1). Figure 1 shows a patient example with trends of patients' CPP, CPP targets, and CPPopt over time. The CPPopt trendline was available for 76.6% (SD, 16.5) of the monitored time in the intervention group. MAP was significantly higher for the intervention group (control, 81 [SD, 6] vs. intervention 85 [SD, 8] mm Hg; $p < 0.05$). Also, mean CPP was significantly higher (control 68 [SD, 4.4] vs. intervention 73 [SD, 6.6] mm Hg; $p < 0.05$), with significantly increased variability for the intervention group ($p < 0.05$). In the intervention group, PRx was, on average, lower compared to the control group (Table 2).

Table 1 | Baseline Patient and Intervention Characteristics

Mean (SD) or median (IQR)	CPP control (*n* = 28)	CPP intervention (*n* = 32)	Total (*n* = 60)
Sex, men, *n* (%)	21 (75)	22 (69)	43 (72)
Age, years (SD)	48 (19)	42 (17)	45 (18)
Initial assessed GCS Motor score (IQR)	4 (2–5)	4 (1–6)	4 (1–5)
Initial assessed GCS score 3–8, *n* (%)	21 (75)	20 (63)	41 (68)
Initial assessed GCS score 9–13, *n* (%)	6 (21)	7 (22)	13 (22)
Initial assessed GCS score 14–15, *n* (%)	1 (4)	5 (16)	6 (10)
Pupil fixed and dilated, *n* (%)			
Unilateral	4 (14)	3 (9)	7 (12)
Bilateral	2 (7)	1 (3)	4 (7)

Table 1 | Baseline Patient and Intervention Characteristics (continued)

Mean (SD) or median (IQR)	**CPP control (*n* = 28)**	**CPP intervention (*n* = 32)**	**Total (*n* = 60)**
CT-Marshall classification, *n* (%)			
Diffuse injury (I)	0 (0)	1 (3)	1 (2)
Diffuse injury (II)	17 (61)	21(66)	37 (63)
Diffuse injury (III)	6 (21)	2 (6)	8 (14)
Diffuse injury (IV)	3 (11)	0 (0)	3 (5)
Evacuated mass lesion (V)	0 (0)	4 (13)	4 (7)
Non-evacuated mass lesion (VI)	2 (7)	4 (13)	6 (10)
Isolated TBI, *n* (%)	9 (32)	17 (53)	26 (43)
IMPACT outcome (mortality) prediction (IQR)[a]	32 (25–46)	29.5 (15–34.5)	31.5 (23.5–39)
Intervention characteristics No. of reviews (%)	**Control (*n* = 459)**	**Intervention (*n* = 552)**	**Total (*n* = 1011)**
Clinical target recommended, *n* (%)[b]	NA	144 (26.1)	NA
Adopting provided CPPopt/CPP range? *n* (%)[c]			
Yes	428 (93.2)	374 (92)	802 (93)
No	31 (6.8)	34 (8.3)	65 (7.5)
Problems with reaching previous CPP target? *n* (%)[d]			
Yes	99 (22)	121 (22)	220 (22)
No	353 (76.9)	424 (76.8)	777 (77)
Uncertain	7 (1.5)	7 (1.3)	14 (1.4)
Which intervention(s) needed? *n* (%)[e]			
Only ABP intervention	117 (26)	237 (43)	354 (35)

Table 1 | Baseline Patient and Intervention Characteristics (continued)

Mean (SD) or median (IQR)	CPP control (*n* = 28)	CPP intervention (*n* = 32)	Total (*n* = 60)
Both ABP + ICP intervention	89 (19)	84 (15)	173 (17)
Only ICP intervention	18 (3.9)	10 (1.8)	28 (2.8)
No intervention	231 (50)	220 (40)	451 (45)
Other interventions	4 (0.87)	1 (0.18)	5 (0.5)
Reason to stop the intervention protocol, *n* (%)			
(1) Deceased	1 (4)	0 (0)	1 (2)
(2) ICP monitoring discontinued[f]	11 (39)	13 (41)	24 (40)
(3) Active treatment withdrawal	1 (4)	3 (9)	4 (7)
(4) Study protocol stopped at day 5	10 (36)	10 (31)	20 (33)
(5) Other reason to stop	5 (18)	6 (19)	11 (18)

Presented percentages may not be equal to 100% as a result of rounding. *n* = number.
[a]The IMPACT score for moderate-to-severe TBI. Included patient characteristics in the prognostic model for mortality prediction at 6 months using the Core model: age, GCS Motor score, and pupillary reactivity. IMPACT is validated for TBI patients having an initial GCS ≤12 (control, *n* = 27; intervention, *n* = 26). In addition, 3 patients with missing Glasgow Outcome Scale at 6 months (control, *n* = 1 and intervention, *n* = 2) were not included for the average IMPACT outcome prediction scores.
[b]When the software recommendation was to use a "clinical target," the question "adopting CPPopt target" was not presented.
[c]Exact question: "Will you be adopting the advised CPPopt target/CPP range (yes/no)?" The percentages were computed in the intervention group without the "clinical target" reviews (*n* = 144).
[d]Exact question: "Where there any clinical problems with reaching the previous CPP target?"
[e]Exact question: "Which interventions are you planning to achieve the new CPP target?"
[f]ICP monitoring discontinuation was a clinical decision and not influenced by the intervention protocol.
SD, standard deviation; IQR, interquartile range; GCS, Glasgow Coma Scale; CT, computed tomography; TBI, traumatic brain injury; IMPACT, the International Mission for Prognosis and Analysis of Clinical Trials in TBI; CPP, cerebral perfusion pressure; CPPopt, optimal CPP; ABP, arterial blood pressure; ICP, intracranial pressure; NA, not applicable.

Table 2 | Primary and Secondary Outcomes

Mean (SD) or median (IQR)	CPP control (*n* = 28)	CPP intervention (*n* = 32)	p value[a]	p value[b](for variance)
Primary end-point				
Percent time CPP concordant with the CPP target value ±5 mm Hg	NA	46.5 (41.2–58)	NA	NA
Secondary end-points				
Safety, daily therapy intensity level (TIL)	7 (6–10)	7 (5–9)	0.882	NA
MAP (mm Hg)	81 (6)	85 (8)	<0.05	0.123
HR (min -1)	69 (12)	96 (12)	0.211	0.838
ICP (mm Hg)	13 (4.7)	12 (8.1)	0.753	0.228
CPP (mm Hg)	68 (4.4)	73 (6.6)	<0.05	<0.05
PRx	0.0331 (0.199)	–0.0417 (0.231)	0.200	0.454
Total ICP/CPP monitoring time, h	71.8 (37.7–104)	61.7 (41.2–105)	0.761	0.498
Neuromonitoring (CPP) interruptions, min	49 (2–141)	55 (8–109)	0.404	0.281
CPP target value (mm Hg)[c]	NA	70 (66–75)	NA	NA
CPPopt trendline value (mm Hg)[d]	69 (67–73)	72 (66–77)	0.448	<0.05
CPPopt trendline yield (%)[e]	73.9 (18.5)	76.6 (16.5)	0.564	0.378
Percent time CPP concordant with the CPPopt trendline value[d] ±5 mm Hg	36 (31.4–46.7)	42.6 (35.4–51.8)	0.150	0.976
Percent time CPP >70 mm Hg	30.7 (23–46.6)	64.9 (44–82.5)	<0.001	0.077

Table 2 | Primary and Secondary Outcomes (continued)

Mean (SD) or median (IQR)	CPP control (*n* = 28)	CPP intervention (*n* = 32)	p value[a]	p value[b](for variance)
Percent time CPP <60 mm Hg	11.7 (5.46–21.5)	6.71 (1.5–10.4)	<0.05	0.745
Percent time CPP target concordant with 60–70 mm Hg range	NA	37.9 (18.2–58.3)	NA	NA
GCS score at ICU discharge, *n* (%)				
Dead	11 (39)	7 (22)	0.160	NA
3–5	1 (4)	0 (0)		
6–8	2 (7)	3 (9)		
9–12	9 (32)	8 (25)		
13–15	5 (18)	14 (44)		
GOS, 6-month outcome, *n* (%)[f]				
Dead (%)	12 (44)	7 (23)		
Favorable outcome, GOS[g] 4–5	9 (34)	15 (50)		

[a]Unpaired sample *t*-test, Mann-Whitney *U* test, or chi-squared or Fisher's exact test was used.
[b]Levene's test was used to test equality of variances between groups.
[c]CPP target. At a review alert, a CPP target was set by the clinical team either by adopting the recommended CPPopt or by taking a "clinical" CPP target.
[d]CPPopt trendline is the 1-minute updated CPPopt over time.
[e]Calculated as the percentage of time CPPopt was available given the CPP value being present.
[f]The number of outcome values missing were one in the control group and two in the intervention group.
[g]Statistics are added in Suppplementary Figure S7.
SD, standard deviation; IQR, interquartile range; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; HR, heart rate; ICP, intracranial pressure; PRx, pressure reactivity index; CPPopt, optimal cerebral perfusion pressure; GCS, Glasgow Coma Scale; ICU, intensive care unit; GOS, Glasgow Outcome Scale; NA, not applicable.

Feasibility end-point

In the intervention group, CPPopt-based software recommendations were provided in 74% of the 552 reviews (i.e., no CPP targets were given in 26% of the reviews, where the clinicians were to choose an appropriate "clinical" target until the next review; Table 1). Figure 2 shows the distribution of the CPP recommendations and final CPP targets in the intervention group (with the individual CPP targets and distributions over time in Fig. 3 and Supplementary Fig. S4). The number of deviations from the CPP recommendations in both groups was low (control 6.8% vs. intervention 8.3%, respectively; Table 1).

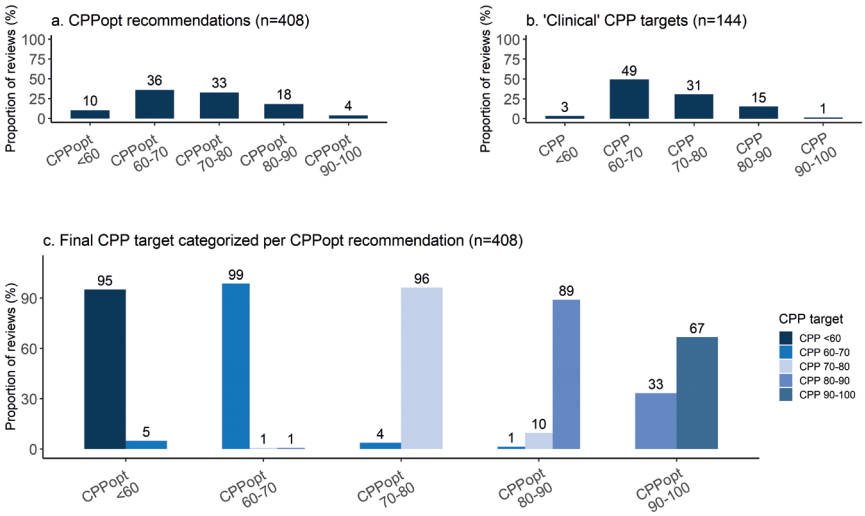

Figure. 2 | Six times daily CPP review recommendations and targets for the intervention group. In total, 552 reviews were done in the intervention group. The software suggested a CPPopt in 74% of the reviews (*n* = 408 reviews; median CPP, 71 [IQR, 64–78] mm Hg). The clinical team adopted this target in 92% of the reviews or rejected this recommendation (8%). In 26% of the reviews, the software was not able to provide a CPPopt. In this case, the clinical team had to choose a "clinical" CPP target for the upcoming period (*n* = 144 reviews; median CPP, 66.5 [IQR, 65–74] mm Hg). (**A**) Distribution of all CPPopt recommendations. (**B**) Distribution of the "clinical" CPP target recommendations. (**C**) The final CPP targets set by the clinical team when a CPPopt recommendation was available (*n* = 408). The adjacent bars per CPP category present the percentage (%) of review recommendations adopted and rejected (together, 100%). Figure 2 was constructed in R (R Foundation for Statistical Computing). CPP, cerebral perfusion pressure; CPPopt, "optimal" CPP; IQR, interquartile range.

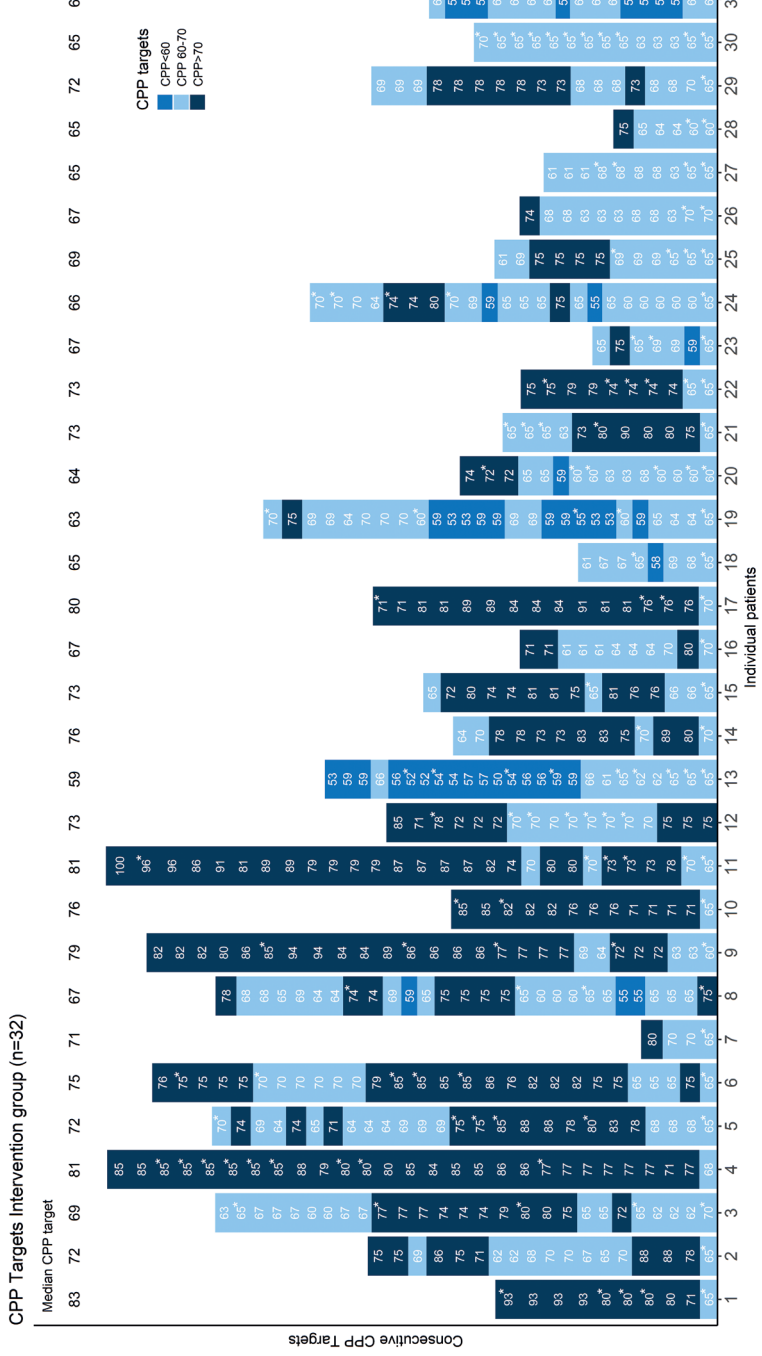

Figure 3 | CPP targets in individual patients over time. The individual CPP targets (updated six times a day) for patients randomized to the intervention group are shown over time. Each bar represents a patient. The CPP targets are grouped by three colors: 1) below 60 mm Hg (blue); 2) above 70 mm Hg (dark blue); or 3) within 60–70 mm Hg (light blue). Numbers in the bars represent the specific CPP targets. "Clinical" targets are marked with an asterisk (*). Median CPP target values for each individual are shown on top. Seventeen patients (53%) had a median CPP target outside the BTF CPP guideline (60–70 mm Hg) range. BTF, Brain Trauma Foundation; CPP, cerebral perfusion pressure.

The median CPP target was 70 mm Hg (IQR, 66–75) in the intervention group. In 37.9% (IQR, 18–58) of the time, the target was within the BTF CPP range (Table 2 and Supplementary Table S1). The median CPPopt trendline was slightly higher in the intervention group (control 69 [IQR, 67–73] vs. intervention 72 [IQR, 66–77] mm Hg; $p = 0.448$). In the intervention group, patients spent 46.5% (IQR, 41.2–58) of the monitoring time with CPP concordant with the set CPP targets. This is significantly higher than the powered 36% ($p < 0.001$; Table 2 and Supplementary Table S2). Table 2 and Supplementary Table S2 show the between-group comparisons of the retrospectively available CPPopt trendline values. Patients in the intervention group spent more time with their CPP concordant and above the CPPopt trendline ($p = 0.150$ and $p = 0.573$, respectively), but significantly less time below the CPPopt trendline (control 34.6% [IQR, 22.4–43.5] vs. intervention 19.1% [IQR, 13.8–29.3]; $p < 0.001$). Patients in the intervention group spent less time with CPP values <60 mm Hg (control 11.7% [IQR, 5.46–21.5] vs. intervention 6.71% [IQR, 1.5–10.4]; $p < 0.05$), but more time with a CPP >70 mm Hg (control 30.7% [IQR, 23–46.6] vs. intervention 64.9% [IQR, 44–82.5]; $p < 0.001$).

Safety end-points

The median TIL score showed no significant difference between the groups (control 7 [IQR, 6–10] vs. intervention 7 [IQR, 5–9]; $p = 0.882$). Data on individual TIL items are available in Supplementary Table S3. In addition, no significant between-group differences in parameters suggestive for lung, cardiac, and kidney damage were observed (Table 3). Both groups received similar amounts of fluids, and the median daily dose of noradrenaline was comparable between the groups (control 12.2 mg [IQR, 7.42–18.8] vs. intervention 10.4 [IQR, 4.51–20.7]; $p = 0.514$). No significant between-group differences over time were found for any of the secondary end-points, including TIL ($p = 0.245$) and CPPopt ($p = 0.106$; Supplementary Table S4; Supplementary Figs. S5 and S6). Similar numbers of AEs (control 7 vs. intervention 9) and SAEs (control 1 vs. intervention 1) were observed. (Table 3 and Supplementary Table S5).

Outcome

The distribution of 6 months' GOS of both groups is shown in Supplementary Figure S7. Fewer patients died in the intervention group (23%) compared to the control group (44%). None of the outcome results reached statistical significance (Table 2 and Supplementary Figure S7).

Table 3 | Safety Measures during Study Period

Median (IQR)	CPP control (*n* = 28)	CPP intervention (*n* = 32)	p value[a]
Daily creatinine level (µMol/L)[b]	62.2 (52.8–76.5)	64.2 (49.2–59.9)	1.0
Troponin below critical threshold, *n* (%)[c]	18 (64.3)	23 (71.9)	0.725
Troponin above critical threshold, *n* (%)[c]	10 (35.7)	9 (28.1)	
Daily NT-pro BNP (ng/L)[d]	138 (67.1–301)	109 (53–268)	0.641
Highest daily PaO_2/FiO_2 ratio (mm Hg/%)	346 (284–448)	380 (303–461)	0.667
Lowest daily PaO_2/FiO_2 ratio (mm Hg/%)	235 (202–314)	267 (29–387)	0.227
Noradrenaline (mg)	12.2 (7.42–18.8)	10.4 (4.51–20.7)	0.514 0.719[e]
Daily total fluids given (mL)	+1470 (878–2210)	+1330 (1020–2170)	0.784 0.569[e]
Daily net fluid balance (mL)	+860 (397–1370)	+901 (391–1460)	0.784 0.882[e]
Monitoring time with ICP >22 mm Hg (%)	2.25 (1.09–9.71)	1.27 (0.565–4.56)	0.216
Monitoring time with ICP >25 mm Hg (%)	1.19 (0.36–2.42)	0.71 (0.356–2.06)	0.254
Monitoring time with CPP >100 mm Hg (%)	0.0691 (0.0–0.235)	0.401 (0.0–1.16)	0.055
Monitoring time with CPP <50 mm Hg (%)	0.95 (0.239–2.07)	0.261 (0.346–0.778)	<0.05
Adverse events, *n*[f]	7	9	
Serious adverse events, *n*[f]	1	1	

The laboratory and fluid administration values in Table 3 concern median values. The values were first calculated per patient over the intervention period (values collected per day). Then, the study group median values are reported. *n* = number. The control and intervention group had *n* = 107 and *n* = 122 measurement days, respectively.
[a]Unpaired sample *t*-test, Mann Whitney *U* test, or chi-squared or Fisher's exact test was used.
[b]Missing days: control group, 1 day (0.9%); intervention group, 3 days (2.5%). Missing patients, *n* = 0.
[c]High-sensitive troponin, including high-sensitive troponin T and high-sensitive troponin I, were divided in values above/below a critical threshold (high-sensitive troponin T, 14 ng/L; high-sensitive troponin I, 58.1 ng/L (male); 39.6 ng/L (female). Missing patients, 0. Missing days: control group, *n* = 8/107 (7.5%); intervention group, *n* = 9/122 (7.4%).
[d]Missing days: control group, 12 (11%) days; intervention group, 11 (9%) days. Missing patients, *n* = 0.
[e]Levene's test was used to test equality of variances between groups.
[f]The specific adverse events and serious adverse events can be found in the Supplementary Materials, Supplementary Table S5.
IQR, interquartile range; NT-proBNP, N-terminal pro-brain natriuretic peptide; PaO_2/FiO_2, partial pressure of oxygen/ fraction of inspired oxygen ratio; ICP, intracranial pressure; CPP, cerebral perfusion pressure.

DISCUSSION

The current study represents the first RCT evaluating CA-guided CPP management in TBIicp patients. Compared to retrospective pilot data,[11] we showed that patients in the intervention group spent a significantly higher percentage of time with CPP concordant with the set CPP target given by CPPopt. Given that most CPP review recommendations were adopted (>90%), these results demonstrate the feasibility of using CPPopt as a novel digital biomarker for precision medicine in TBIicp management. Safety was demonstrated by a similar between-group TIL scores, number of AEs/SAEs, and biomarkers of organ damage. Although the study was not designed to assess clinical outcomes, we found these to be comparable. The hemodynamic support, represented by the amount of administered fluids and vasopressors use, was (non-significantly) lower in the intervention group, although these patients ended up with significantly higher mean absolute MAP/CPP values. Dynamic CPP targets probably explain the increased CPP variability in patients in the intervention group.

The BTF guideline mentions that TBIicp patients with intact autoregulation are best served by higher CPP values whereas pressure-passive patients with dysfunctional pressure autoregulation do better with lower CPP values.[7] The recent Severe Traumatic Brain Injury Consensus Conference consensus ICP treatment suggests the use of intermittent MAP challenges for CA assessment.[8] This represents an effort to integrate CA into ICP management. However, MAP challenges are infrequent, occupy nursing and medical time, and may provoke ICP elevation when CA is compromised. Further, MAP challenges are only likely to be undertaken when ICP control is a problem, which neglects the optimization of CPP as a continuous parameter. PRx offers a more, dynamic, safe, automated, and repeated evaluation of CA. Perhaps most critically, the protocol we suggest moves CA-related management beyond just a means of ICP control, to ensuring optimal physiology and wider beneficial impact on outcome. Moreover, PRx requires only invasive ICP and MAP for its calculation. However, this also implies that PRx values may be unreliable after periods with limited MAP fluctuations. This presumed effect might have contributed to CPPopt trendline values not being available in ~25% of the monitoring time (Table 2).

Mean CPP in the intervention group was 73 (SD, 6.6) mm Hg. However, mean values might mask intra- and interpatient variability over time as shown by the individual target distribution (Fig. 3), increased CPP variability (Table 2), and large proportion of time with CPP targets outside the BTF guideline range in the intervention group (Supplementary Table S1). We postulate that these

individual dynamic targets allow continuous fine-tuning of perfusion pressure, potentially leading to outcome benefit. Both groups spent <1% of the monitoring time with a CPP outside our pre-defined safety ranges (50–100 mm Hg), which is reassuring. These periods were attributed to drops in arterial blood pressure (ABP) given that ICP was, on average, well controlled in both groups (Table 3). Patients in the intervention group spent significant less time with their CPP below the CPPopt trendline and below the CPP threshold of 60 mm Hg (group difference of 15.5% and 5%, respectively). In the intervention group, the chosen CPP target was in only 37.9% (IQR, 18.2–58.3) of the monitored time between 60 and 70 mm Hg (Table 2 and Supplementary Table S2). This supports the potential benefits of our intervention protocol.

Other retrospective TBIicp analyses demonstrated that impaired CA reduces the tolerability for low CPP and high ICP.[18–21] On average, CPP targets <60 mm Hg were less common (10%; Fig. 2) compared to targets ≥70 mm Hg (55%; Fig. 2). This might indicate that TBIicp patients indeed need (on average) higher CPP targets. An alternative explanation is that our understanding of CA and its monitoring are both imperfect. Tzeng and colleagues hypothesized that the CA may be better adapted to compensate for increasing than for decreasing MAP.[22] Moreover, animal studies have described less clear or more variable (individualized) upper CA limits.[23,24]

Multimodality neuromonitoring allows for a better understanding of the pathophysiology and therefore for the application of individualized, targeted treatments in TBIicp patients.[1,25] Large RCTs are underway to prove the clinical benefit of using combinations of monitoring signals and/or physiological concept protocols. The Brain Oxygen Optimization in Severe TBIicp phase-II (BOOST-II) multi-center RCT reported that $PbtO_2$ augmentation could be safely implemented in patients where such monitoring was available. Interventions to optimize CPP were restricted to the ICP and $PbtO_2$ group only, showing parallels to our intervention study.[26] The main difference is that in COGiTATE, the CPP management target was generated using an automated, dynamically adaptive algorithm as opposed to fixed, pre-defined thresholds.

Although the difference in CPP between the intervention and control groups was small across the study population, this does not exclude the possibility that, at an individual level, CA-guided CPP management results in a more individualized treatment given that we know that the CA varies substantially between patients and over time.[27] Given that the study centers have a history of using CPPopt in clinical research settings, it is also possible that these institutions already tend to target higher CPP values (i.e., closer to 70 mm Hg) in control patients. Our study set out to examine feasibility and safety

end-points. A detailed examination of the effect of CA-guided management on neurological recovery or suitable surrogate outcome will require further prospective, randomized studies.

Our study has limitations. First, our sample size limits conclusions about physiological interactions, organ complications, and outcome results. Second, both groups still spent a considerable amount of time away from the CPP target (±5 mm Hg) or outside the BTF target range. This is likely related to the lack of a continuous feedback about significant deviations from the target to the nursing team.[28] Adding a continuous feedback may improve the percentage of time CPP concordant with CPPopt and probably the clinical relevance of the therapy. Third, our study was necessarily not blinded, and the outcome assessors were aware of the group assignment. Fourth, in the intervention group, in 26% of the reviews CPPopt was not available. This is a limitation of the current methodology.[29] Fifth, we did not treat the patients according to a standardized hemodynamic management protocol. Sixth, we noticed a considerable delay before starting the intervention protocol after trauma ictus in both groups (Supplementary Fig. S3). For a phase II study, this is less important, but in a phase III study, the delay between ICU admission and start intervention can be minimized with application of a deferred consent procedure in all eligible patients.[30,31] Seventh, the study was performed in centers with experience in ICM+ research software. This limitation has to be taken into account with future study setup in less-experienced centers. Finally, the software used in the intervention protocol is labeled as research software and therefore not commercially available for clinical purposes. Our study also has several unique strengths. The study protocol was pre-specified,[11] with a pragmatic design to test, for the first time, the interaction between a software algorithm and clinical team at the bedside six times daily. This innovative approach was studied in four centers with different clinical teams involved over the 24-h patient care. No additional invasive monitoring was required. Lastly, we limited our protocol to a maximum of 5 days to overcome the over-representation of certain patients in the analysis.

CONCLUSION

Individualizing care by targeting a dynamic optimal CPP using CA guidance six times daily is feasible and safe in TBIicp patients. These findings encourage a larger phase III outcome study of this novel digital biomarker for precision medicine in these patients.

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Authors' Contributions
All authors contributed to the study conception and design. Material preparation and data collection by Jeanette Tas, Erta Beqiri, Ruud C. van Kaam, Analisa L. Liberti, C.W.E. Hoedemaekers, Bart Depreitere, Peter Smielewski, Ari Ercole, David K. Menon, Geert Meyfroidt, and Marcel J.H. Aries. Data analysis was performed by Jeanette Tas, Erta Beqiri, Marek Czosnyka, Sander M.J. van Kuijk, David K. Menon, Peter S. Smielewski, Ari Ercole, and Marcel J.H. Aries. The first draft of the manuscript was written by Jeanette Tas and Marcel J.H. Aries, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY APPENDIX S1. Supplementary explanation of the intervention protocol

In this supplemental document a background of CPPopt, a summary of items from the published study protocol and in depth description of certain analysis are provided that supports the methodological section in the main article. The full study protocol can be found here with a link to the publication.[1] The described items are:

- Panel summarizing background and calculation of PRx, CPPopt and the CPPopt trendline
- Ethics approval
- Sample size calculation
- Patient randomization tool
- Clinical outcome follow-up
- Hemodynamic protocol
- Additional cerebral monitoring
- Termination of the intervention protocol
- CPP target recommendation
- Primary feasibility endpoint
- Secondary endpoints
- Longitudinal analysis (LME)
- Outcome model (proportional odds logistic regression model)

Panel summarizing background and calculation of PRx, CPPopt and the CPPopt trendline

Cerebrovascular pressure reactivity was studied by observing the effects of changes in arterial blood pressure slow waves (ABP) on intracranial pressure slow waves(ICP).[2] Trends in the cerebrovascular pressure reactivity are closely related to global changes in cerebral autoregulation.[3] Knowing the physiological model is important to understand the clinical concept of cerebral autoregulation guided CPP treatment in traumatic brain injury (TBI) patients. In three figures the clinical concept is visualized.

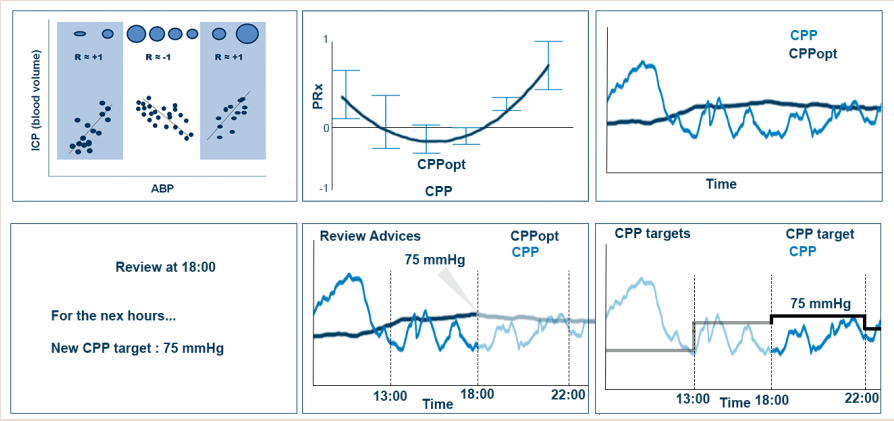

Figure appendix a-f

(Figure a) *PRx*: The Pressure Reactivity index is the statistical Pearson correlation between 10 sec averaged values of ABP and ICP over a 5-minute calculation window. The Pearson correlation index is updated every minute to provide a (moving) trend value. A negative PRx value indicates an intact cerebral autoregulation as slow increases in ABP are counteracting ICP by active vasoconstriction (Figure a, middle panel). A positive value indicates impaired cerebrovascular pressure reactivity as slow changes in ABP are passively followed by changes in ICP.[2] Both vasoconstriction (Figure a, left panel) and vasodilatation (Figure a, right panel) cannot control cerebral blood volume/flow and therefore ICP. A positive PRx is found.

(Figure b) *CPPopt*: The 'optimal' cerebral perfusion pressure concept was introduced in 2002. In a retrospective TBI cohort Steiner et al. showed that over a monitoring period of days plotting the PRx values against CPP showed a U-shaped curve. The nadir of the U-shape curve represents the CPP value for which PRx is minimal, and therefore cerebral autoregulation is best preserved.[4] Aries et al. extended this concept with a curve fitting algorithm that calculates automated CPPopt values over a 4- hourly moving time window (Figure b). They showed that individual CPP deviations from CPPopt were related to poor outcome in TBI patients.[5]

(Figure c) *CPPopt trendline:* Liu et al. added multiwindow and weighted features to the CPPopt algorithm that improved the availability and stability of individual CPPopt values at the bedside (Figure c).[1,6]

(Figure d-f) *CPPopt –Module:* The ICM+ software was further extended with the implementation of a customized research module that presents a CPPopt value on a review screen at set time-points. The CPPopt value presented in the review screen (Figure d) is the CPPopt value extracted from the CPPopt trendline (Figure e) at that specific timepoint (referred to as 'CPP target'). This CPP value is the target value to follow-up to the next review (Figure f). No CPP recommendation is provided when (1) no CPPopt value can be calculated or (2) the CPPopt value is outside the pre-defined safety ranges (50 > CPPopt >100). Then the clinician decides which CPP target to follow (referred to as 'clinical target').

Screenshots of the research module are shown in Supplementary Figure S1.

Ethical approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Coordinating center in Maastricht by Ethics Committee of Maastricht University Medical Center (29 December 2017/METC171023). Local approval and feasibility was granted by the Health Research Authority National Health System United Kingdom (30 October 2017, Research Ethics Reference 17/LO/119), the Ethics Committee of Academic Hospital Leuven (9 January 2018 B322201834820) and Ethics Committee of Radboud University Medical Center (20 February 2019 RvB19.51633).

Sample size calculation details

The study was powered using retrospective data from TBI patients. Retrospectively, we observed a target adherence of 30%, meaning that on a group level the CPP was on average concordant with CPPopt (± 5 mmHg) in 30% of the monitoring time. We expected a pragmatic relative increase of 20% resulting in a percentage of time concordant ± 5 mmHg CPP target from 30% to 36% (SD 8%). With an alpha of 5% and beta of 20% (power estimate of 80%), the estimated number of patients needed for the primary endpoint was 56. This number was increased to 60 to allow for drop-out, technical problems or need for a non-parametric analysis. The PWR library in R was used for the power calculation.[1,7]

Patient randomization tool

In our study we used a centralised electronic randomisation system that was incorporated in our electronic case report form (eCRF). An automatic email was sent to the central coordinator of the study in Maastricht with every new randomisation. Block randomisation, with stratification according to trial site, was used to ensure a uniform patient distribution.

Clinical outcome follow-up

Neurological outcome on the intensive care unit was assessed by the clinician prior to discharge to the ward in surviving patients using the Glasgow Coma Scale (GCS). Six-month neurological outcome was assessed using the Glasgow Outcome Scale (GOS) according to local TBIicp clinical follow-up strategies by either a physical or a telephone structured interview. Outcome assessors were not blinded of the group assignment.

Hemodynamic protocol

How to get to the CPP targets was left to the discretion of the clinical team. The protocol did not mandate a hemodynamic management policy which prioritised either fluids of vasoactive agents for CPP maintenance, since this had a high likelihood of changing local practice in other ways than either targeting dynamic CPP or BTF targets. This would have meant that we would

be unable to robustly attribute any trial findings to the CPPopt intervention per se (rather than the means used to achieve it).

Additional cerebral monitoring
Additional cerebral monitoring was available according to local protocols but was not part of the study protocol.

Termination of the intervention protocol
The maximum duration of the intervention protocol was 5 days for both groups. Reasons for discontinuing the protocol earlier were: (1) the patient died; (2) ICP monitoring discontinued for clinical reasons; (3) Active treatment withdrawal.

CPP target recommendation
Six-times a day the software algorithm provided a CPP target recommendation. This was either a CPPopt based value or a 'clinical' target for the intervention group. A 'clinical' CPP target was recommended if: (1) the output of the automated CPPopt algorithm was null (no CPPopt target) and (2) the current CPPopt value was out of the set safety range defined as CPP between 50 and 100 mmHg. One important point is that the recommended CPPopt was not allowed to increase or decrease of more than 10 mmHg from the previous target. In the control group the software algorithm recommended the use of the Brain Trauma Foundation CPP guideline target range of 60-70 mmHg.[8]

Primary feasibility endpoint
The primary endpoint of this study is the percentage of CPP monitored time with patients' CPP concordant (± 5 mmHg) with the CPP target. The primary endpoint was calculated for the intervention group patients only. For this analysis, we calculated the percentage of monitoring time (%) each patient had one minute CPP values concordant (± 5 mmHg) with the CPP target. Monitoring time was defined as the period with CPP values being available from the first review till the termination of the intervention protocol (see above). The period till the first review was not used as during this period the protocol advised to target 60-70 mmHg in both groups.

Secondary safety endpoint calculation
The main secondary safety endpoint was powered to detect an average daily TIL score difference of > 3 between the groups as evidence for escalation of intracranial hypertension therapy. While designing the study we took into account that patients in the intervention group might require more CPP interventions to finetune CPP targets. This might lead to more fluid loading and vasopressor administration for maintenance of cerebral perfusion (each 1 point in TIL score). Therefore, a difference of 2 was expected and hence a difference of daily TIL ≥ 3 was thought as excess use of therapies for TBI management. As additional

secondary analysis, we calculated, for both the intervention and control group, the percentage of time (%) each patient had CPP values concordant with (± 5 mmHg) the CPPopt trendline. The CPPopt trendline was for both groups retrospectively available (see Figure 1 in main manuscript).[9]

Longitudinal analysis (LME)

We performed different longitudinal analysis to evaluate temporal profiles for variables of interest. *CPPopt* One possible clinical concern is that CPPopt guided therapy may drive ever-increasing CPPopt values over time.[10] Therefore, we explored the between-group difference in time course of CPPopt by fitting the one-hour average CPPopt trendline values using a linear mixed effect model (LME, R-package *nlme*)[11] with 'patient' and 'time (hours)' as random intercept and random slope, respectively and 'CPPopt trendline', 'time (hours)' and 'randomisation group' as fixed effects. We included the interaction term 'time*group' to assess differences in trajectory over time between the groups. *Safety measures* We explored the time course of daily creatinine level, troponin I, troponin T, NT-proBNP, highest daily PaO2/FiO2 ratio, lowest daily PaO_2/FiO_2 ratio, noradrenalin, PRx, daily fluids given and daily net fluid balance in both groups. Therefore, in addition to between-group average differences (Table 3), we explored the between-group differences over time using a LME model with 'patient' and 'days' as random intercept and random slope, respectively and 'safety measure', 'day' and 'randomisation group' as fixed effects. We included the interaction term 'time*group' to assess differences in trajectory over time between the groups.

Outcome model (proportional odds logistic regression model)

A proportional odds logistic regression model[12] was constructed to explore the between-group difference in distribution of 6-months GOS clinical outcome (R-package, *MASS*).[13] The Brant function tested the proportional odds assumption (R-package, *brant*).[14,12]

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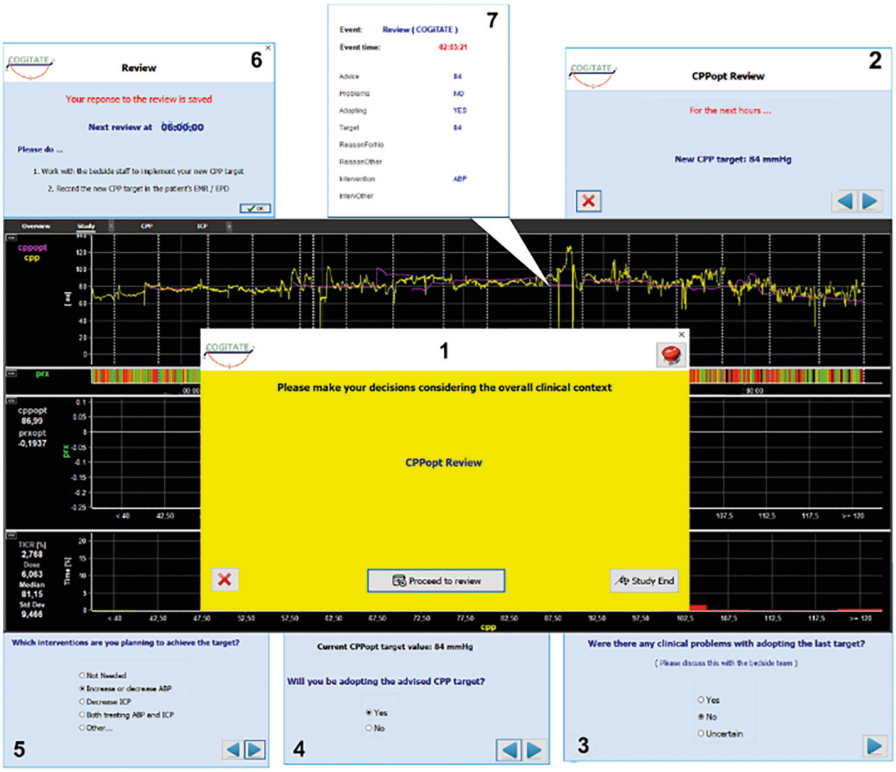
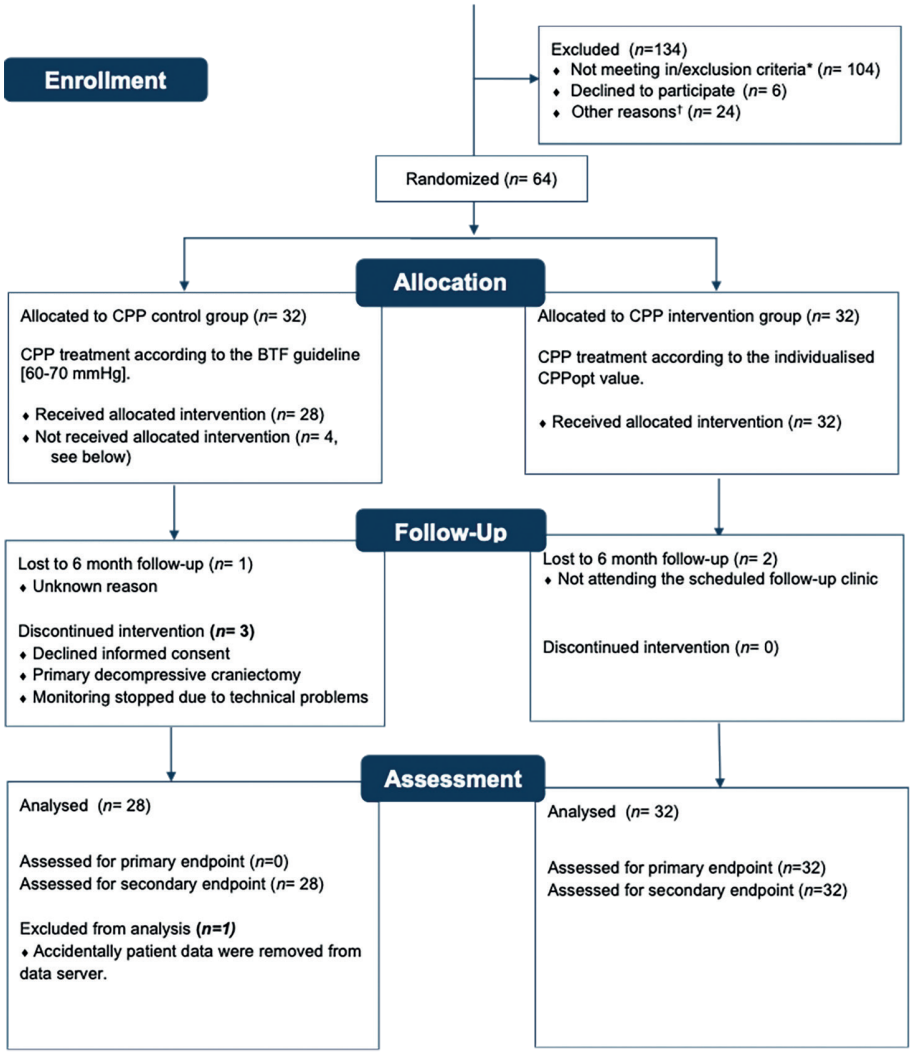
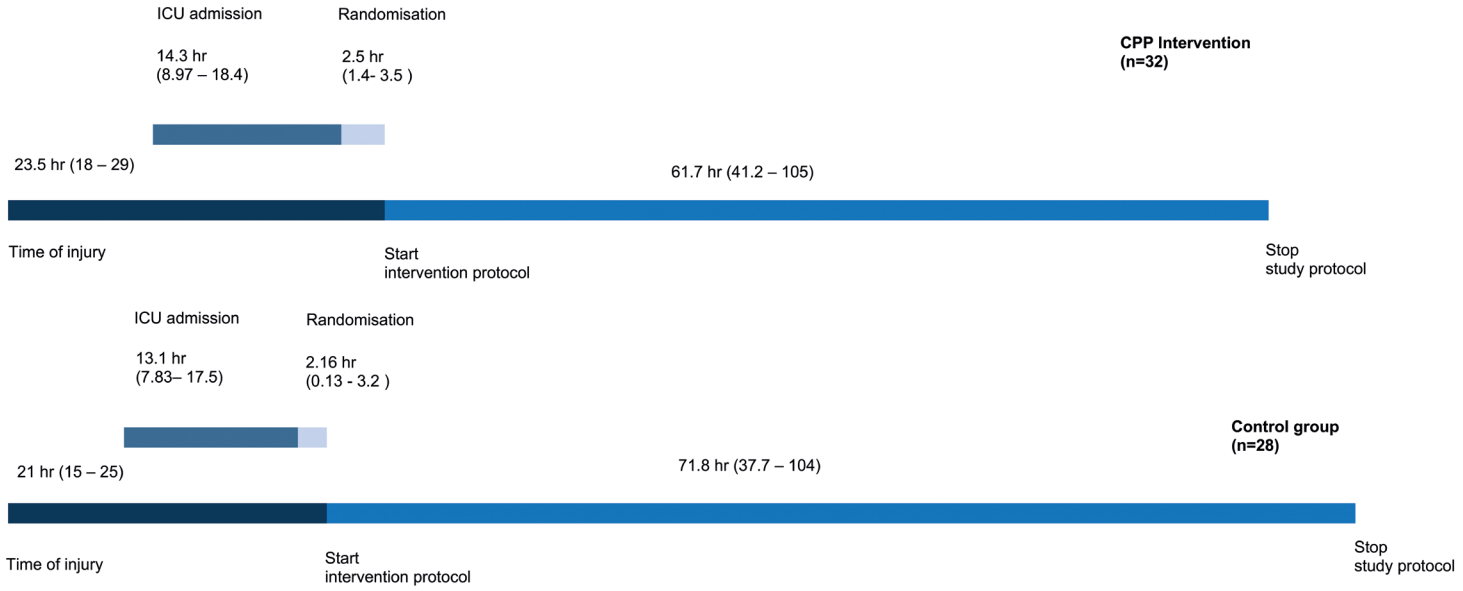


Supplementary Fig. S1 | Example of the different review screens

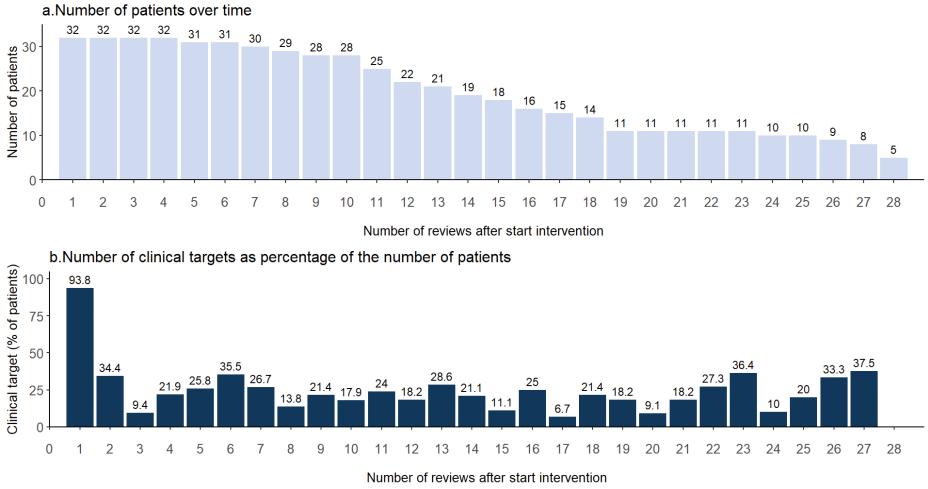
Example of the different review screens from a patient in the intervention group. In the background the neuromonitoring trends are shown. The seven sections in the figure are explained in detail. Six-times a day (section 1) the review alert appeared as a yellow pop-up screen; the CPP target recommendation was presented to the clinical team (section 2) followed by additional questions (section 3-5); after saving the review report, the reviewing clinician was requested to instruct the bedside nursing staff about the new target and record the new target in the electronic patient dossier (section 6); in addition, the report summary was automatically saved in the ICM+ monitoring software. The summary of the review report could be viewed at any time (section 7). CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; ICM+ = Intensive Care Monitoring software; PRx = Pressure Reactivity Index.



Supplementary Fig.S2 | Study flow diagram: Traumatic Brain Injury patients admitted to the intensive care unit. *Reasons for not meeting the inclusion and exclusion criteria (53%) are: age <18 (*n*=5), deemed unsurvivable at presentation (*n*=10), primary or early decompressive craniectomy (*n*=26), no family present for informed consent < 24 hours after ICU admission (*n*=14), estimated duration of ICP monitoring < 24 hour (*n*=21), ICP monitoring started > 24 hour after ICU admission (*n*=9) and patient included in another intervention study (*n*=19). †Other reasons for not including were (12%): no researcher available to set up brain monitoring software (*n*=15), uncertainty of contribution of acute stroke or intoxication to TBI injury (*n*=2), sedation and neuromonitoring mainly for severe agitation (*n*=2), severe hemodynamic instability with active abdominal hemorrhage (*n*=1), planned decompressive craniectomy not performed within 24 hour from ICU admission (*n*=1), technical maintenance of monitoring capacities (*n*=3). ICU = intensive care unit; TBI = traumatic brain injury; ICP = intracranial pressure; BTF = Brain Trauma Foundation



Supplementary Fig. S3 | Study timeline. Timeline from trauma ictus until study completion. The timeline starts with the estimated time of trauma (from admission notes) followed by time of ICU admission and study randomisation. Randomisation time is the time that the patient was randomised in the eCRF. During the first period after randomisation, the protocol recommended for both groups to target a CPP value between 60-70 mmHg. 'Start intervention' is the moment that the first CPP target recommendation was provided by the software algorithm. Figure constructed in MATLAB (Release 2019b, The MathWorks, Inc., Natick, Massachusetts, United State. CPP = cerebral perfusion pressure; ICU = intensive care unit; eCRF = electronic case record form.



Supplementary Fig. S4 | Extended information regarding patient numbers and percentage of 'clinical' CPP targets per review period in the intervention group.a. The total number of patients per consecutive review period in the intervention group are depicted. The duration between the reviews is approximately 4 hour. b. The percentage of CPP recommendations with a 'clinical target', expressed as the percentage of the CPP recommendations per review period. The algorithm required at least 4 hours of continuous data before the first CPPopt recommendation becomes available. The first period after randomisation was in most cases shorter than 4 hours explaining the high percentage of 'clinical targets' (93.8%) during the first review.[1]

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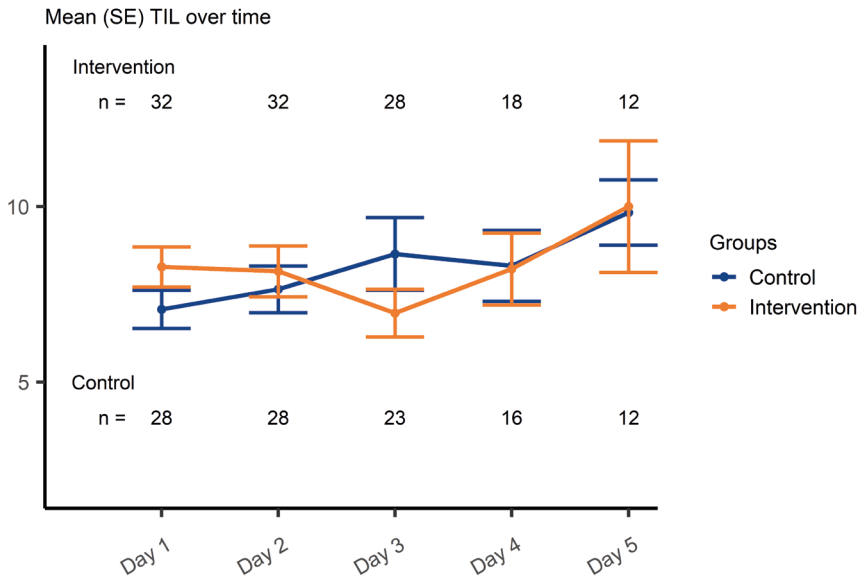
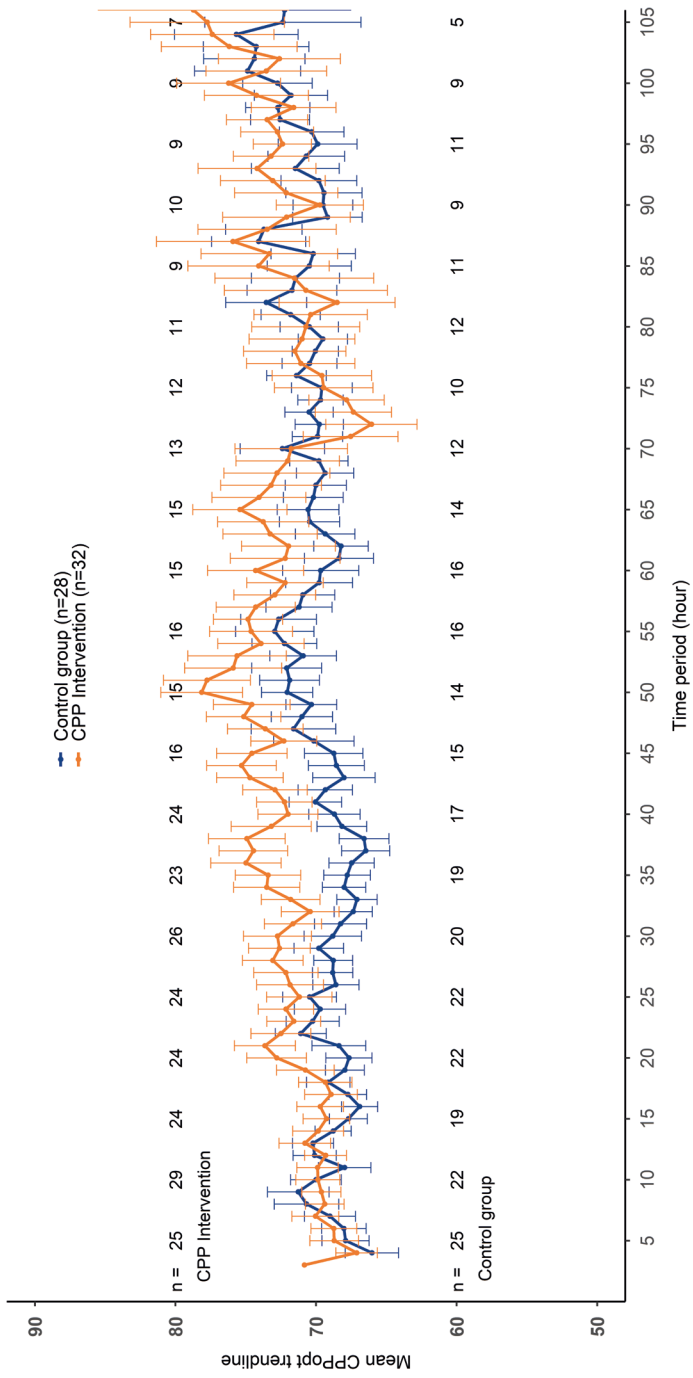
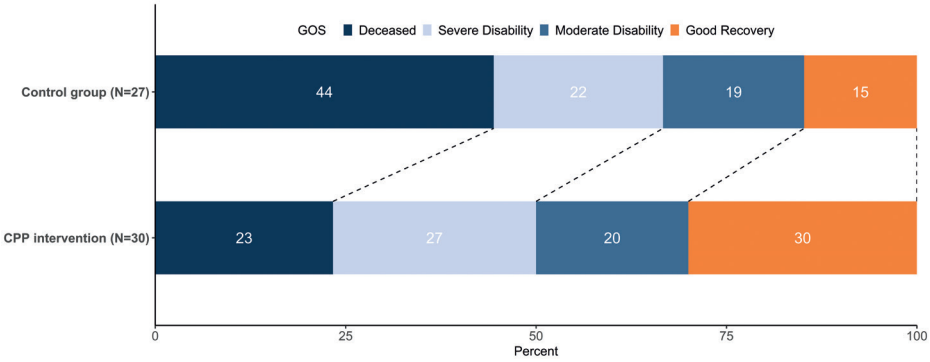


Supplementary Fig. S5 | Therapy Intensity Level (TIL) over time**.** Therapy Intensity Level (TIL) score was depicted over time. During the intervention period the daily TIL score was collected. The trajectories of the TIL for both randomization groups are presented. The number of patients (*n*) that contribute to the median values for each day are put above and below the error bars (with median and interquartile ranges). The result of the linear mixed effect model (LME) showed that the interaction term 'group * time' did not show a significant influence and was not included in the final LME model (RC -0.35 (95%-CI -1; 0.302), *p*=0.291). Overall, the slope was not different for the groups (RC 0.94 (-0.67; 2.56), *p*=0.245), with the control group as the reference. Figure constructed in R (R-Core Team, version 4.0.3). RC = regression coefficient; 95%-CI: 95%-confidence interval.



Supplementary Fig. S6 | CPPopt values over time. CPPopt trajectory is visualized with one hour average (± standard error) CPPopt values over time. The CPPopt trendline was prospectively available for the intervention group (*n*=32) and retrospectively for the control group (*n*=28). Above and below the trendlines the number of patients that contribute to a certain CPPopt value are noted. The result of the linear mixed effect (LME) model shows that the interaction term 'group * time' did not show a significant influence and was not included in the final model (RC 0.004 (95%-CI -0.09; 0.090), *p*=0.928). Overall, the slope was not different for the groups (RC 2.17 (95%-CI -0.48; 4.8), *p*=0.106), with the control group as the reference. Figure constructed in R (R-Core Team, version 4.0.3). RC= regression coefficient, 95%-CI = 95%-confidence interval.



Supplementary Fig. S7 | Glasgow Outcome Scale at six-months follow-up. At six months after randomisation, the distribution of GOS is presented as a bar chart with following categories: deceased (GOS=1), severe disability (GOS=3), moderate disability (GOS=4) and good recovery (GOS=5). No patients were assigned as with a vegetative state (GOS=2). The number of outcome values missing were 1 in the control group and 2 in the intervention group. The proportional odds logistic regression model showed a non-significant difference in distribution between groups with an odds ratio of 2.35 (95%-CI 0.9 – 6.12) for improved outcome (χ^{-2} *test, p*=0.08). The proportional odds ratio assumption was confirmed to be valid. Figure constructed in R. GOS = Glasgow Outcome Scale; 95%-CI = 95%-confidence interval.

Supplementary Table S1 | CPP targets compared to the Brain Trauma Foundation CPP guideline

Median (IQR)	CPP intervention group (*n*=32)
%time with CPP target within 60-70 mmHg CPP range (%)	37.9 (18.2 - 58.3)
%time with CPP target above 70 mmHg (%)	49.7 (21.9 - 81.8)
%time with CPP target below 60 mmHg (%)	0 (0 – 0)*

*Four patients had values different from 0%. The %time with CPP target below 60 mmHg for these patients were 4%,11%, 42%, 68%, respectively.
CPP = cerebral perfusion pressure

Supplementary Table S2 | Percentage of monitoring time concordant, above or below CPP targets of interest

Median (IQR)	CPP control group (*n*=28)	CPP intervention group (*n*=32)	*p*-value (for effect)*	*p*-value (for variance)†
%time CPP concordant with the CPPopt trendline value‡ ± 5 mmHg (%)	36 (31.4 – 46.7)	42.6 (35.4 – 51.8)	0.150	0.976
%time CPP concordant with the CPP target value§ ± 5 mmHg (%)	NA	46.5 (41.2 – 58)	NA	NA
%time CPP within the 60 - 70 mmHg range (%)	49.6 (42.4 – 58)	30.2 (16 – 43.8)	<0.001	0.271
%time CPP above the CPPopt trendline value + 5 mmHg (%)	22.2 (13.2 – 33.1)	32.3 (23.8 - 43)	0.573	0.507
%time CPP above the CPP target value + 5 mmHg (%)	NA	36.5 (25.4 – 43.4)	NA	NA
%time CPP above 70 mmHg (%)	30.7 (23 – 46.6)	64.9 (44 – 82.5)	<0.001	0.077
%time CPP below the CPPopt trendline - 5 mmHg (%)	34.6 (22.4 – 43.5)	19.1 (13.8 – 29.3)	<0.001	0.191
%time CPP below CPP target - 5 mmHg (%)	NA	15.2 (10.4 - 17)	NA	NA
%time with CPP below 60 mmHg(%)	11.7 (5.46 – 21.5)	6.71 (1.50 – 10.4)	<0.05	0.745

*Mann Whitney *U* test was used.
†Levene's Test was used to test equality of variances between groups.
‡CPPopt trendline is the updated CPPopt values over time.
§Calculated as the percentage of time CPPopt being available given CPP value being present.
‖CPP target. At a review time point a CPP target was set by the clinical team either by adopting the provided CPPopt or by taking a 'clinical' CPP target.
CPP = cerebral perfusion pressure; CPPopt = optimal cerebral perfusion pressure; IQR = interquartile range; NA = not applicable

Supplementary Table S3 | Individual 12 items of Therapy Intensity Level (TIL) score

Number of patients, *n (%)*	Control group (*n*=28)	Intervention group (*n=32)*	*p*-value*
(1) Positioning			
Head elevation for ICP control	28 (100)	31 (97.5)	1.0
Nursed flat (180°) for CPP management	0	1 (2.5)	
(2) Sedation†			
No sedation	1 (3.6)	1(3.12)	1.0
Low dose sedation	3 (10.7)	4 (12.5)	
Higher dose sedation for ICP control	18 (64.3)	21 (65.6)	
High dose propofol or barbiturates for ICP control	6 (21.4)	6 (18.8)	
(3) Neuromuscular blockade			0.482
No	25 (89.3)	26 (81.2)	
Yes	3 (10.7)	6 (18.8)	
(4) CSF drainage			
No	25 (89.3)	30 (93.8)	0.331
CSF drainage-low volume, < 120 mL/day (< 5 mL/h)	0	1 (3.1)	
CSF drainage-high volume, > 120 mL/day (> 5 mL/h)	3 (10.7)	1 (3.1)	
(5) Fluid loading			
No	21(75)	24 (75)	1.0
Yes	7 (25)	8 (25)	
(6)Vasopressor therapy			
No	1 (3.6)	2 (6.3)	
Yes	27 (96.4)	30 (93.8)	
(7)Ventilatory management			
Normocapnia (>5.3 kPa)	6 (21)	6 (18.8)	1.0
Mild hypocapnia (4.6-5.3 kPa)	15 (54)	16 (50)	
Moderate hypocapnia (4.0-4.5 kPa)	7 (25)	9 (28)	
Intensive hypocapnia (< 4 kPa)	0	1 (3.1)	
(8) Mannitol bolus infusion			
No	25 (89.3)	30 (93.8)	0.794
≤ 2g/kg/24h	1 (3.6)	0 (0)	
> 2g/kg/24h	2 (7.1)	2 (6.3)	

Supplementary Table S3 | Individual 12 items of Therapy Intensity Level (TIL) score (continued)

Number of patients, *n (%)*	Control group (*n*=28)	Intervention group (*n=32)*	*p*-value*
(9) Hypertonic bolus saline infusion			
Not received	24 (85.7)	27 (84.4)	0.578
≤ 0.3g/kg/24h	3 (10.7)	5 (15.6)	
> 0.3g/kg/24h	1 (3.6)	0 (0)	
(10)Temperature control			
No	18 (64.3)	23 (71.9)	0.872
Treatment of fever (T>38°C) or spontaneous T<34.5°C	5 (17.9)	4 (12.5)	
Cooling for ICP control (≥35°C)	3 (10.7)	4 (12.5)	
Hypothermia (<35°C)	2 (7.1)	1 (3.1)	
(11) Intracranial operation during intervention period			
No	27 (96.4)	31(96.9)	1.0
Yes	1(3.6)	1(3.1)	
(12) Decompressive craniectomy during intervention period			
No	26 (92.9)	29 (90.6)	1.0
Yes	2 (7.1)	3 (9.4)	

* Chi-squared or Fisher exact test was used.
The numbers presented are calculated as follows: First, the presented numbers are calculated as the median value per patient over the intervention period; Second, the frequencies (%) of these median values are represented per TIL item. Exceptions are item 11 and 12 as these frequencies (%) include the total number of operations performed during the intervention period.
† Low sedation means 'as required for mechanical ventilation'; 'Higher dose sedation for ICP control' means not aiming for burst suppression; 'High dose propofol or barbiturates used for ICP control' includes therapy to achieve metabolic suppression.
TIL = therapy intensity level score; ICP = intracranial pressure; CSF = cerebral spinal fluid; CPP = cerebral perfusion pressure; T = temperature

Supplementary Table S4 | Longitudinal analysis for safety parameters

Variables	Regression coefficient (95%-confidence interval) *Group difference (reference = control)*	*p*-value	Regression coefficient (95%-confidence interval) *Interaction 'group' * 'time' (reference = control)*	*p*-value
TIL score	0.94 (-0.67; 2.56)	0.245	-0.35 (-1; 0.302)	0.291
PRx	-0.06 (-0.17; 0.06)	0.318	-0.00094 (-0.0; 0.0)	0.457
Creatinine level (µMol/L)*	-6.6 (-18.2; 5.07)	0.264	-1.56 (-9.13; 6.02)	0.685
Troponin T (ng/L)†	-8.9 (-40.2; 22.4)	0.572§	9.23 (-13.0 ; 31.5)	0.419
Troponin I (ng/L)‡	-11.4 (-35.4; 12.6)	0.332§	14.3 (-0.83; 29.5)	0.063
NT-pro BNP (ng/L)	13.7 (-324; 352)	0.936	45.2 (-44.1;134)	0.319
Highest daily PaO_2/FiO_2 ratio (mmHg/ %)	21.6 (-38.1; 82.2)	0.473	-2.7 (-29.1; 23.7)	0.840
Lowest daily PaO_2/FiO_2 ratio (mmHg/ %)	20.4 (-31.6; 72.4)	0.436	1.57 (-18.8; 21.9)	0.879
Noradrenalin (mg)	-0.049 (-5.51; 5.41)	0.986	-0.30 (-3.5; 2.9)	0.853
Daily fluids given (ml)	78.8 (-399; 556)§	0.743§	-16.3 (-226; 194)	0.879
Daily net fluid balance (ml)	136 (-211; 483)	0.437	-35.8 (-317; 245)	0.802

The results of the linear mixed effect (LME) models showed that the interaction terms (group*time) - indicating a different trajectory over time between the groups – was not significant for any of the tested variables and therefore not including in the final model. The variables have time in days except from PRx which has time in hours. In the final model, none of the variables showed a difference in regression coefficients indicating similar trajectories of safety parameters in both groups.

* Missing days: Control: 1 day (0.9%), Intervention: 3 days (2.5%). Missing patients *n*=0.

† High Sensitive Troponin T was used in three centres (Control *n*=19; Intervention *n*=21). Missing patients: *n*=0; Missing days: Control *n*=7 (9.6%); Intervention *n*=7 (9.3%).

‡ High Sensitive Troponin I was used in one centre (Control *n*=9; Intervention *n*=11). Missing patients: *n*=0. Missing days: Control *n*=1 (2.9%); Intervention *n*=2 (4.3%).

Note: Control *n*=27 (79%); Intervention *n*=41 (87%) values were '0' indicating a High Sensitive Troponin I value < 17.

NA = not applicable; TIL = therapy intensity level; PaO_2/FiO_2 ratio = partial pressure of oxygen/ fraction of inspired oxygen ratio.

Supplementary Table S5a | Adverse- and serious adverse events during intervention period

Categories	CPP control group (*n*=28)	CPP intervention group (*n*=32)
AE		
Neurological	1	4
Pulmonary	2	3
Cardiovascular	2	2
Gastro-intestinal	2	0
Nephrological	0	0
SAE		
Cardiovascular	1	1
Total number	8	10

The total number of adverse events (AE) and serious adverse events (SAE) per organ system were scored during the intervention period (maximal 5 days) on the intensive care unit.

Supplementary Table S5b | Predefined adverse events (AE) during the intervention period

Neurological	Central nervous system infection (proven by culture and treated with antibiotics)
	Hyponatraemia (SIADH/CSWS/iatrogenic)
	Hypernatremia (central diabetes insipidus/iatrogenic)
	(any) Seizures
	New diagnosed motor weakness (focal/general)
Pulmonary	Haematothorax
	Pneumothorax
	Pneumonia (proven by culture and treated with antibiotics)
	Adult Respiratory Distress Syndrome
Cardiovascular	Myocardial ischaemia (diagnosed by cardiologist)
	Aortic dissection
	Major intrathoracic hemorrhage, needing > 1unit packet cell transfusion
	Limb ischemia
	Infectious endocarditis
	Cardiac tamponade
	Heart failure (diagnosed by cardiologist)
	New arrhythmias (requiring treatment)

Supplementary Table S5b | Predefined adverse events (AE) during the intervention period (continued)

Gastro-intestinal	Intestinal perforations
	Ileus (mechanical or paralytic)
	Pancreatitis
	Hepatitis
	Peritonitis
	Abdominal hemorrhage, needing >1 unit packed cell transfusion
	Acute or acute on chronic liver failure
	Cholecystitis/cholangitis (proven by culture and treated with antibiotics)
Nefrological	Acute Kidney Injury defined as stage 2 or 3 according to KDIGO criteria
	Any renal replacement therapy
	Urinary tract infections (proven by culture and treated with antibiotics)
Other	Vascular catheter-related bloodstream infections (proven by culture)
	Pressure sores (decubitus)
	Skin infections
	Bacteriaemia (proven by culture) without focus

The predefined adverse events (AE) that were listed and reported during the study period (maximum five days). SIADH = syndrome of inappropriate antidiuretic hormone; KDIGO = kidney disease improving lobal outcome guideline; CSWS = cerebral salt wasting syndrome

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5

Inducing Oscillations in Positive End-Expiratory Pressure Improves Assessment of Cerebrovascular Pressure Reactivity in Patients with Traumatic Brain Injury

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**J Tas and KDJ Bos contributed equally to this work.*

ABSTRACT

The cerebral pressure reactivity index (PRx), through intracranial pressure (ICP) measurements, informs clinicians about the cerebral autoregulation (CA) status in adult-sedated patients with traumatic brain injury (TBI). Using PRx in clinical practice is currently limited by variability over shorter monitoring periods. We applied an innovative method to reduce the PRx variability by ventilator-induced slow (1/min) positive end-expiratory pressure (PEEP) oscillations. We hypothesized that, as seen in a previous animal model, the PRx variability would be reduced by inducing slow arterial blood pressure (ABP) and ICP oscillations without other clinically relevant physiological changes. Patients with TBI were ventilated with a static PEEP for 30 min (PRx period) followed by a 30-min period of slow [1/min (0.0167 Hz)] +5 cmH_2O PEEP oscillations (induced (*i*PRx period). Ten patients with TBI were included. No clinical monitoring was discontinued and no additional interventions were required during the *i*PRx period. The PRx variability [measured as the standard deviation (SD) of PRx] decreased significantly during the *i*PRx period from 0.25 (0.22–0.30) to 0.14 (0.09–0.17) (P = 0.006). There was a power increase around the induced frequency (1/min) for both ABP and ICP (P = 0.002). In conclusion, 1/min PEEP-induced oscillations reduced the PRx variability in patients with TBI with ICP levels <22 mmHg. No other clinically relevant physiological changes were observed. Reduced PRx variability might improve CA-guided perfusion management by reducing the time to find “optimal” perfusion pressure targets. Larger studies with prolonged periods of PEEP-induced oscillations are required to take it to routine use.

NEW & NOTEWORTHY Cerebral autoregulation assessment requires sufficient slow arterial blood pressure (ABP) waves. However, spontaneous ABP waves may be insufficient for reliable cerebral autoregulation estimations. Therefore, we applied a ventilator “sigh-function” to generate positive end-expiratory pressure oscillations that induce slow ABP waves. This method demonstrated a reduced variability of the pressure reactivity index, commonly used as continuous cerebral autoregulation measure in a traumatic brain injury population.

INTRODUCTION

Cerebral autoregulation (CA) is the cerebral mechanism to adapt cerebrovascular resistance after slow changes in arterial blood pressure (ABP). As CA regulates cerebral blood flow, impairments in CA may result in cerebral hypo- or hyperperfusion. In patients with traumatic brain injury (TBI) with intracranial pressure (ICP) monitoring, CA is commonly calculated as the Pearson correlation between slow changes in ABP and ICP and referred to as the pressure reactivity index (PRx) (1, 2). A positive ABP-ICP correlation (positive PRx) indicates impaired CA, whereas a negative PRx indicates intact dynamic CA (2). CPPopt is the cerebral perfusion pressure (CPP) value at which the CA is best preserved. PRx monitoring can delineate "optimal" CPP (CPPopt) for patients with TBI with curve fitting software at the bedside. A large retrospective observational study showed that deviation from automated CPPopt is associated with increased mortality when CPP is less than "optimal" and with a permanent neurological disability when CPP is greater than "optimal" (3).

Targeting a CPPopt value may, therefore, improve cerebral physiology and clinical outcome. Current strategies for PRx monitoring require prolonged recordings of continuous PRx measurements averaged over time for CA trends or over CPP intervals for CPPopt calculation. Such time-averaging is necessary to reduce variability in PRx due to incoherent, physiological variability of ABP and ICP slow waves. When spontaneous ABP fluctuations are used to calculate PRx, CPPopt cannot be calculated in up to 25% of the monitoring time (4). Inadequate power and reduced variability of spontaneous ABP slow waves have been proposed as a cause of failure to delineate CA and CPPopt (5, 6). In 2012, Brady et al. (13) reduced the variability of PRx, recorded from anesthetized piglets, by inducing 1/min (0.0167 Hz) ABP sinusoidal waves with oscillations of positive end-expiratory pressure (PEEP) during volume-controlled ventilation. So far, the use of PEEP oscillation for the purpose of monitoring PRx has not been applied to patients with TBI to demonstrate feasibility and safety in a clinical intensive care unit (ICU) setting. We sought to reduce the PRx variability using controlled PEEP oscillations offered by repetitively applying the ventilator "sigh function." We tested the feasibility of using this adaptation of the mechanical ventilation to reduce the variability in the PRx calculation. A previous study showed that applying repetitive ventilator sighs was feasible and safe in ICU patients with respiratory insufficiency (8).

In this clinical study, we hypothesized a reduced variability of PRx in adult-sedated patients with TBI with volume-controlled ventilation and significant transmission of PEEP oscillations to ABP and ICP signals and no other relevant physiological changes.

METHODS

Ethical Considerations and Patient Selection

A single-center, observational prospective study was performed between May 2020 and November 2021. Our local ethical committee approved monitoring and data collection (METC 16-4-243). Written proxy informed consent was obtained for each subject. Adult (≥ 18 yr old) patients with TBI with ICP monitoring were screened for inclusion within 48 h after ICU admission. Exclusion criteria were moribund (neurological) status, primary decompressive craniectomy, significant thoracic trauma, ICP > 22 mmHg, and PEEP > 12 cmH_2O. The management of our patients is in line with the recently published tier-based TBI consensus treatment protocol (9). Parenchymal ICP probes (NEUROVENT-TEMP, RAUMEDIC, Helmbrechts, Germany) were used in all patients. The patients were not participating in the COGiTATE intervention study (4).

Ventilation Strategy

For this study, the ventilation mode was changed from Bilevel Positive Airway Pressure (BiPAP) to Intermittent Positive Pressure Ventilation (IPPV) using settings that maintained similar minute ventilation (MV), PEEP, and FIO_2 values (Evita XL or Infinity V500 ventilator, Dräger, Lubeck, Germany). IPPV was applied to guarantee unchanged MV (and $PaCO_2$ levels) during PEEP oscillation application. Baseline PEEP levels were at least 5 cmH_2O with 100% endotracheal tube compensation and AutoFlow option turned on. Nursing interventions (like turning or suctioning) were kept to a minimum during the observation periods. A baseline period of 30 min (named PRx period) was followed by a cyclic PEEP oscillation period (named induced *i*PRx period) of 30 min. As a safety precaution, the sigh function had to be switched off (and discontinuation of the study) when peripheral oxygen saturation (SpO_2%) decreased below 92% for 1 min or ICP > 25 mmHg or CPP < 50 mmHg or CPP > 100 mmHg for more than 5 consecutive minutes.

Sigh Settings on the Ventilator to Generate Cyclic PEEP Oscillations

The ventilator has the option to apply sighs of different repeatability, duration and intensity, offered by the following settings: number of sigh cycles, interval repeat time (s), and PEEP-sigh levels (cmH_2O). When the number of cycles exceeds the interval period, the expiration pressure sensor sets the new PEEP level. Consequently, the machine pressure changes and the expiration valve opens to end up with the new set PEEP value for the duration of the interval period (personal communication by Dräger Company).

As in Brady et al. (13), we intended to retrieve slow oscillations of 0.0167 Hz (1/min) with limited intensity (+5 cmH_2O). This oscillation frequency falls within the PRx calculation frequency range (0.003–0.05 Hz) and was shown to be an optimal frequency for measuring PRx in a piglet model (10). Therefore, the settings were set per patient (without any spontaneous breathing effort due to deep sedation) as follows: the number of sigh cycles as the ventilator breathing frequency per minute divided by two, the interval repeat time as 30 s, and the sigh level on 5 cmH_2O (on top of the applied baseline PEEP level).

Data Collection

The following patient characteristics were collected: sex, age, pupil reactivity, the best Glasgow coma scale motor score before ICU admission, presence of major extracranial injuries (11), the Marshall computed tomography admission score (12), the time between the estimated time of injury and start (*i*)PRx period and the 6-month Glasgow Outcome Scale Extended (GOSE). We collected signals at a sample rate of 250 Hz including ABP (mmHg), ICP (mmHg), heart rate (HR, /min); electrocardiography (ECG, μV), end-tidal carbon dioxide (Et_{CO2}, kPa), heart rate (HR; /min), and peripheral oxygen saturation (SpO_2, %). The data were collected using intensive care monitoring (ICM+) software (Cambridge Enterprise, University of Cambridge, Cambridge, UK, http://www.neurosurg.cam.ac.uk/icmplus). Before the PRx- and after the *i*PRx period, the ventilator settings (PEEP, cmH_2O), tidal volume per body weight (VT, mL/kg), dynamic lung compliance (Cdyn, mL/cmH_2O), MV (L/min), fraction of inspiratory oxygen (FIO_2, %), and arterial blood gas (ABG, including arterial oxygen saturation (SaO_2, %), pH, carbon dioxide tension ($PaCO_2$, kPa), and oxygen tension ($PaCO_2$, kPa) were noted.

Pressure Reactivity Index Data Collection

PRx was real time calculated by the ICM+ software as the moving (80% overlap) Pearson correlation between 10-s mean values of ABP and ICP over a 300-s window (30 data points) to capture slow cyclic waves between 0.003 (300 s) and 0.05 (20 s) Hz (2). PRx values were sampled every minute and exported for further retrospective analysis. The first 4 min were removed for both the baseline (PRx) and study (*i*PRx) periods to correct the 80% overlap due to moving average application. The mean PRx and associated standard deviation (SD) over the remaining 26-min periods were calculated for each patient and used for further statistical analysis.

Data Analysis

Raw ABP, ICP, ECG, and Et_{CO2} signals were exported from the bedside ICM+ software. The signals were visually inspected and artifacts were removed. Missing ABP values from data gaps shorter than one heartbeat were removed. ABP, HR,

ICP, CPP, and Et_{CO2} were averaged for each 30-min study period. For the *i*PRx period, we calculated the average difference in MAP between the peak and nadir of the PEEP oscillation. First, we averaged the ABP values over 10 s to calculate the MAP. We then calculated the peak (maximum) and nadir (minimum) of the MAP using the MATLAB function *findpeaks*. The minimal peak distance was set at 30 s (to capture each peak and nadir) and the minimal amplitude of the peak height at 1 mmHg (to exclude detection of small peaks). The obtained difference between maximum and minimum value per minute was averaged for the *i*PRx period. Frequency analysis was applied for studying the transmission of PEEP oscillations to the ABP and ICP signals. The power spectrum density (PSD) was computed over detrended data using Welch's method (333-s rectangular window, 50% overlap) for the frequency range of 0.003–0.05 Hz. We calculated the following for both PRx and *i*PRx periods: *1*) the peak frequency, which is the frequency with the maximum PSD value in the PRx frequency range (0.003–0.05 Hz); *2*) the power calculated for the frequency range around the induced frequency (0.015–0.018 Hz); *3*) the power calculated for the PRx frequency range (0.003–0.05 Hz), and *4*) the relative power (%) defined as the power in the induced frequency range (0.015–0.018 Hz) compared with the power of the PRx frequency range (0.003–0.05 Hz). The data processing and analysis were performed in MATLAB software (v. 2019a, The MathWorks, Natick, MA).

Statistical Analysis

To evaluate reduced PRx variability, we compared the SD of PRx between the PRx and the *i*PRx periods. The transmission of PEEP oscillations to the ABP and ICP signals was studied using PSD calculations. We also compared relevant discrete and continuous physiological variables between the PRx and *i*PRx periods to evaluate potential effects on systemic and brain physiology in our patients with TBI.

Gaussian distribution was not assumed for the sample size in this study. Data are therefore reported as median and the first and third quartile (Q1–Q3). The Wilcoxon-signed rank test was used to compare distributions of variables during the PRx- and *i*PRx period, taking into account the repetitive (paired) measures and nonparametric assumptions. However, no statistics were applied to the mean absolute PRx, as we had no predefined hypothesis about the absolute PRx values itself during the *i*PRx period besides observation. An α of 0.05 was set for statistical significance. The statistical analyses were conducted in GraphPad (GraphPad Prism v. 6.0 for Windows, GraphPad Software, La Jolla, CA, www.graphpad.com).

RESULTS

In the study period, 16 patients with TBI were screened. Two patients underwent an urgent primary decompressive craniectomy, one patient was considered neurologically moribund, one patient had ICP levels > 22 mmHg before the start of the measurement, and no researcher was available for one scheduled measurement. In addition, the first patient was excluded due to an incorrect set number of cycles on the ventilator. The remaining 10 patients were included for data analysis. We included only male patients with 6-month mortality of 50%. Patient demographics can be found in Table 1.

Pressure Reactivity Index Variability

An example of a patient recording is given in Fig. 1. During the pressure reactivity index (PRx) period, the ABP and ICP signals showed very limited slow wave activity, resulting in PRx values fluctuating around zero (i.e., signifying apparent no correlation between the two signals). The slow wave activity however became clearly apparent in the ABP and ICP signals as soon as the cyclic PEEP oscillations started. This in turn led to stable, consistently negative, PRx values indicating intact CA. For the cohort, the SD of PRx decreased significantly during the *i*PRx period compared with the PRx period [0.14 (0.09–0.17) vs. 0.25 (0.22–0.30), $P = 0.006$]. The cohort change in SD between PRx and *i*PRx is summarized in Fig. 2. In addition, we observed that PRx values became decisively more negative in seven patients, consistent with a presumed intact CA. However, importantly, in one patient, PRx numbers increased to a value above 0.25 and in another patient, the PRx remained positive, signifying impaired CA after PEEP oscillations in two patients (Fig. 3)

Table 1 | Baseline patients' characteristics and outcome results (n = 10)

Number of Patient with TBI	Sex, Male	Age, yr	Fixed and Dilated Pupils at Admission	GCS-Motor pre-ICU Admission	Extracranial Trauma Presence*	Marshall CT-Score on Admission Scan†	The Period Between Estimated Time of Injury and Start PRx Period (h)	GOSE
1	Yes	38	No	5	No	Diffuse injury (II)	41	NA§
2	Yes	68	No	6	No	Diffuse injury (II)	26	Dead
3	Yes	27	No	NA	Yes	Diffuse injury (I)	14	8
4	Yes	32	One	1	Yes	Nonevacuated mass lesion (VI)	44	Dead
5	Yes	32	No	6	No	Nonevacuated mass lesion (VI)	81‡	Dead
6	Yes	20	No	1	Yes	Diffuse injury (II)	48	Dead
7	Yes	19	No	6	Yes	Diffuse injury (I)	6	8
8	Yes	18	No	4	No	Nonevacuated mass lesion (VI)	28	4
9	Yes	68	No	3	No	Evacuated mass lesion (V)	14	Dead
10	Yes	32	No	5	Yes	Nonevacuated mass lesion (VI)	23	5

The baseline and patient characteristics of the included *n* = 10 patients with TBI. *Extracranial trauma was defined as requiring hospital admission on its own right (11); †Marshall CT-score classification score (12); ‡a patient with secondary deterioration of consciousness. The patient was enrolled within 48 h after the start of ICP monitoring; §lost to follow up. CT, computed tomography; GCS-motor, Glasgow coma scale motor score; GOSE, Glasgow outcome scale extended; ICP, intracranial pressure; NA, not available; TBI, traumatic brain injury.

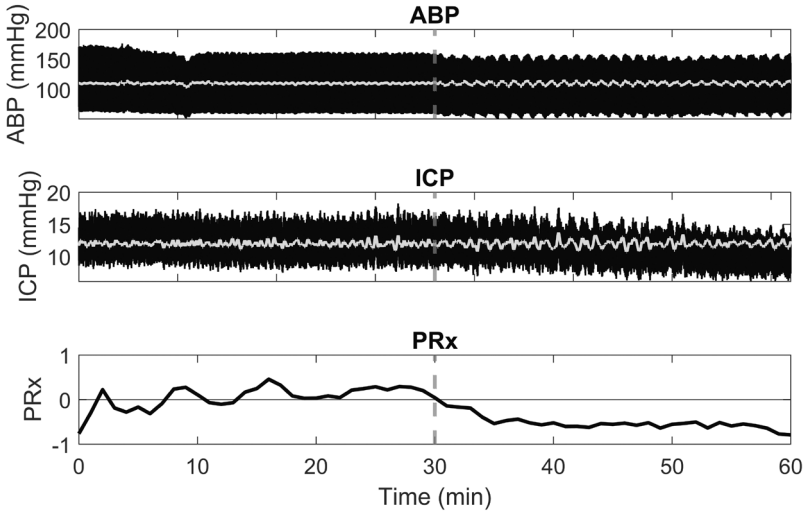

Figure 1 | Data recording (n = 1 patient) showing reduced variability of the pressure reactivity index. Example of a data recording from a patient with TBI with stable and negative PRx during the induced cyclic PEEP oscillations PRx period (*i*PRx). The top two rows show high-frequency ABP (mmHg) and ICP (mmHg) signals. On top of the high-frequency ABP and ICP signals, slow waves are shown (gray lines). The bottom row shows the updated PRx signal during both periods (PRx and *i*PRx). The dotted gray vertical line represents the end of the PRx period and the start of the iPRx period. The ABP and ICP signals are stable during the PRx period, whereas both signals show slow waves with a frequency of 1/min (0.0167 Hz) during the *i*PRx period. The mean PRx signal fluctuates around zero during the PRx period (SD of PRx 0.20), whereas during the *i*PRx period, PRx is more stable and decreases to a value of −0.58 (SD of PRx 0.10) ABP, arterial blood pressure; ICP, intracranial pressure; PEEP, positive end-expiratory pressure; PRx, pressure reactivity index; SD, standard deviation; TBI, traumatic brain injury

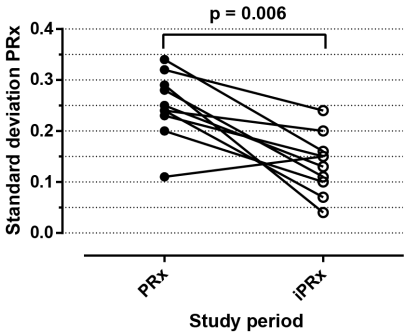

Figure 2 | Standard deviation of the pressure reactivity index (*n* = 10). The variability of the PRx during PRx period (*n* = 10) and the *i*PRx period (*n* = 10). The SD for each individual patient with TBI and both study periods is shown. The SD of PRx significantly decreased during the induced PRx (*i*PRx) period with induced cyclic PEEP oscillations, except for one patient. For the cohort, the SD of PRx decreased for the *i*PRx period compared with the PRx period [0.14 (0.09–0.17) vs. 0.25 (0.22–0.30), *P* = 0.006, Wilcoxon-signed rank test]. *i*PRx, induced pressure reactivity index; PEEP, positive end-expiratory pressure; PRx, pressure reactivity index; SD, standard deviation; TBI, traumatic brain injury.

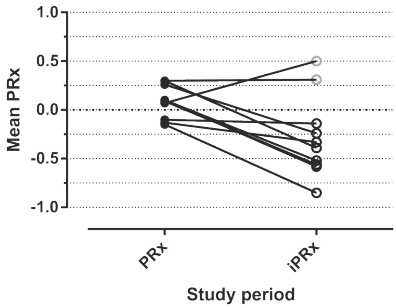

Figure 3 | Mean differences in the pressure reactivity index (*n* = 10). The mean PRx for the PRx period (*n* = 10) and the *i*PRx period (*n* = 10). The mean values for each patient with TBI during both study periods are shown. Eight patients show a decrease in mean PRx (all below 0), consistent with intact CA and two patients ended up with positive values (above 0.25 level, consistent with impaired CA, gray dots) during the cyclic-induced PEEP oscillations. CA, cerebral autoregulation; (*i*)PRx, (induced) pressure reactivity index; PEEP, positive end-expiratory pressure; TBI, traumatic brain injury.

Frequency Analysis: Transmission of PEEP Oscillations

Cyclic PEEP oscillations resulted in slow induced cyclic ABP waves in all patients. The peak frequency in the ABP signal transferred to the induced frequency of 0.0167 Hz in nine patients, as shown in Fig. 4*A*. In the ICP signal, the peak frequency transferred in eight patients to 0.0167 Hz frequency, as shown in Fig. 4*B*.

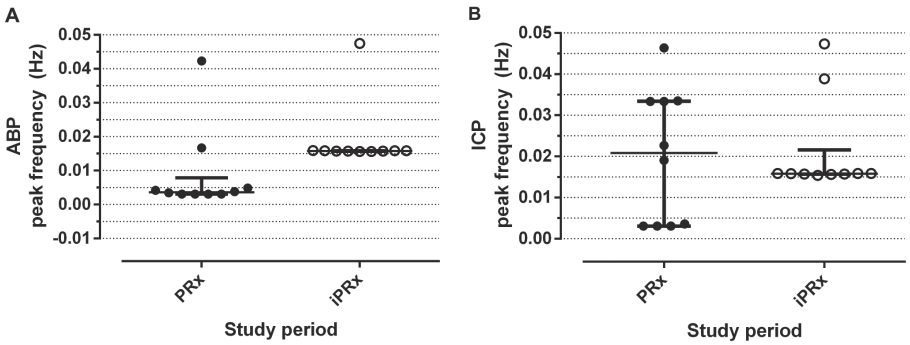

Figure 4 | Peak frequency in the arterial blood pressure (ABP) and intracranial pressure (ICP) signals (*n* = 10). The peak frequency calculated within the frequency range of 0.003–0.05 Hz for the PRx period (*n* = 10) and the *i*PRx period (*n* = 10). *A*: the ABP peak frequencies of the ABP signal are shown. The peak frequency transferred to the induced frequency (0.0167 Hz) in nine patients with TBI. *B*: peak frequencies of the ICP signal for the PRx period (*n* = 10) and the *i*PRx period (*n* = 10). During the *i*PRx period, the peak frequency of the ICP signal is 0.0167 Hz in eight patients. ABP, arterial blood pressure; (*i*)PRx, (induced) pressure reactivity index; ICP, intracranial pressure; TBI, traumatic brain injury.

The ABP power within the PRx frequency range significantly increased during cyclic PEEP oscillations [PRx period 1.3 (0.43–2.6) vs. *i*PRx period 7.7 (3.0–9.4) mmHg^2, $P = 0.002$]. Also, the relative ABP power in this frequency range increased [PRx period 6.4 (4.5–8.3) vs. *i*PRx period 58% (41–78), $P = 0.004$]. The power of ICP increased in the PRx frequency range [PRx period 0.23 (0.12–0.52) vs. *i*PRx period 0.43 mmHg^2 (0.33–0.62), $P = 0.027$]. Similarly, the relative power of ICP also increased significantly [PRx period 5.9 (1.8–7.8) vs. *i*PRx period 31% (17–59), $P = 0.002$] (Table 2).

Table 2 | Frequency analysis for both study periods (n = 10)

Median (Q1–Q3)	PRx Period	*i*PRx Period	*P* Value*
ABP–power (mmHg^2) (0.015–0.018 Hz)	0.053 (0.020–0.16)	4.9 (0.88–7.0)	0.002
ABP–power (mmHg^2) (0.003–0.05 Hz)	1.3 (0.43–2.6)	7.7 (3.0–9.4)	0.002
ABP – relative power† (%)	6.4 (4.5–8.3)	58 (41–78)	0.004
ICP–power (mmHg^2) (0.015–0.018 Hz)	0.01 (0.0025–0.031)	0.13 (0.10–0.22)	0.002
ICP–power (mmHg^2) (0.003–0.05 Hz)	0.23 (0.12–0.52)	0.43 (0.33–0.62)	0.027
ICP–relative power† (%)	5.9 (1.8–7.8)	31 (17–59)	0.002

*Wilcoxon-signed rank test was used for statistical comparison.
†The relative power is computed as the power in the frequency range (0.015–0.018 Hz) compared with the PRx frequency range (0.003–0.05 Hz). ABP, arterial blood pressure; ICP, intracranial pressure; (*i*)PRx, (induced) pressure reactivity index; Q1–Q3, first and third quartile.

Physiological Changes after PEEP Cyclic Oscillations

No patients showed clinical deterioration that required discontinuation of the sigh function. In other words, no patients exceeded the predefined safety thresholds. No additional medication and/or change in the ventilator setting was needed during the *i*PRx period. The physiological changes are summarized in Tables 3 and 4. ABP decreased by a clinically insignificant amount during the *i*PRx period [PRx period 80 (75–82) vs. *i*PRx period 78 mmHg (74–81), $P = 0.055$]. In addition, the difference in peak-nadir MAP during the *i*PRx period was 6.9 (4.4–7.8) mmHg. No changes were observed in median ICP and CPP signals.

Table 3 | Hemodynamic and cerebral parameters during both study periods (n = 10)

Median (Q1–Q3)	PRx Period	*i*PRx Period	*P* Value*
Mean ABP, mmHg	80 (75–82)	78 (74–81)	0.055
Heart rate, min^{-1}	79 (58–94)	82 (58–95)	0.193
Mean ICP, mmHg	12 (8–18)	12 (9–16)	0.625
CPP, mmHg	69 (64–70)	66 (63–69)	0.375
Et_{CO2}, kPa	4.3 (3.6–4.7)	4.3 (3.7–4.7)	0.426

*Wilcoxon-signed rank test was used for statistical comparison. ABP, arterial blood pressure; CPP, cerebral perfusion pressure; Et_{CO2}, end-tidal carbon dioxide tension; ICP, intracranial pressure; (*i*)PRx = (induced) pressure reactivity index; Q1–Q3, first and third quartile.

Table 4 | Ventilation parameters during both periods (n = 10)

Median (Q1–Q3)	Pre PRx Period	Post *i*PRx Period	*P* Value*
Arterial blood gas analysis			
pH	7.44 (7.40–7.45)†	7.43 (7.40–7.45)	0.656
PaO_2, kPa	11.6 (10.4–14.6)†	12.4 (9.7–18.8)	0.039
$PaCO_2$, kPa	4.6 (4.2–4.8)†	4.6 (4.3–4.9)	0.668
SaO_2, %	95 (94–96)	95 (94–96)	0.500
Ventilation parameters			
PEEP, cmH_2O	8 (5–8)	8 (5–8)	NA
Tidal volume per body weight, mL/kg	6.1 (5.8–6.8)	6.0 (5.7–6.7)	0.141
Minute volume, L/min	8.8 (7.9–9.0)	8.7 (7.5–9.1)	0.461
Dynamic lung compliance, mL/cmH_2O	51 (41–61)	57 (46–66)	0.002
PaO_2/FIO_2, mmHg/%	330 (255–435)†	360 (285–458)	0.281

*Wilcoxon-signed rank test was used for statistical comparison.
†One missing component. (*i*)PRx, (induced) pressure reactivity index; PaO_2, partial pressure of oxygen; $PaCO_2/FIO_2$, partial pressure of oxygen/ fraction of inspired oxygen ratio; $PaCO_2$, partial pressure of carbon dioxide; PEEP, positive end-expiratory pressure; Q1–Q3, first and third quartile; SaO_2, arterial oxygen saturation.

An effect of cyclic PEEP oscillations on the respiratory variables was observed. The dynamic lung compliance increased [PRx period 51 (41–61) vs. *i*PRx period 57 mL/cmH_2O (46–66), $P = 0.002$]. Simultaneously, the $PaCO_2$ increased [PRx period 11.6 (10.4–14.6) vs. *i*PRx period 12.4 kPa (9.7–18.8), $P = 0.039$]. The $PaCO_2$ and the Et_{CO2} remained unchanged (Tables 3 and 4).

DISCUSSION

In this clinical study, we demonstrated the effect of slow PEEP-induced cyclic ABP waves on cerebral autoregulation (PRx) estimations in patients with TBI. The main observations are that with cyclic PEEP oscillations *1*) PRx showed a reduced variability, as the SD of the PRx significantly decreased, and an improved demarcation between intact and impaired CA was observed, *2*) a clear transfer from PEEP oscillations to the ABP and ICP signal was seen, and *3*) only limited interaction with other physiological variables of which improved dynamic lung compliance and PaO_2 might be attributed to the cyclic alveolar recruitment maneuver. Based on our data, some observations deserve further discussion.

Change in Pressure Reactivity Index

With the improved transmission of waves during the *i*PRx period, we found a clear indication of positive PRx in two patients (suggestive of impaired CA) and clear negative PRx in eight patients with TBI (suggestive of intact CA) (Fig. 2). Although only studied in a limited number of patients, our results seem to suggest much improved discrimination of intact from impaired CA with reduced PRx variability at the bedside in a short period (30-min recordings). It is important to note that in general, due to the nature of the PRx calculations, values around 0 may indicate partially functioning pressure reactivity, but at the same time, they could also mean there is insufficient power of waves being transferred between ABP and ICP, thus violating the assumptions and invalidating any interpretations of the PRx. Therefore, a shift in PRx values toward clearly positive and clearly negative, as observed during the *i*PRx period, is highly meaningful.

However, it must also be acknowledged here that these estimates of CA functioning could not be verified against a gold standard. Our findings parallel the experimental results of Brady et al. in a piglet model in 2012. The authors studied slow PEEP-induced ABP waves with programming an additional sine wave component in the ventilator in two experimental conditions. In the first condition, the 10 sedated piglets showed a significant reduced variability of PRx with cyclic PEEP oscillations and a consistent negative PRx. Intact CA is expected in healthy piglets without brain damage and stable hemodynamic and respiratory conditions. Although the metrics to define PRx variability were slightly different, both studies showed a large reduction in PRx variability (44% in patients with TBI and 35% improvement in the piglets, respectively) (13). During the second experimental condition, the piglets were hemorrhaged with deep hypotension showing a sudden and consistent increase in PRx at the lower limit of autoregulation (LLA). The LLA was measured with continuous

invasive cortical Doppler flux monitoring. With the cyclic PEEP oscillations turned on, the PRx above LLA was −0.42 (−0.67 to −0.29) and below LLA was 0.32 (0.22–0.43, $P < 0.0004$) (13). We monitored our patients with TBI during hemodynamic stable periods (with unknown LLA), but due to extensive neurological injury, some patients showed PRx values consistent with impaired CA during the cyclic PEEP oscillation period (Fig. 3). Therefore, despite the absence of a gold standard, the animal results of Brady et al. and our clinical results suggest that we have not changed the cerebral physiology, but improved the reliability of the methodology given the reduction in PRx variability.

Transmission Cyclic PEEP Oscillations

Slow PEEP oscillations were transmitted to the ABP signal (Fig. 4*A*), except for one patient. We speculate that this patient had autonomic dysfunction causing an intrinsic dominant oscillation in the ABP (0.045 Hz) signal. We observed a significant increase in absolute and relative ABP power. Comparing the interquartile ranges, the variability seems largely similar between the periods. This suggests a comparable intervention in our patients. In 8 out of 10 patients, the ICP peak frequency transferred to the PEEP-induced frequency (Fig. 4*B*). The transmission of intrathoracic pressure changes to the ICP signal not only depends on extracranial factors but also on complex intracranial factors like brain compliance, CA, and cerebral venous drainage (14, 15).

Interaction with Other Physiological Variables

The absolute ICP, CPP, and $PaCO_2$ values were not influenced by the cyclic PEEP oscillations. The PaO_2 and the dynamic lung compliance increased after the *i*PRx period. An intermittent increase in PEEP level probably causes increased alveolar pressure, which could result in higher alveolar recruitment in our respiratory stable patients. We only applied low sigh PEEP levels of +5 cmH_2O in all our patients with TBI as applied in Brady et al. (13). Higher PEEP levels might cause lung hyperextension and, together with lower MV and (cervical) venous drainage obstruction, lead to unwanted ICP increases.

Clinical Applicability

We consider our observations relevant for CA monitoring and related therapies in ventilated ICU patients. Previous studies investigated various methods to induce ABP waves, for example, thigh cuff inflation and deflation and cyclic leg raising (16, 17). However, these methods are limited to patients with TBI, because they might cause large and unwanted drops in ABP and/or affect the $PaCO_2$ levels. Another method applied in the ICU is deep and slow breathing, which has successfully been done in awake (18) and comatose patients for CA assessment. The breathing frequency was decreased to 0.1 Hz (6/min) for a short (<10 min) duration in subarachnoid hemorrhage and patients

with TBI (19, 20). However, lowering the breathing frequency is undesirable for long periods, as it results in large tidal volumes when aiming for sufficient MV to control $PaCO_2$ levels.

Continuous CA assessment is preferred, as reduction in PRx variability may be an appropriate method to improve the availability (yield) of CPPopt calculations to guide cerebral perfusion management (5). Liu et al. attempted to reduce PRx short-term variability by applying the wavelet technique together with coherence filtering instead of the moving Pearson correlation method (21, 22). The authors showed a stronger relationship between the individual deviation of wavelet-based CPPopt values and poor clinical outcomes in patients with TBI compared with classic PRx-based CPPopt (22). However, no amount of filtering will account for the fact that if no sufficient variability in ABP is there, calculation based on it will not yield valid results. On the other hand, PEEP oscillations seem to be able to ensure this critical prerequisite. Therefore, it might be speculated that with PEEP oscillations, reducing PRx variability, the applicability of CA-guided therapy is improved by increasing the yield and decreasing the variability of CPPopt at the bedside (4). This will, however, require prolonged recordings as CPPopt calculation requires at least 4 h of monitoring before the first CPPopt value becomes available (23).

Limitations

We have to acknowledge several limitations of our clinical study. First, we studied the applicability of PEEP oscillations in a selected and limited group of patients. For example, a more heterogeneous sex-balanced population including patients with difficult to control intracranial hypertension and/or accompanying significant thorax trauma. This provides more insight into the applicability of PEEP oscillations. Second, for the assessment of CA estimations, no gold standard is available at the moment at the bedside, with exception of transcranial Doppler, which has not been used. However, Brady et al. (13) validated the use of PRx monitoring to detect the LLA in their animals with the application of PEEP oscillations which is reassuring. Finally, a multimodality approach, including advanced hemodynamic and respiratory measurements, could provide more insight into the complex interplay between heart, lungs, and brain and retrieve more information about the individual PEEP response in our patients.

CONCLUSIONS

Cyclic 1/min PEEP oscillations for around 30 min reduces the PRx variability at the bedside in ventilated patients with TBI with ICP levels <22 mmHg. No other clinically relevant physiological changes were observed. Reduced PRx

variability might improve cerebral autoregulation-guided perfusion management methodology, but for this prolonged periods with PEEP oscillations of at least 4 h are required.

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Author contributions
J.T., K.D.J.B., I.C.C.v.d.H., U.S., and M.J.H.A. conceived and designed research; J.T., K.D.J.B., and M.J.H.A. performed experiments; J.T. and K.D.J.B. analyzed data; J.T., K.D.J.B., J.L.F., E.B., M.C., S.M.J.v.K., K.M.B., P.S., and M.J.H.A. interpreted results of experiments; J.T. and K.D.J.B. prepared figures; J.T., K.D.J.B., and M.J.H.A. drafted manuscript; J.T., K.D.J.B., J.L.F, E.B., M.C., R.H., I.C.C.v.d.H., S.M.J.v.K., K.M.B., P.S., and M.J.H.A. edited and revised manuscript; J.T., K.D.J.B., J.L.F, E.B., M.C., R.H., I.C.C.v.d.H., S.M.J.v.K., U.S., K.M.B., P.S., and M.J.H.A. approved final version of manuscript.

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6

Anti-Decubitus Bed Mattress may Interfere with Cerebrovascular Pressure Reactivity Measures due to Induced ICP and ABP Cyclic Peaks

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J Clin Monit Comput. 2021 Apr;35(2):423-425

ABSTRACT

Severe traumatic brain injury (TBI) patients are monitored with continuous arterial blood pressure (ABP) and intracranial pressure (ICP). The pressure reactivity index (PRx) is a frequently used correlation coefficient between ABP and ICP to inform clinicians at the bedside about trends in global cerebrovascular pressure regulation status. We present an unexpected influence of cyclic anti-decubitus mattress inflations and deflations on invasive ICP, ABP and PRx calculations in our TBI patients. This might affect autoregulation guided management. In our database, 23% (9/39) of the patients show recurrent peaks in the monitoring signals. We hypothesize that these peaks are caused by (a combination) of hydrostatic change, local (cervical) compression and/or incorrect sensor zeroing due to positional changes induced by the anti-decubitus mattress. This warrants further investigation by the manufacturer and exploration of data filters.

To the Editor,

International guidelines suggest to monitoring severe traumatic brain injury (TBI) patients with continuous arterial blood pressure (ABP) and intracranial pressure (ICP) to assess the cerebral perfusion pressure with these signals [1]. Additional, information about brain vessel reactivity and compensatory reserve can be computed. The pressure reactivity index (PRx) may inform clinicians at the bedside about trends in global cerebrovascular pressure reactivity status [2]. Currently, a randomized controlled phase II intervention trial (acronym COGiTATE; www.cppopt.org) evaluates the feasibility and safety of PRx guided management of cerebral perfusion pressure therapy in severe TBI patients [3]. PRx is computed as the moving correlation coefficient between spontaneous slow waves in ABP and ICP [2, 4]. In this letter, we present an unexpected influence of cyclic anti-decubitus mattress inflations and deflations on invasive ICP, ABP and PRx calculation in TBI patients.

During retrospective data examination in one of our TBI patients recordings we noticed a sudden onset of regular, periodic (10 min cycle) increases in the ICP (intraparenchymal Neurovent P-TEMP sensor, Raumedic AG) and ABP signals (radial artery, Edward Lifesciences). The duration and amplitude of the peaks was around 3.5 min and 1.5–2 mmHg, respectively, for both signals. PRx became positive during these periods suggesting sudden deterioration of cerebrovascular pressure reactivity (Fig. 1). Upon further scrutiny of previously monitored patients, we noticed similar patterns occurring in 9 out of 39 TBI patients (23%) admitted in our unit during the period 2016–2019.

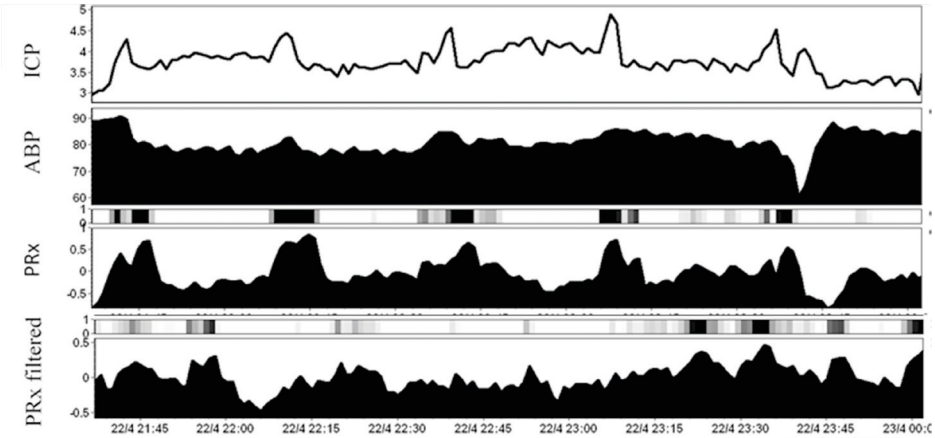

Figure 1 | A representative signal recording from a TBI patient showing cyclic peaks in the ICP signal. These peaks are difficult to observe visually in the ABP signal. The mean PRx value of this period is around 0 indicating preserved cerebrovascular pressure reactivity. However, during the ICP peaks PRx temporarily exceeds 0.5, indicating cerebrovascular pressure reactivity impairment. 'PRx filtered' is based on high pass filtered ABP and ICP signal, which removes frequencies < 0.004 Hz. The filtered signal shows a more stable PRx trend. *ICP* intracranial pressure, *ABP* arterial blood pressure, *PRx* pressure reactivity index, *TBI* traumatic brain injury

We hypothesized that the peaks were caused by the repetitive deflation and inflation of the anti-decubitus bed mattress (type 750 ESRI NV, Belgium) which has a default cycling frequency of once per 10 min. Changing the setting to 25 min cycles or switching to a static mode had indeed a direct effect on the signals (Fig. 2). Supplemental Fig. S1 shows in detail how this mattress works. To obtain a better understanding of the effect of the bed mattress we recorded the upper body of a TBI patient showing the cyclic peaks. The recording shows that the whole body moves around 1 cm upwards. The head region—which rests on the static part of the mattress—moves also backwards (supplemental video S2). Several hypotheses were tested to understand the cause of this phenomenon.

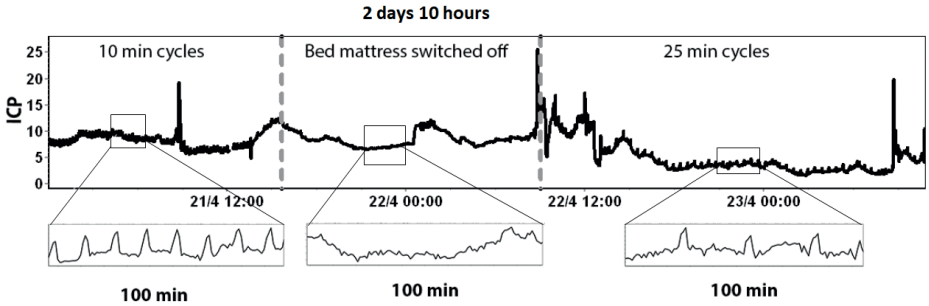

Figure 2 | The ICP signal was recorded with different bed mattress settings in a TBI patient. During the first period, the bed mattress was set at 10 min cycles. During the second period, the cyclic deflation-inflation was temporarily switched off. During the third period, the bed mattress was set at 25 min cycles. The figures at the bottom are magnifications of each period spanning 100 min periods and ICP peak height between 1.5 and 2 mmHg. *ICP* intracranial pressure, *TBI* traumatic brain injury

ICP peaks

We constructed a 'phantom' consisting of a Neurovent ICP sensor inserted into a 500 ml soft plastic (closed) bottle filled with water and put it on the 30° head up upper (static) part of the bed mattress. The bed mattress was set at the static mode and subsequently at 10 min cycles. The cyclic ICP peaks appeared with similar patterns as observed in our patients. However, the peaks disappeared when we put the bottle in a firm open plastic box on the head up part, excluding an electromagnetic cause of the interference. This experiment also excludes a flow or pressure phenomenon originating from the systemic circulation (induced by the bed mattress) as the peaks were induced in a closed bottle. From this experiment we hypothesize that the mattress exerts localized pressure on structures positioned on top of it or induces a hydrostatic effect by tilting, or a combination of both. In a TBI patient with low brain compliance changes in head position or local compression of cervical venous structures might be responsible for the observed cyclic ICP peaks. To test the latter, we put a hard plate under the patient's pillow down to the shoulders in a TBI patient with cyclic peaks in the ICP signal. With this intervention the ICP peaks disappeared (supplemental Fig. S3).

ABP peaks

Besides ICP peaks we also detected cyclic peaks in the ABP signals. These peaks had a similar duration and amplitude (and were in phase with the ICP signal (Fig. 2). However, the pattern of the ABP peaks over time was less pronounced, likely due to higher absolute values and higher amplitude of natural fluctuations in the signal. In contrast to the intraparenchymal ICP measurement, leveling and zeroing is needed for reliable ABP and CVP

monitoring. For correct monitoring the zero level needs to remain fixed during the recording. As can be seen in the video this requirement is not fulfilled (supplemental video S2). We hypothesized that the peaks in ABP were predominantly caused by an upward movement in patients' body relative compared to the (fixed) transducer. We also measured the central venous pressure (CVP) in one TBI patient clearly showing cyclic peaks of around 3 mmHg. Indeed, when we fixed the zero transducer to the patient's body the cyclic peaks disappeared.

Autoregulation (correlation based) measurements

As mentioned earlier, the observed changes in the absolute ABP and ICP signals are small and seem of limited clinical relevance. However, these cyclic phenomena may become clinically relevant in the context of waveform derived parameters like PRx, which, being a simple correlation coefficient, is influenced by simultaneous, signal changes. The point here is that ABP and ICP peaks seem to be independently affected by the mattress. They are likely not related to cerebrovascular pressure reactivity mediated transmission of ABP waves to ICP.

The peaks were present in only 23% of our monitored patients. It is unknown whether individual differences in trauma or brain pathology, anatomy or body position have any effect on the presence of the peaks.

In conclusion, we have shown that the cyclic anti-decubital mattress has effects on physiological signal recordings like ICP and ABP in severe TBI patients. Clinicians should be aware of this and that widely used autoregulation correlation indices like PRx may be somewhat adversely influenced by these cyclic phenomena.

Acknowledgements

The excellent medical and technical support of the medical and nursing staff of the intensive care unit at the Maastricht University Medical Center is gratefully acknowledged.

Ethics declarations

Conflict of interest

ICM+ software for brain monitoring (https://icmplus.neurosurg.cam.ac.uk) is licensed by the University of Cambridge (Cambridge Enterprise Ltd, Cambridge, UK). Marek Czosnyka and Peter Smielewski have a financial interest in part of the licensing fee.

Informed consent

Informed consent was obtained from all individual participants included in the study.

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SUPPLEMENTARY MATERIAL

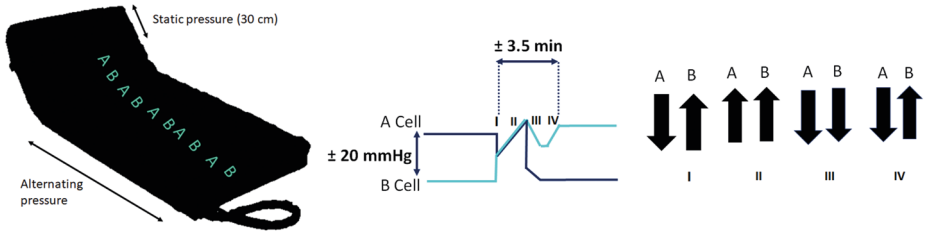


Figure S1 | The ESRI 750 mattress has transverse alternating A and B cells, and a static head region covering the upper 30 centimetres. When the A cells deflate, the B-cells inflate (period I) until the A and B cells are on a similar level (starting position), Then both the A and B cells start to inflate to the maximum inflation (period II). During period III, both cells start deflating together to the starting position whereupon the A cells further deflate and the B-cells further inflate (period IV). A whole period of inflation and deflation is one bed mattress cycle. This bed mattress cycle repeats - depending on the bed mattress setting - every 10, 15 or 25 minutes. Combined period II and III, when A and B cells inflate and deflate in phase, is similar to the width of the peaks that we detected in our ICP signal (around 3.5 minute).

Video S2 | A 64 times speed up recording of a patient's neck and upper body (written consent provided by the family). Three cycles of inflation and deflation are shown. The patient's head and neck moves upwards and backwards and the lower body moves upwards.

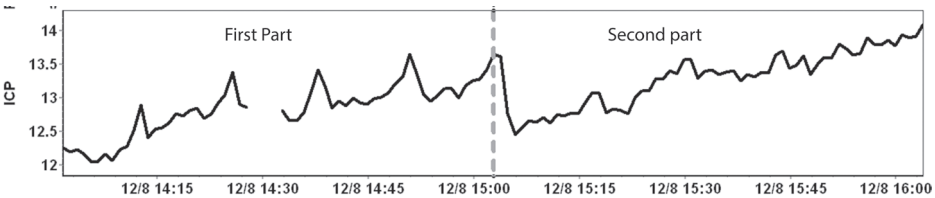
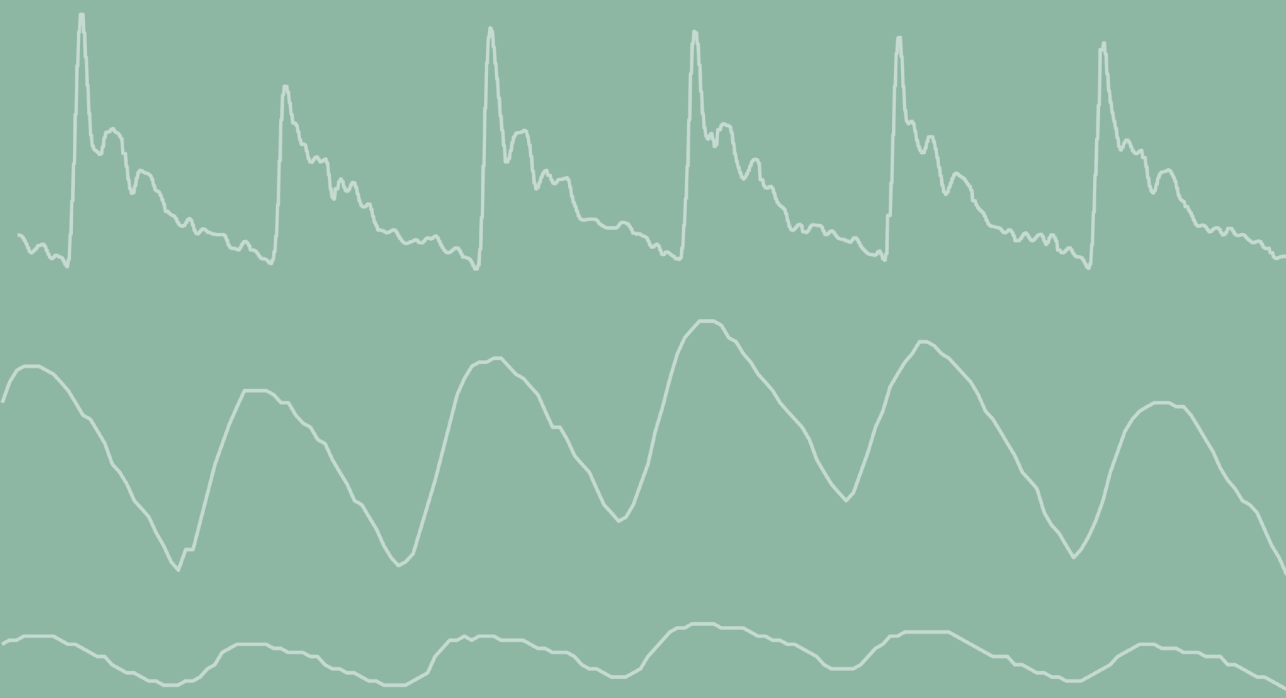


Figure S3 | A recording from a TBI patient showing cyclic ICP peaks. In the first part of the recording the ICP peaks are visible every 10 minutes. In the second period a hard plate is placed underneath the patient's pillow covering the patient's head and neck until the shoulders. The peaks are visibly dampened. *ICP* intracranial pressure.

PART III
NON-INVASIVE NEUROMONITORING



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7

Dynamic Cerebral Autoregulation Estimates Derived from Near Infrared Spectroscopy and Transcranial Doppler

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J Cereb Blood Flow Metab. 2020 Jan;40(1):135-149.

**Both authors contributed equally to this work.*

ABSTRACT

We analysed mean arterial blood pressure, cerebral blood flow velocity, oxygenated haemoglobin and deoxygenated haemoglobin signals to estimate dynamic cerebral autoregulation. We compared macrovascular (mean arterial blood pressure-cerebral blood flow velocity) and microvascular (oxygenated haemoglobin-deoxygenated haemoglobin) dynamic cerebral autoregulation estimates during three different conditions: rest, mild hypocapnia and hypercapnia. Microvascular dynamic cerebral autoregulation estimates were created by introducing the constant time lag plus constant phase shift model, which enables correction for transit time, blood flow and blood volume oscillations (TT-BF/BV correction). After TT-BF/BV correction, a significant agreement between mean arterial blood pressure-cerebral blood flow velocity and oxygenated haemoglobin-deoxygenated haemoglobin phase differences in the low frequency band was found during rest (left: intraclass correlation=0.6, median phase difference 29.5° vs. 30.7°, right: intraclass correlation=0.56, median phase difference 32.6° vs. 39.8°) and mild hypocapnia (left: intraclass correlation=0.73, median phase difference 48.6° vs. 43.3°, right: intraclass correlation=0.70, median phase difference 52.1° vs. 61.8°). During hypercapnia, the mean transit time decreased and blood volume oscillations became much more prominent, except for very low frequencies. The transit time related to blood flow oscillations was remarkably stable during all conditions. We conclude that non-invasive microvascular dynamic cerebral autoregulation estimates are similar to macrovascular dynamic cerebral autoregulation estimates, after TT-BF/BV correction is applied. These findings may increase the feasibility of non-invasive continuous autoregulation monitoring and guided therapy in clinical situations.

INTRODUCTION

Analysis of cerebral vasoregulation can be based on macrovascular or microvascular measurements. The standard for macrovascular measurements is mean arterial blood pressure (MABP) and cerebral blood flow velocity (CBFV), which can be used as input–output variables for transfer function analysis (TFA) to obtain estimates of dynamic cerebral autoregulation (DCA).[1–3] To calculate cerebral microvascular characteristics, such as the capillary transit time, microvascular autoregulation and changes in blood flow and blood volume,[4,5] near infrared spectroscopy (NIRS) may be used. To achieve this, several mathematical models that describe the complex cerebral microvascular hemodynamics and tissue oxygenation in terms of NIRS variables, such as oxygenated haemoglobin (OxyHb), deoxygenated haemoglobin (HHb), total haemoglobin (totalHb) and oxygenation index, have been proposed.[6–8] A logical next step is to combine macro- and microvascular measurements to create a more complete picture of the cerebral circulation.[9,10] Comparisons between macrovascular- and microvascular-based estimates of cerebral autoregulation can be made to answer the question if these measurements are related, and if they capture features of the same physiological processes. The rationale for assuming a relation between macrovascular- and microvascular-based estimates of DCA is that for both methods cerebral arteriolar myogenic activity is assumed to be the main regulator (Figure S1 in Appendix 1). Therefore, the terms macrovascular and microvascular relate only to the measurement site and not to the presumed site of action of cerebral autoregulation.

Discrepancies between both types of DCA estimates have been reported,[5] but direct comparisons between microvascular- and macrovascular-based DCA estimates with simultaneous measurements of all relevant variables have rarely been described.[9–11] If microvascular- and macrovascular-based estimates of DCA were similar, this would be of considerable practical importance, since the feasibility of non-invasive continuous autoregulation monitoring and guided therapy in clinical situations would certainly increase with easy to apply NIRS methodology.[12]

An important difference between the microvascular and macrovascular measurements is that microvascular measurements are part of a serial system, while macrovascular measurements can be viewed as a parallel system; except for frequencies in the autoregulation range, oscillations in MABP and CBFV arrive at their measurements sites simultaneously.[3] For microvascular measurements, oscillations in HHb are delayed compared to OxyHb as a result of passage through the capillary network. This creates transit time effects, which are visible in the frequency domain as the linear phase difference trend

phenomenon of group delay: a constant transit time produces a different phase difference between the input and output signal for different frequencies[13] (see Appendix 1, Part 4 for an example). Another factor that may induce additional constant phase differences between OxyHb and HHb is the 'washout' phenomenon: during changes in blood flow, an increase in OxyHb will be matched by a concurrent decrease in HHb, which will induce a constant phase difference of 180° between OxyHb and HHb oscillations. By contrast, when blood volume changes, OxyHb and HHb changes will be synchronous, which will create a 0° phase difference.[14,15] Both transit time effects and effects of varying blood flow and blood volume oscillations are superimposed on phase differences induced by cerebral autoregulation. Without additional analysis, it may therefore be impossible to separate autoregulation effects from transit time effects and blood flow and blood volume effects. In the field of movement disorders, the group delay phenomenon has been used to estimate corticomuscular conduction time by using a constant time lag plus constant phase shift model.[16,17] A similar analysis strategy may aid the TFA of NIRS data; we assume that the constant time lag is equivalent to the microvascular transit time, and the constant phase shift is generated by the balance between blood flow and blood volume oscillations. By applying this model to the NIRS data, we correct the OxyHb-HHb phase difference for transit time and blood flow and blood volume oscillation induced effects, which *could* enable an unbiased estimation of DCA induced phase differences. From a frequency domain-based system analysis perspective, this is equivalent to converting the serial OxyHb-HHb system back to a parallel system (see Supplementary Data, Appendix 1, Part 1). This is why MABP-CBFV and OxyHb-HHb phase differences can be similar in theory, and this formed one of our main hypotheses.

In this study, we combined DCA measurements based on MABP and CBFV with simultaneous bilateral high-frequency NIRS measurements in healthy human participants. To facilitate the autoregulation analysis, it is helpful to include the response to stimuli with a known effect on DCA, like changes in CO_2. Hypercapnia is known to change the autoregulatory state to a less efficient level and may also decrease cerebral transit times, with concomitant increases in cerebral blood flow and blood volume as a result of the microvascular dilatation that is induced.[18–21]

We compared three different conditions: rest, mild hypocapnia and hypercapnia. Standard procedures for DCA assessment were used on MABP and CBFV, while the constant time lag plus constant phase shift model was applied to OxyHb and HHb. We evaluated three main hypotheses:

1. Uncorrected cerebral autoregulation estimates will be different for MABP-CBFV and OxyHb-HHb.
2. Transit time and the balance between cerebral blood flow and blood volume oscillations can be determined by applying the constant time lag plus constant phase shift model to NIRS data.
3. Transit time, blood flow and blood volume oscillations (TT-BF/BV) corrected cerebral autoregulation estimates based on microvascular measurements (OxyHb-HHb) are similar to macrovascular (MABP-CBFV) estimates of cerebral autoregulation.

MATERIALS AND METHODS

Measurement protocol

Fifteen healthy participants (three male; median age (range) 28 years (21–45)) volunteered for this study after providing informed consent. The measurement protocol was approved by the ethics committee of the University Medical Centre Groningen and was in accordance with the latest version of the Declaration of Helsinki. During the measurements participants lay supine in a 30° head up position. Bilateral 2 MHz Transcranial Doppler (TCD) transducers (Delica, Shenzhen, China) were placed over the transtemporal bone window to record CBFV in both middle cerebral arteries (MCA). The NIRS sensors (Portalite, Artinis Medical Systems, Elst, The Netherlands: http://www.artinis.com/portalite/) were placed bilaterally on the forehead to measure OxyHb, HHb and TotalHb (μmol/litre tissue). A lateral position on the forehead was chosen to ensure the measurement would be in brain tissue within the vascular territory of the MCA. An optode distance of 40 mm was used for this study. A Portapress device (Finapres Medical Systems, Amsterdam, The Netherlands) was placed on the middle finger to measure MABP and heart rate (HR) continuously. The end-tidal CO_2 concentration ($ETCO_2$) was measured by mask capnography, except during the 8% CO_2 inhalation (hypercapnia). The measurement protocol consisted of 5-minute periods of rest (REST), followed by cyclic deep breathing (DB; hypocapnia) and finally DB with 8% CO_2 ($DBCO_2$; hypercapnia) inhalation periods. During REST, further analysis with TFA was based on spontaneous oscillations in MABP, CBFV, OxyHb and HHb during normocapnia. The reason to use DB is twofold: firstly, it will induce MABP oscillations at a higher amplitude than spontaneous MABP oscillations.[22] Several studies have shown that reproducibility of the DCA measurements may be improved by using induced MABP oscillations.[23–25] Secondly, DB will induce a mild degree of hypocapnia, which can be contrasted with hypercapnia. The participants had to follow audio instructions that included breathing cycles of 8, 10, 14 and 20 s, covering the frequency range of 0.05–0.125 Hz. This frequency range was chosen such that it would include the upper very low frequency (VLF) and low

frequency (LF) ranges that are used for the determination of DCA parameters. Individual variations in the sequence of breathing cycles were implemented by changing the order of the breathing frequencies semi-randomly, to approximate the condition of naturally occurring spontaneous oscillations as closely as possible.

Cerebral autoregulation analysis without TT-BF/BV correction

The 250 Hz (TCD) and 50 Hz (NIRS) data were pre-processed online to generate beat-to-beat data, but high-frequency data were also captured and stored separately. Other processing steps were performed retrospectively. Artefacts were removed after visual inspection. Occasional spike artefacts occurred and were removed by linear interpolation. In two cases, major movement related artefact occurred during REST, but this was identified during measurement and was corrected for by extending the registration. The data were thereafter linearly interpolated to 10 Hz. The data were split into the different frequency bands: VLF (0.02–0.07 Hz), LF (0.07–0.2 Hz) and high frequency (HF: 0.2–0.5 Hz). Power spectral density estimates were performed using the Welch method (100 s epochs, 50% window overlap). The relationships between MABP and CBFV and between OxyHb and HHb were determined with TFA using the recommendations of the international Cerebral Autoregulation Research Network.[1] After computing the gain, phase and coherence, the phase results were corrected for phase wrap around by visually inspecting the phase plots for sudden large phase changes, and subsequently adding or subtracting 360°. To estimate mean effects, we also created grand average waveform plots by averaging the TFA results across all participants. For the TFA results, the averaging was done on the real and imaginary parts of the transfer function, separately, which were subsequently transformed back to gain and phase estimates. This is a standard procedure for creating averages of circular data.[26]

Transit time and blood flow and blood volume oscillation estimates

Because autoregulation effects are minimal above 0.2 Hz, the transit time analysis was performed on the phase difference spectrum in the HF range (0.2–0.5 Hz). For this part of the analysis, we used the high-frequency data, after low pass filtering the data with a sixth-order zero phase butterworth filter with a cut off frequency of 0.5 Hz. This resulted in higher coherences and smaller confidence limits for the phase difference estimates in the HF band compared to the beat to beat data. This is important as the transit time analysis is based on the HF band data.

The constant time lag plus constant phase shift model states that the phase shift at a specific frequency f_j between two oscillations, x and y, is given as[27]

$$\phi(fj)xy = 360.t.fj + \theta \qquad (1)$$

where *t* is the constant time lag (in seconds) and θ is the constant phase shift between them. Applying equation (1) to NIRS, *t* is equivalent to the transit time *TT* and can be calculated from a phase difference spectrum with a linear slope between frequency f_i and frequency f_j as[16]

$$TT = \frac{\phi(fi)xy - \phi(fj)xy}{(fi - fj).\ 360} \qquad (2)$$

With short *TT*, the slope is low, while with longer *TT* it will become steeper.

The constant phase shift θ is particularly relevant when considering OxyHb and HHb data: the well-known 'washout' effect will induce a constant phase shift of 180° between OxyHb and HHb oscillations. This effect will be present if blood flow oscillations are prominent. On the other hand, we assume the constant phase shift to be 0° if blood volume oscillations are dominant, as has been suggested previously.[14,15] Although blood flow oscillations are usually dominant in brain tissue,[28] a mixture of both blood flow and blood volume oscillations may be present, as has been previously reported in the literature, which may result in a constant phase difference in between 0° and 180°.[29,30] Figure 1 illustrates these effects on simulated data. These effects were further examined and quantified in a simulation experiment, the details of which can be found in Appendix 1, Parts 1 and 2. Importantly, these simulations show that the slope of the linear phase difference trend can change as a result of different transit times but also as a result of different percentages of blood flow and blood volume oscillations. However, with changing transit times and constant blood flow and blood volume oscillations, the Y-axis intercept of the linear phase trend will remain constant, while with different percentages of blood flow and blood volume oscillations but constant transit time, the X-axis intercept of the linear phase trend will remain constant (Figure 1, bottom row). On the basis of these results, one can deduce that the percentage of blood flow oscillations (*%BF*) can be estimated from the Y-axis intercept (*Yx*=0) as:

$$\%BF = \frac{Yx = 0}{180}.100 \qquad (3)$$

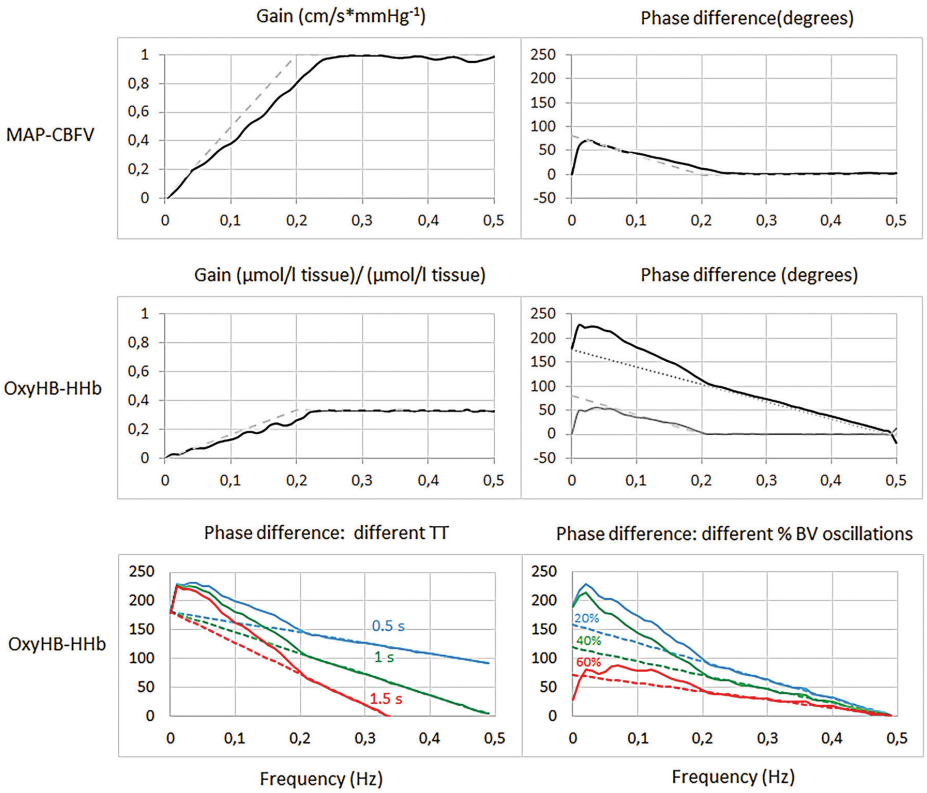

Figure 1 | Transfer function results on simulated data. Five data segments were used in the averaging procedure that is part of TFA. Top row: MABP-CBFV comparison: reference data are depicted in grey dashed lines, while solid black lines indicate the TFA results. Middle row: OxyHb-HHb comparison: in the phase difference plot, the dotted line indicates the linear trend in the HF data. Subtracting this linear trend from the OxyHb-HHb data (black solid line) results in the transit time corrected phase difference (solid grey line), which is very close to the reference data. Bottom row: OxyHb-HHb phase difference spectra for different TTs and different percentages of blood volume oscillations (%BV). %BV was varied by changing the percentage of data segments with synchronous OxyHb and HHb oscillations. Note that for different transit times, the Y-axis intercept of the linear phase trend due to transit time does not change but the X-axis intercept does, while for different percentages of blood volume oscillations the X-axis intercept remains constant and the Y-axis intercept changes. For details see Appendix 1, Parts 1 and 2. MABP-CBFV: mean arterial blood pressure-cerebral blood flow velocity; OxyHb-HHb: oxygenated haemoglobin-deoxygenated haemoglobin; TT: transit time; BV: blood volume.

With an increasing percentage of blood volume oscillations, the 0-s transit time associated with blood volume changes will reduce the slope of the linear phase difference trend, but the X-axis intercept (Xy=0) will still be determined by the transit time associated with blood flow oscillations. The transit time associated with blood flow changes ($TT(BF)$) can be retrieved by drawing a line between the point Y = 180; X = 0 and the X-axis intercept and determining its slope according to equation (2):

$$TT(BF) = \frac{180}{X_{y=0}\ .360} \qquad (4)$$

For this study, the mean transit time *TT* was determined by fitting a straight line to the phase difference bins with significant coherence in the HF range (0.2–0.5 Hz), by using a least squares fitting procedure. The mean transit time *TT*

reflects the transit time associated with the relative contributions of both blood flow and blood volume oscillations. Only data sections that yielded at least five consecutive bins with significant coherence were accepted, thereby avoiding inclusion of bins with significant coherence that arose by chance.[27] The mean transit time was calculated according to equation (2), and extrapolation of the linear trend outside the HF range was performed by applying equation (1).

Cerebral autoregulation analysis with TT-BF/BV correction

We assume that the measured OxyHb-HHb phase difference is the result of transit time induced phase differences, the relative contribution of blood flow and blood volume oscillations and the effects of cerebral autoregulation. Therefore, to correct the OxyHb-HHb phase difference estimate for transit time effects and blood flow and blood volume oscillations, we subtracted the linear phase trend in the HF range generated by transit time and blood flow and blood volume oscillations from the measured OxyHb-HHb phase difference. After subtraction, the remaining phase difference should then be determined by cerebral autoregulation only.

Statistical analysis

The statistical analysis was performed in SPSS (version 21). Data were expressed as median (IQR) values because of non-normal distributions. Friedman's two-way analysis of variance was used to test for significant differences between the conditions REST vs. DB, REST vs. $DBCO_2$ and DB vs. $DBCO_2$, and was applied to the left and right sides, separately. Bonferroni post hoc corrections for multiple comparisons were used in all analyses. Differences between microvascular and macrovascular DCA estimates were evaluated with related samples Wilcoxon signed-rank test. Intraclass correlation (ICC) analysis was used to evaluate the agreement between microvascular and macrovascular TFA results, using the two-way mixed model with absolute agreement option in SPSS. When necessary, data were log-transformed to obtain a normal distribution. ICCs were tested for significance by applying an F-test with true value 0. For all tests, we assumed a significance level of $\alpha = 0.05$.

RESULTS

Hemodynamic variables

Table 1 provides an overview of the hemodynamic variables obtained from the 15 participants during the experiment. MABP increased during $DBCO_2$ and was significantly higher compared to REST. Heart rate was significantly higher during DB compared to the other conditions, although the absolute difference was only small (± 5 beats/min). $ETCO_2$ decreased during DB (REST: 5.1 vs. DB: 4.7 kPa, $p = 0.03$). $ETCO_2$ monitoring was not possible during $DBCO_2$. As expected, the power in both the LF and VLF range of the ABP signal increased significantly during both DB periods (REST vs. DB vs. $DBCO_2$: LF: 13.2 vs. 41.1 vs. 40.5 $mmHg^2 \cdot Hz^{-1}$, $p < 0.001$ vs. REST for both DB and $DBCO_2$, VLF: 52.8 vs. 105.9 vs. 110.3 $mmHg^2 \cdot Hz^{-1}$, $p = 0.02$ for DB vs. REST, $p = 0.09$ for $DBCO_2$ vs. REST), but power in the HF range remained unchanged. CBFV decreased during DB, and increased during $DBCO_2$, with significant differences only between DB and $DBCO_2$. OxyHb, HHb and totalHb showed highly significant changes between the three conditions, with an increase in OxyHb and totalHb and a decrease in HHb during $DBCO_2$, and a reversed pattern during DB. Figure 2 shows an example of a raw data recording in a volunteer.

Cerebral autoregulation analysis without TT-BF/BV correction

Tables 2 (LF band data) and 3 (VLF band data) present an overview of the MABP-CBFV and OxyHb-HHb TFA results in the cerebral autoregulation range, without TT-BF/BV correction.

Table 1 | Hemodynamic variables, MABP-power spectral density data, and statistical comparisons.

	Median values (IQR)			Post hoc Friedman test (*p*-value)		
Test condition	**REST (n = 15)**	**DB (n = 15)**	**$DBCO_2$ (n = 15)**	**REST-DB**	**REST-$DBCO_2$**	**DB-$DBCO_2$**
MABP (mmHg)	85.1 (20.4)	88.7 (20.7)	95.5 (20.2)	1.0	0.02	0.09
Heart rate (min^{-1})	68.1 (22.9)	73.0 (21.3)	68.1 (18.8)	0.03	1.0	0.02
$ETCO_2$ (kPa)	5.1(0.6)	4.7 (0.4)	[a]	0.03	–	–
MABP PSD ($mmHg^2/Hz^{-1}$)						
VLF (0.02–0.07 Hz)	52.8 (65.5)	105.9 (71.3)	110.3 (159.6)	0.02	0.09	1.0
LF (0.07–0.2 Hz)	13.2 (13.2)	41.1 (52.6)	40.5 (44.2)	<0.001	<0.001	1.0
HF (0.2–0.5 Hz)	1.0 (1.1)	1.2 (1.2)	2.2 (2.3)	1.0	0.09	0.09
CBFV (cm/s)						
Left	63.8 (22.0)	48.8 (22.7)	73.6 (30.1)	0.06	0.13	<0.001
Right	60.1 (15.3)	49.5 (15.0)	77.4 (22.6)	0.06	0.13	<0.001
OxyHb (μmol/l tissue)						
Left	0.5 (1.6)	−0.07 (2.2)	2.6 (5.8)	<0.001	<0.001	<0.001
Right	0.5 (0.5)	−0.2 (1.6)	2.7 (6.7)	<0.001	<0.001	<0.001
HHb (μmol/l tissue)						
Left	−0.05 (0.5)	0.1 (0.2)	−2.5 (3.0)	<0.001	<0.001	<0.001
Right	0.0 (0.5)	0.02 (0.9)	−2.4 (2.7)	<0.001	<0.001	<0.001
totalHb (μmol/l tissue)						
Left	0.4 (1.6)	0.08 (1.9)	0.5 (4.6)	<0.001	0.167	<0.001
Right	0.3 (1.6)	−0.3 (1.5)	0.4 (5.1)	<0.001	0.024	<0.001

All values are reported as median (IQR) for the three test conditions: REST, DB and $DBCO_2$ inhalation; p-values are given for the post hoc Friedman test. The MABP PSD was calculated for the frequency ranges: VLF, LF and HF.
MABP: Mean arterial blood pressure; $ETCO_2$: end-tidal CO_2; PSD: power spectral density; CBFV: cerebral blood flow velocity; OxyHb: oxyhaemoglobin; HHb: deoxyhaemoglobin; totalHb: total haemoglobin; VLF: very low frequency; LF: low frequency; HF: high frequency; REST: 5-minute periods of rest; DB: deep breathing; $DBCO_2$: deep breathing with 8% CO_2. [a] End-tidal CO_2 monitoring was not possible during the inhalation of 8% CO_2.

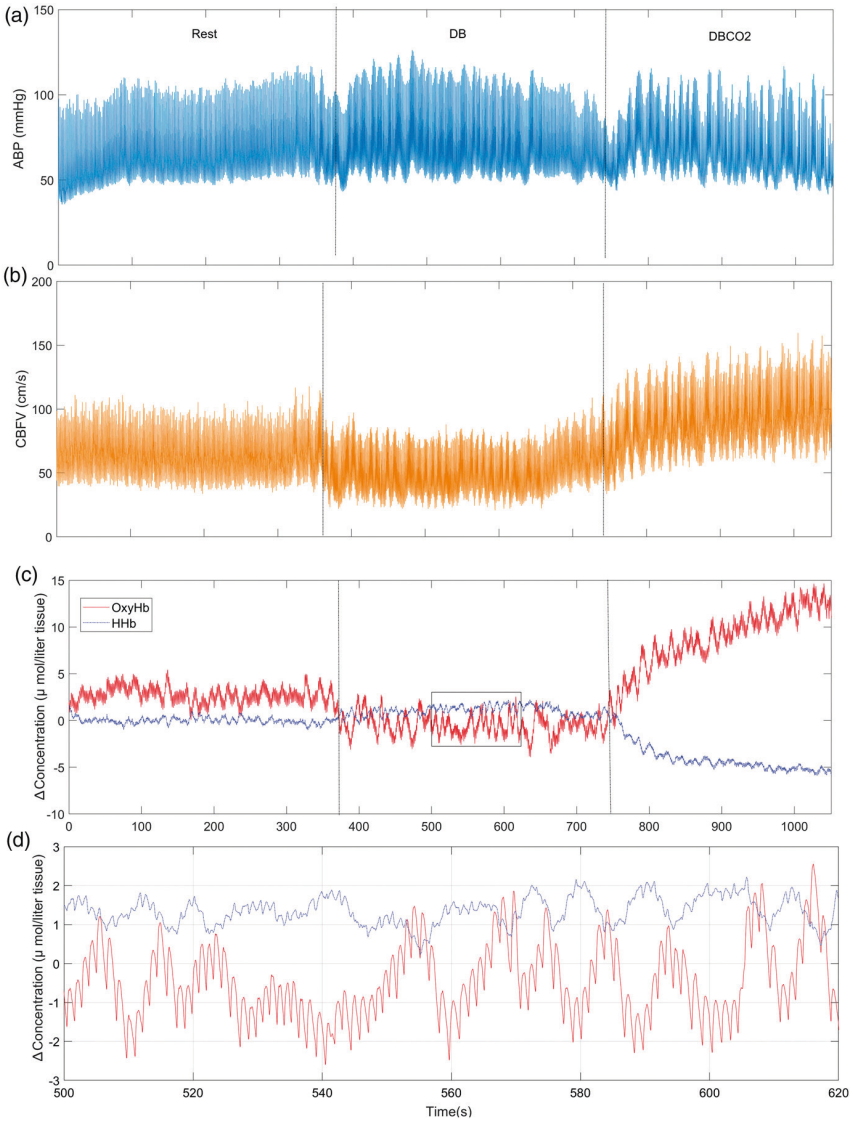

Figure 2 | Raw data recording in a representative healthy volunteer. (a) the ABP, (b) the CBFV in the (left) middle cerebral artery and (c) the (left) OxyHb and (left) HHb signals expressed as concentration differences compared to baseline. The vertical lines separate the different conditions. From left to right: REST, DB, and $DBCO_2$. The lower panel (d) zooms in on the 120 s of data during the DB task framed in (c), which shows the typical antiphase relation between OxyHb and HHb for slow oscillations during high blood flow conditions. Note that the amplitude of oscillations in the OxyHb signal was higher compared to the HHb signal, with increasing amplitudes during both DB periods. During $DBCO_2$, CBFV and OxyHb increase clearly with a comparatively smaller decrease in absolute values of HHb, which is caused by increased CBF and CBV during hypercapnia while assuming stable brain metabolism. ABP: arterial blood pressure; CBFV: cerebral blood flow velocity; OxyHb: oxygenated haemoglobin; HHb: deoxygenated haemoglobin.

LF band data

Using MABP-CBFV data, a significant phase difference decrease during $DBCO_2$ (left 23.4°; right 22.9°) was seen compared to DB (left 58.4°; right 54.2°, $p < 0.001$ for both sides) and to a lesser degree also compared to REST (left 35.4° ; right 36.1°, left $p = 0.01$, right $p = 0.13$). Relative gain values also decreased significantly during $DBCO_2$ compared to REST and DB. Coherence increased significantly during $DBCO_2$ compared to DB, but not compared to REST. Using the OxyHb-HHb data, the phase difference decreased markedly during $DBCO_2$ compared to REST (left 30.4°; right 57.7°, REST: left 118.2°; right 122.3°, $p < 0.01$ for both sides) but no significant change occurred during DB (left 125.4°; right 139.9°, $p = 1$ for both sides). Gain decreased during $DBCO_2$, but not significantly for both hemispheres. Coherence showed no clear changes.

VLF band data

Using the MABP-CBFV data, no significant differences between conditions were found for gain or coherence. Although phase values were lower during $DBCO_2$ and during DB compared to REST, variability was high, and phase was only significantly lower for the left hemisphere for the REST-$DBCO_2$ comparison. Using the OxyHb-HHb data, no major changes were found for gain or coherence, but phase decreased during $DBCO_2$, and was significantly different from REST, but not from DB.

OxyHb-HHb vs. MABP-CBFV

When comparing the OxyHb-HHb analysis with the MABP-CBFV analysis, gain was much lower for OxyHb-HHb in all conditions for both the VLF and LF band (all comparisons $p < 0.05$). The phase difference was consistently and significantly higher for the OxyHb-HHb analysis in all conditions and for both the VLF and LF band data (all comparisons $p < 0.05$), but the median (OxyHb-HHb) − (MABP-CBFV) phase difference was much smaller during $DBCO_2$ (VLF: left 75.0° right 66.9°, LF: left: 40.8° right 17.8°) compared to REST (VLF: left 117.5° right 110.2°, $p > 0.05$ for both sides, LF: left: 85.7° right 83.9°, left $p < 0.001$ right $p = 0.004$) and DB (VLF: left 140.8° right 130.9°, $p > 0.05$ for both sides, LF: left: 82.7° right 69.6°, left $p = 0.032$ right $p = 0.017$), although these differences were only significant for the LF band data. The ICC analysis showed a uniform absence of significant agreement between OxyHb-HHb and MABP-CBFV TFA results, for both gain and phase in both the VLF and LF band during all conditions. Regression analysis also showed an absence of a significant linear relation between uncorrected OxyHb-HHb and MABP-CBFV phase differences during all conditions, except for the right sided measurements during $DBCO_2$ (MABP-CBFV = 13.7 + 0.14 × OxyHB-HHB phase difference, $p = 0.01$). Coherence was lower in all conditions for OxyHb-HHb compared to MABP-CBFV for the LF band data but not for the VLF band data.

Table 2 | Transfer function analyses and statistical comparisons: LF band data.

		Median values (IQR)			Post hoc Friedman test (p-value)		
Test condition	**Side**	**REST (n = 15)**	**DB (n = 15)**	**$DBCO_2$ (n = 15)**	**REST-DB**	**REST-$DBCO_2$**	**DB-$DBCO_2$**
MABP-CBFV							
Gain (cm/s)/mmHg	Left	1.0 (0.5)	0.9 (0.5)	0.9 (0.5)	NC	NC	NC
	Right	1.1 (0.6)	0.8 (0.4)	0.8 (0.4)	0.006	0.002	1.0
Gain (%/%)	Left	1.5 (0.3)	1.6 (0.7)	1.1 (0.3)	0.82	0.02	<0.001
	Right	1.5 (0.5)	1.4 (0.2)	1.1 (0.3)	1.0	0.001	0.002
Phase (°)	Left	35.4 (17.6)	58.4 (30.7)	23.4 (18.2)	0.01	0.20	<0.001
	Right	36.1 (10.1)	54.2 (24.7)	22.9 (24.7)	0.13	0.03	<0.001
Coherence	Left	0.7 (0.2)	0.6 (0.1)	0.8 (0.2)	0.30	0.30	0.003
	Right	0.7 (0.2)	0.6 (0.2)	0.8 (0.2)	0.13	0.43	0.002
OxyHb-HHb							
Gain (µmol/l tissue)/	Left	0.2 (0.1)	0.3 (0.1)	0.2 (0.1)	1.0	0.09	0.02
(µmol/l tissue)	Right	0.3 (0.1)	0.3 (0.1)	0.2 (0.1)	1.0	0.04	0.11
Gain (%/%)	Left	0.5 (0.2)	0.5 (0.3)	0.3 (0.1)	1.0	0.03	0.01
	Right	0.5 (0.3)	0.5 (0.3)	0.3 (0.2)	1.0	0.05	0.13
Phase (°)	Left	118.2 (52.4)	125.4 (49.3)	30.4 (59.1)	1.0	<0.001	0.02
	Right	122.3 (41.7)	139.9 (56.5)	57.7 (72.8)	1.0	0.007	0.004
Coherence	Left	0.5 (0.2)	0.4 (0.2)	0.6 (0.3)	1.0	0.20	0.03
	Right	0.4 (0.3)	0.5 (0.3)	0.5 (0.2)	NC	NC	NC

Transfer function analysis with input parameters MABP and OxyHb and output parameters CBFV in the middle cerebral artery and HHb, respectively. Values are given as median values (IQR) for the three test conditions; REST, DB and $DBCO_2$; p-values are given for the post hoc Friedman test. NC indicates no post-hoc statistics were calculated as the Friedman test detected no overall significance difference. Gain (%/%) refers to normalised data while (cm/s)/mmHg and (µmol/l tissue)/(µmol/l tissue) refer to data that were mean subtracted. Coherence: values are means of the LF band. MABP: Mean arterial blood pressure; CBFV: cerebral blood flow velocity; OxyHb: oxyhaemoglobin; HHb: deoxyhaemoglobin; totalHb: total haemoglobin; LF: low frequency; REST: 5-minute periods of rest; DB: deep breathing; $DBCO_2$: deep breathing with 8% CO_2.

Table 3 | Transfer function analyses and statistical comparisons: VLF band data.

		Median values (IQR)			Post hoc Friedman test (p-value)		
Test condition	**Side**	**REST (n = 15)**	**DB (n = 15)**	**$DBCO_2$ (n = 15)**	**REST-DB**	**REST-$DBCO_2$**	**DB-$DBCO_2$**
MABP-CBFV							
Gain (cm/s)/mmHg	Left	0.5 (0.5)	0.6 (0.4)	0.6 (0.2)	NC	NC	NC
	Right	0.7 (0.4)	0.6 (0.4)	0.6 (0.3)	NC	NC	NC
Gain (%/%)	Left	0.8 (0.3)	0.9(0.5)	0.8 (0.3)	NC	NC	NC
	Right	0.9 (0.3)	1.0 (0.6)	0.8 (0.3)	NC	NC	NC
Phase (°)	Left	52.0 (47.2)	36.6 (36.3)	26.3 (28.9)	0.15	0.02	1.0
	Right	54.4 (18.1)	24.5 (38.1)	25.9 (29.3)	0.12	0.07	1.0
Coherence	Left	0.3 (0.2)	0.4 (0.2)	0.5 (0.2)	NC	NC	NC
	Right	0.3 (0.3)	0.4 (0.2)	0.5 (0.3)	0.6	0.06	0.20
OxyHb-HHb							
Gain (μmol/l tissue)/	Left	0.3 (0.1)	0.2 (0.2)	0.2 (0.1)	0.79	0.01	0.22
(μmol/l tissue)	Right	0.3 (0.2)	0.3 (0.1)	0.2 (0.1)	NC	NC	NC
Gain (%/%)	Left	0.6 (0.1)	0.5 (0.2)	0.4 (0.2)	0.20	0.03	1.0
	Right	0.6 (0.2)	0.5 (0.1)	0.3 (0.1)	0.43	0.01	0.43
Phase (°)	Left	166.6 (53.5)	161.9 (91.4)	80.0 (91.3)	0.22	0.01	0.79
	Right	172.1 (18.1)	165.0 (45.8)	117.1 (85.1)	0.35	0.005	0.35
Coherence	Left	0.4 (0.4)	0.3 (0.4)	0.4 (0.4)	NC	NC	NC
	Right	0.5 (0.3)	0.4 (0.3)	0.4 (0.2)	NC	NC	NC

Transfer function analysis with input parameters MABP and OxyHb and output parameters CBFV in the middle cerebral artery) and HHb, respectively. Values are given as median values (IQR) for the three test conditions; REST, DB and $DBCO_2$; p-values are given for the post hoc Friedman test. NC indicates no post-hoc statistics were calculated as Friedman test detected no overall significance difference. Gain (%/%) refers to normalised data while (cm/s)/mmHg and (μmol/l tissue)/(μmol/l tissue) refer to data that were mean subtracted. Coherence: values are means of the VLF band. MABP: Mean arterial blood pressure; CBFV: cerebral blood flow velocity; OxyHb: oxyhaemoglobin; HHb: deoxyhaemoglobin; totalHb: total haemoglobin; VLF: very low frequency; REST: 5-minute periods of rest; DB: deep breathing; $DBCO_2$: deep breathing with 8% CO_2.

Cerebral autoregulation analysis with TT-BF/BV correction

Figure 3 shows the grand average phase difference spectra for all three conditions and is based on the data of all 15 subjects. During REST and DB, subtraction of the linear trend in the HF data results in a phase difference spectrum that is very similar to the MABP-CBFV phase difference spectrum. This result is qualitatively equal to the result that was obtained using the simulated data (Figure 1). However, during $DBCO_2$, the slope of the linear trend in the HF data is almost zero, suggesting a high percentage of blood volume changes, and subtraction of this trend does not result in major changes in the OxyHb-HHb spectrum. Note that despite the different slopes, the X-axis intercept for the linear phase difference trend is similar for all three conditions. For the LF band, the OxyHb-HHb and MABP-CBFV phase difference spectra are still similar, but for the VLF the difference is high. This result was not predicted from analysis of the simulated data.

Table 4 shows the results of the cerebral autoregulation analysis after TT-BF/BV correction in individual subjects. In four subjects, coherence in the HF band was insufficient for reliable calculation of transit time. These subjects were left out of the analysis which is presented in Table 4.

During all conditions, median phase differences were not significantly different between MABP-CBFV and corrected OxyHb-HHb, except for the VLF band data on the left side during $DBCO_2$, which showed higher values for corrected OxyHb-HHb compared to MABP-CBFV (52.3° vs. 30.3°, $p = 0.03$). All (MABP-CBFV) – (corrected OxyHb-HHb) phase differences were much lower compared to the autoregulation analysis without TT-BF/BV correction. The ICC analysis indicated significant agreement between MABP-CBFV and corrected OxyHb-HHb phase differences for the LF band data during rest and DB on both sides, but for the VLF band and HF band no significant agreement was found. The mean absolute phase difference between MABP-CBFV and corrected OxyHb-HHb was much lower for the LF and HF band data compared to the VLF band data.

The mean transit time was similar during REST (left 0.68 ± 0.23, right 0.74 ± 0.20) and DB (left 0.70 ± 0.63, right 0.87 ± 0.34), but decreased markedly during $DBCO_2$ (left: 0.22 ± 0.32, right 0.33 ± 0.13, $p < 0.05$ vs. REST and DB for both sides). However, the transit time related to blood flow changes was remarkably stable during all conditions, with mean values of around 1.1 to 1.2 s, with no significant differences between the three conditions. The estimated percentage of blood flow changes was similar during REST (left 66 ± 22, right 73 ± 16) and DB (left 63 ± 28, right 65 ± 23), but decreased significantly during $DBCO_2$ (left 21 ± 31, right 26 ± 19, $p < 0.05$ vs. REST and DB for both sides).

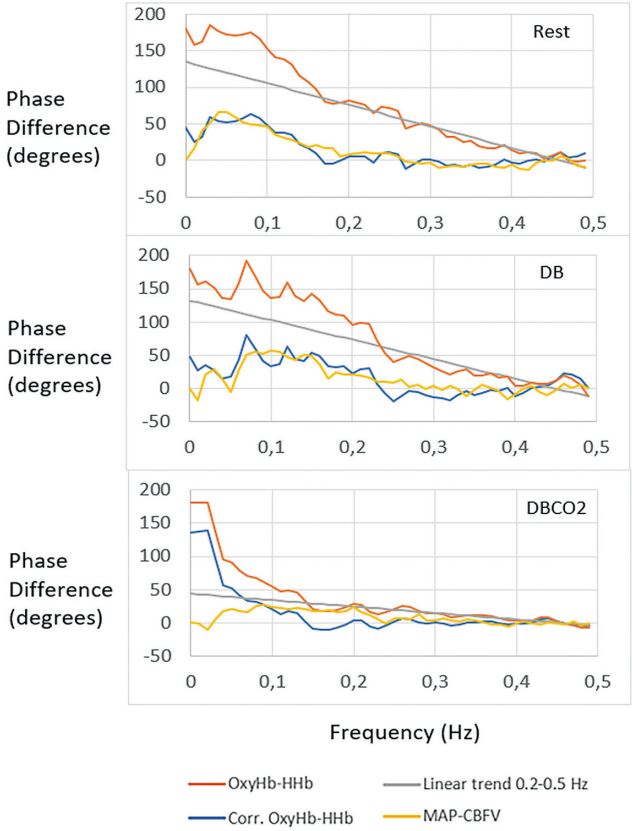

Figure 3 | Grand average phase difference spectrum results. The grand average mean arterial blood pressure (MABP)-cerebral blood flow velocity (CBFV) phase difference and oxyhaemoglobin (OxyHb)- deoxyhaemoglobin (HHb) phase difference for the frequency range 0–0.5 Hz for REST, DB and $DBCO_2$. Outside the autoregulatory frequency range in the HF band, the MABP-CBFV phase shift (yellow lines) fluctuates around 0° for the three conditions, indicating that these calculations are not influenced by transit time. This is the typical spectral profile of a parallel system. The OxyHb-HHb HF phase difference shows a linear trend during REST and DB (grey lines). This is the typical spectral profile of a serial system with transit time. Subtracting the linear trend from the OxyHb-HHb phase difference results in the TT-BF/BV corrected OxyHb-HHb phase difference (blue lines). Note that during REST and DB, the TT-BF/BV corrected phase difference is very similar to the MABP-CBFV phase difference. During CO_2 inhalation ($DBCO_2$), the slope of the linear phase difference trend decreases, indicating a decrease in mean transit time. However, the X-axis intercept does not change compared to REST and DB, suggesting prominent blood volume changes. In the VLF range, blood flow changes remain dominant, and a mismatch between the MABP-CBFV and TT-BF/BV corrected OxyHb-HHb phase difference spectrum is present. MABP-CBFV: mean arterial blood pressure-cerebral blood flow velocity; OxyHb-HHb: oxygenated haemoglobin-deoxygenated haemoglobin; $DBCO_2$: deep breathing with the inhalation of 8% CO_2.

Table 4 | Results of the phase difference values between OxyHb and HHb after TT-BF/BV correction.

Frequency Band	Corrected OxyHb-HHb	MABP-CBFV	p-value	Mean Abs Error	ICC	TT mean	TT BF	%BF
REST								
VLF left	48.7 (23.4)	46.3 (11.5)	>0.05	17.2 (27.4)	−0.14			
VLF right	46.1 (34.5)	40.9 (12.3)	>0.05	33.6 (67.8)	0.1			
LF left	30.7 (7.5)	29.5 (6.5)	>0.05	4.5 (7.2)	0.60[a]			
LF right	39.6 (23.6)	32.6 (8.9)	>0.05	9.8 (9.5)	0.56[a]			
HF left	4.1 (5.6)	1.2 (6.3)	>0.05	4.3 (3.3)	−0.07	0.68 (0.23)	1.14 (0.14)	66 (22)
HF right	6.8 (6.8)	0.2 (7.8)	>0.05	6.0 (10.0)	−0.36	0.74 (0.20)	1.14 (0.10)	73 (16)
DB								
VLF left	59.5 (50.9)	27.1 (7.7)	>0.05	35.6 (38.6)	0.44			
VLF right	66.7 (75.0)	29.7 (4.6)	>0.05	60.9 (22.5)	−0.62			
LF left	43.3 (29.4)	48.6 (20.9)	>0.05	10.6 (11.7)	0.73[a]			
LF right	61.8 (32.6)	52.1 (10.9)	>0.05	8.5 (17.3)	0.70[a]			
HF left	1.1 (19.7)	1.9 (11.3)	>0.05	9.5 (12.8)	−0.03	0.70 (0.63)	1.22 (0.20)	63 (28)
HF right	7.3 (4.9)	5.8 (7.8)	>0.05	10.0 (8.3)	0.17	0.87 (0.34)	1.14 (0.22)	65 (23)
$DBCO_2$								
VLF left	52.3 (72.3)	30.3 (16.1)	0.03	53.9 (31.3)	0.42			
VLF right	65.6 (57.0)	23.4 (17.9)	>0.05	51.1 (31.9)	−0.21			
LF left	27.9 (22.2)	20.4 (9.0)	>0.05	14.0 (6.5)	0.33			
LF right	19.8 (14.7)	21.2 (11.8)	>0.05	8.8 (7.0)	0.37			
HF left	2.2 (5.0)	3.5 (6.3)	>0.05	6.1 (10.4)	−0.17	0.22 (0.32)[b]	1.11 (0.22)	21 (31)[b]
HF right	5.4 (5.2)	4.0 (11.4)	>0.05	9.9 (4.2)	−0.28	0.33 (0.13)[b]	1.22 (0.18)	26 (19)[b]

Due to lack of sufficient coherence in the HF band, 4 subjects were left out of the analysis, leaving 11 subjects for this analysis. For comparison, the MABP-CBFV phase difference is also presented. Mean Abs error: mean of the absolute angular difference between the corrected OxyHb-HHb and MABP-CBFV phase difference; ICC: intraclass correlation coefficient; TT mean: mean transit time; TT BF: transit time for blood flow changes; %BF: estimated percentage of blood flow changes.

[a] ICC value significantly different from 0.

[b] Significant difference vs. REST and DB for TT mean and %BF.

DISCUSSION

In this study, we performed detailed analysis of MABP, CBFV and NIRS signals to answer the question if microvascular- and macrovascular-based estimates of DCA are similar. The comparisons were made both with and without TT-BF/BV correction. TT-BF/BV correction was implemented by applying the constant time lag plus constant phase shift model, which is a well-known model for the analysis of serial systems in the frequency domain. Our main findings are:

1. Without TT-BF/BV correction, microvascular-based estimates of cerebral autoregulation are different from macrovascular-based estimates of cerebral autoregulation, with much higher phase differences for microvascular-based estimates in all conditions.
2. Transit time and the percentage of blood flow and blood volume oscillations can be calculated from the OxyHb-HHb phase difference spectrum in the HF band by using the constant time lag plus constant phase shift model, provided that coherence is large enough for reliable analysis.
3. After TT-BF/BV correction, microvascular-based estimates of DCA are similar to macrovascular-based DCA estimates. For grand average data, this is true for the entire phase difference spectrum, while for individual data this applies to the LF band only.
4. $DBCO_2$ resulted in a decrease of both microvascular and macrovascular measurement-based phase differences in the LF band, but not in the VLF band. A decrease in mean transit time was also observed, but the transit time related to blood flow oscillations was remarkably stable during all conditions. During $DBCO_2$, the percentage of blood volume oscillations increased in the LF and HF band, but not in the VLF band.

Cerebral autoregulation estimates without TT-BF/BV correction

The finding that macrovascular- and microvascular-based estimates of DCA are different was expected and can be explained by the transit time effects and blood flow and blood volume effects that are present for the microvascular-based estimates and absent for macrovascular-based estimates. In response to DB and $DBCO_2$, LF phase differences between MABP and CBFV increased and decreased, respectively. This is a well-known phenomenon and has been reported several times by other authors and was interpreted as a stronger vs. weaker autoregulatory response during hypo- and hypercapnia respectively.[19,31,32] The uncorrected OxyHb-HHb VLF and LF phase differences showed a similar pattern, but the values were significantly higher compared to the MABP-CBFV phase difference during all conditions. With $DBCO_2$, this difference was significantly lower compared to the other conditions. This can be explained by the increase in cerebral blood volume oscillations

during hypercapnia which will decrease the mean transit time due to the 0-s transit time that is associated with blood volume oscillations. The lack of any agreement and the prevailing lack of a significant linear relation between uncorrected microvascular- and macrovascular-based cerebral autoregulation estimates demonstrate that uncorrected OxyHb-HHb phase differences cannot be used to estimate cerebral autoregulation.

Transit time, blood flow and blood volume oscillations

The results of the OxyHb-HHb grand average data during rest and DB are very similar to the simulated data results, which strongly suggest that the underlying assumptions behind the constant time lag plus constant phase shift model are correct during these conditions. However, during $DBCO_2$, the VLF band results deviated from what was predicted by the simulated data, probably because the assumption that blood volume oscillations would increase for every frequency is not correct. The brain is encased in a rigid skull, which may not allow unlimited blood volume changes.[15,33] Especially for the VLF band, induced oscillations are of high amplitude, which may exceed the limits of blood volume expansion induced by hypercapnia. Therefore, blood flow changes must occur in order to prevent a rise in intracranial pressure. For higher frequencies, blood volume changes are of lower amplitude and blood volume changes may not be limited during hypercapnia.

On individual data, in 4 out of 15 subjects, coherence was too small for reliable calculations of transit time and percentages of blood flow and blood volume oscillations. This was probably caused by noise, or by insufficient power in the HF band, in combination with measurements of relatively short duration. The confidence limits of the phase difference spectra depend on the size of coherence and the number of data segments used in the averaging procedure for TFA.[34,35] Using data with low coherence will increase the confidence limits and will therefore result in major error when calculating transit time and blood flow and blood volume oscillations. The solution to this problem could either be to use manoeuvres to increase coherence in the HF band or to increase the duration of the measurement to increase the number of data segments that are used for averaging during TFA. When comparing our transit times with those reported in other types of studies, the average microvascular transit times are quite similar for both human[5] and animal[36,37] data, which supports the validity of these measurements.

Cerebral autoregulation estimates with TT-BF/BV correction

For individual data, after correcting the OxyHb-HHb phase difference spectrum using the constant time lag plus constant phase difference model, the mean absolute difference with the MABP-CBFV phase spectrum was low for the LF

band and HF band, but high for the VLF band data. A significant agreement between OxyHb-HHb and MABP-CBFV phase differences was found for the LF band data during REST and DB, but not during $DBCO_2$. With similar mean absolute phase differences between OxyHB-HHb and MABP-CBFV in the LF band during the three conditions, this can be explained by a reduced range of phase difference values during $DBCO_2$, which will reduce any correlation-based indices including ICC. Therefore, the lower ICC values in the LF band during $DBCO_2$ do not indicate an increase in error or a true decrease in agreement. A similar explanation can account for a lack of agreement in the HF band data. For the VLF band, coherence values were on average much lower compared to the LF band data (0.3 vs. 0.7, Tables 2 and 3) for MABP-CBFV, but not for OxyHb-HHb. This which will increase the error in the phase estimates for MABP-CBFV and will cause a reduced agreement with the OxyHb-HHb estimates. From these results, we can conclude that the LF band data can provide the most reliable estimates of cerebral autoregulation. In the VLF band, the autoregulation system may exhibit strong non-linear and non-stationary properties, or there may be contribution of other variables that cannot be measured.[38,39] Although there may be valuable information in the VLF band, the TFA that was used in the present study does not produce reliable estimates of cerebral autoregulation in this frequency band.

Contrary to other studies,[5] we found a significant agreement between microvascular and macrovascular phase difference estimates of cerebral autoregulation in the LF band, which is to the best of our knowledge a unique finding which has never been reported in the literature. Other studies that have directly compared microvascular with macrovascular estimates of DCA have reported correlations with MABP and NIRS variables only[11,40] and did not evaluate agreement (i.e. ICC analysis) but reported associations or correlations.[9] However, recently DCA estimates obtained with the technique of diffuse correlation spectroscopy DCS showed good agreement with regulation rates measured by TCD.[10] Although time domain DCA estimates based on thigh cuff induced blood pressure decreases were used in that study, the finding of good agreement between microvascular- and macrovascular-based estimates of DCA is essentially similar to the results presented in our study. The fact that high levels of agreement between microvascular- and macrovascular-based estimates of DCA can be found with different techniques and with both time domain and frequency domain estimates of DCA further supports the interpretation that microvascular- and macrovascular-based estimates of DCA can be used to measure the same physiological process. When comparing our method with the DCS method, the advantage of our method is that it can be applied to spontaneous blood pressure oscillations without the need for using thigh cuffs. Another advantage is that blood pressure measurement is

not necessary for the determination of microvascular DCA in our method, while for the rate of regulation parameter in the DCS method, a continuous blood pressure measurement is required. Because measurement of DCA based on NIRS variables alone has practical benefit, we focussed on the OxyHb-HHb comparison in this study. However, it is possible to use the same analysis strategy on different variable combinations (MABP vs. NIRS, CBFV vs. NIRS), and such extensions of this methodology can be further explored in the future.

The effects of hypercapnia

During REST and DB, the results of the analysis with the constant time lag plus constant phase difference model suggest dominant blood flow oscillations, with a minor contribution of blood volume changes. During $DBCO_2$, we found very high levels of blood volume changes in the LF and HF band, which was accompanied by a decrease in mean transit time compared to REST and DB. However, the transit time associated with blood flow changes showed very little change, which suggests that the primary change induced by different levels of CO_2 is the percentage of cerebral blood volume changes, and not a change of the capillary transit time itself. Highly similar results were found in the simulation study, which further supports this interpretation. Similar findings have been published recently, where hypocapnia due to hyperventilation did not result in an altered transit time estimate, but blood volume estimates changed.[5]

The finding of an unchanged transit time associated with blood flow changes during very different conditions with a different balance between oscillations in cerebral blood flow and blood volume is hard to explain using a simple serial capillary system model. We speculate that during hypercapnia, parallel vascular channels such as metarterioles could be recruited and may act as capacitance vessels and arteriovenous shunt channels. The system would then change to a parallel system, with constant transit time in the capillary part, while in the metarterioles oscillations in OxyHb could synchronise with capillary venous oscillations in HHb, to result in a transit time near 0 s. This theory is further explained and illustrated in Appendix 1, Part 3.

Limitations

Firstly, this is a relatively small study with relatively short recordings, and although the main effects are clear, the findings should be expanded to a larger cohort. The sex ratio was heavily skewed towards females in our study population, and it is known that females have different DCA status compared to males.[41] However, the main results of this study should not be affected by the skewed sex distribution, as the most important results are based on intraindividual differences between techniques and conditions.

Secondly, we used $DBCO_2$ in this experiment, but we were unable to measure to which degree the CO_2 level was changed by 8% CO_2 inhalation. Therefore, we were unable to verify if the level of hypercapnia was related to the change in autoregulation, mean transit time and cerebral blood volume oscillation estimates. Similarly, hypocapnia was not controlled in this experiment. We prioritised the measurement protocol towards random breathing instructions, rather that attaining a fixed level of hypocapnia, because establishing blood pressure oscillations is essential for estimating cerebral autoregulation. It is also possible that DB and $DBCO_2$ induced changes in cerebral venous pressure or ICP, but we were not able to verify if such changes occurred and therefore were not able to correct for them. This may have contributed to variability of the measurements and analysis.

Thirdly, the constant time lag plus constant phase shift model was not applicable in every subject due to low coherence. This limits application in individual subjects or patients. Future studies should find ways to increase applicability in every subject or patient. A logical first approach would be to find ways to increase coherence, for example by employing other methods to induce blood pressure oscillations or by using longer registration periods. Compared to other microvascular models,[6] the constant time lag plus constant phase shift model is relatively simple and does not consider other factors such as arterial oxygen saturation, capillary lengths and diffusion coefficients. However, even with a relatively simple model, we observe a significant agreement between MABP-CBFV and OxyHb-HHb oscillations and between simulated data and physiological data, which suggests that the underlying assumptions are realistic. This does not mean that there is no room for improvement; it could be that agreement would increase when other factors are accounted for. On the other hand, one has to aim for the minimum number of variables needed to adequately describe the data and be critical towards the added value of any new variable that is introduced.

Fourth, NIRS measurements are not spatially resolved and although we used a 40 mm optode distance, we cannot exclude contributions from extracranial tissue. However, the finding of similarity between MABP-CBFV and corrected OxyHB-HHb phase differences strongly suggest that at least the oscillatory components of the NIRS signals were predominantly determined by brain tissue. Furthermore, the OxyHb-HHb phase difference spectrum during REST and DB was compatible with dominance of blood flow oscillations, which is typical for brain tissue and atypical for extracranial tissue.[28] NIRS is also a focal measurement and since we only measured in the MCA territory, we cannot generalise our findings to other vascular territories, which precludes investigation of regional heterogeneity of cerebral autoregulation. Finally, the reproducibility

of the findings has not yet been established, and longer measurements may be needed to evaluate if the NIRS-based autoregulation estimates and transit time and blood flow/volume estimates are stable over time and react similarly to repeated challenges.

To conclude, NIRS can provide estimates of DCA that are similar to TCD-based DCA estimates. This is achieved by correcting for transit time and the balance between blood flow and blood volume oscillations, which can be estimated from the OxyHb-HHb phase difference spectrum in the HF band. The transit time and the balance between blood flow and blood volume oscillations may also provide additional valuable information about cerebral microvascular function. These findings may increase the feasibility of non-invasive continuous autoregulation monitoring and guided therapy in clinical situations.

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Authors' contributions
JWJE and JT designed the study, performed experiments, collected and analysed data and wrote the manuscript. MJHA designed the study and contributed to interpretation of data. MC and NMM contributed to interpretation of data. All authors critically reviewed the manuscript and approved the final version to be published.

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APPENDIX 1

Part 1: Simulation Experiment: Generation of the simulated data

General assumptions for healthy vasoregulation

In accordance with previous knowledge and studies, we assume that spontaneous oscillations are present in the circulation. For MABP, these consist of two major components: 1) Mayer waves, in the frequency range of 0.025 to 0.2 Hz, and 2) respiration related oscillations which occur mostly at a frequency of 0.2 to 0.3 Hz [1]. These oscillations travel to the cerebral circulation, where they are modified by the process of cerebral autoregulation. Low frequency MABP oscillations (<0.2 Hz) are not in phase with CBFV oscillations in the large basal arteries (as measured with TCD), but are phase- shifted, while faster frequencies are in phase[2]. This 'phase shift' reflects the dynamics of an active autoregulatory system that acts to counter-regulate repetitive CBFV falls and rises during changes in MABP by arteriolar vasodilatation and vasoconstriction, respectively. The oscillations travel further to the cerebral microcirculation, where they are visible as oscillations in OxyHb and HHb. Although OxyHb is present in all compartments of the cerebral circulation, the oscillatory component of the OxyHb signal is considered to arise mainly from the arterial compartment, i.e. in small vessels such as arterioles with some contribution from capillaries[3], while oscillations in HHb are considered to be present in the capillary and venous compartments. Transit time through the capillary system will delay HHb oscillations compared to OxyHb. We assume arterial oxygen saturation and cerebral metabolic rate to be approximately constant over time. Based on earlier investigations[4], we specifically assume that an isolated increase in cerebral blood *flow*, induces an increase in OxyHb and a decrease in HHb, through the well-known 'washout' effect. By contrast, an increase in cerebral blood *volume* induces an increase in both OxyHb and HHb. For decreases in cerebral blood flow or volume, the changes described above are reversed[4]. As a consequence, in the frequency domain, blood flow oscillations will result in antiphase (180 degrees) phase differences, while blood volume oscillations will result in an in-phase pattern, with 0 degrees phase differences. Other studies have shown that, in reality, both in phase and out of phase oscillations of OxyHb and HHb may occur, with deviations from perfect in phase (0 degree) or antiphase (180 degrees) relations[5,6,7,8]. This can occur due to capillary transit time effects, effects of autoregulation, and mixtures of blood volume and blood flow oscillations. Similar to other researchers, we assume changes in blood volume occur exactly in phase, without any further delay due to transit time effects[3]. As a result of damping by the capillary network, HHb oscillations will be of lower amplitude compared to OxyHb

oscillations. Finally, we assume that all signals are quasi-stationary allowing linear analysis in the form of TFA. A schematic overview of our assumptions for a healthy vasoregulation system is shown in Fig S1.

Although the haemodynamic quantities that are measured are different (blood pressure, cerebral blood flow velocity, OxyHB and HHB concentrations), oscillations in these quantities are related to each other. This is demonstrated by the fact that significant coherence is present between the different haemodynamic signals after conversion to the frequency domain[9], although in this study we did not demonstrate this because we did not study all possible variable combinations. Assuming that the main regulators involved in cerebral autoregulation are the cerebral arterioles, the effect on oscillations will propagate both upstream and downstream from the arterioles (red dashed arrows in fig.S1). From a frequency domain based system analysis perspective, the main difference between MABP-CBFV and OxyHb-HHb phase differences is that the former can be viewed as a parallel system, and the latter as a serial system. Conversion from serial to parallel can be achieved by removing the transit time component, and any constant phase offsets. This is why MABP-CBFV and OxyHb-HHb phase differences can be similar in theory, and this formed one of our main hypotheses.

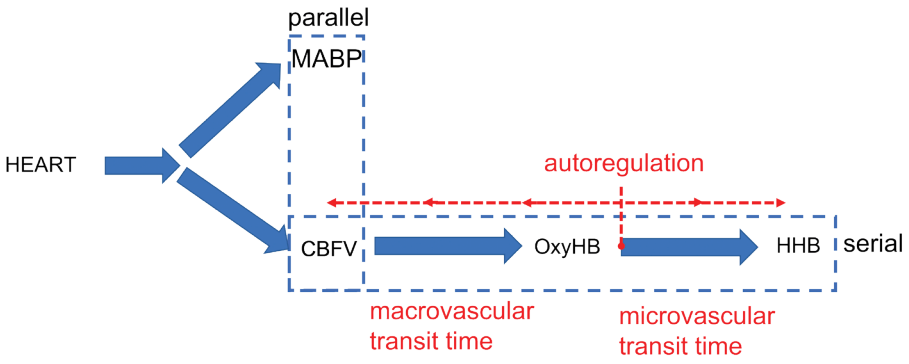

Figure S1 | Overview of the assumptions for a healthy vasoregulation system. Autoregulation effects are present for CBFV, OxyHb and HHb. Transit time effects are present for the serial component of the system (CBFV to OxyHb to HHb), but not for the parallel component of the system (MABP vs CBFV). Note that these assumptions specifically apply to oscillations in the described variables, and not necessarily to static components.

Simulation of signals

We chose to model mean data instead of raw pulsatile data, as this is customary in the analysis of cerebral autoregulation[10]. Simulation of this type of data can be done with sinusoids as basic functions. MABP, CBFV and NIRS signals with a total length of at least 5 minutes, which is the CARNET recommended minimum signal length for cerebral autoregulation, were generated.

MABP and CBFV signals: summation of Mayer waves and respiratory induced oscillations

To simulate slow MABP oscillations (Mayer waves), triple wave length sinusoids with amplitude *A*, initial phase Φ of 0 degrees, and randomly generated frequency $f, f \in (0.01 - 0.2)$ Hz, according to:

$$A = (10 - 40f)\, sin(ft) \qquad \text{(S1)}$$

Then, these triple wave length sinusoids were multiplied by a Hanning window and concatenated. The frequency range was chosen to include frequencies that are affected by cerebral autoregulation. For the CBFV signal, the same sinusoids and the same frequency range were used as for the MAPB signal, but a frequency-dependent phase shift was applied to each of the sinusoids before concatenation, as defined by the initial phase:

$$\Phi(f) = 80 - 400f \qquad \text{(S2)}$$

Similarly, a frequency dependent gain function (G) was applied, as defined by:

$$G(f) = 5f \qquad \text{(S3)}$$

These signal manipulations result in a phase difference between input (MABP) and output (CBFV) signals that is approximately 80 degrees for the lowest frequencies, and gradually decreases to 0 for 0.2 Hz, while gain increases from 0 to 1 over the same range, which is in accordance with cerebral autoregulation transfer function results described in the literature[2].

To simulate respiratory induced oscillations, we generated additional sinusoids with a frequency *f* varying randomly between 0.2 and 0.3 Hz, with an amplitude of 2, and signal length of 5 minutes. To allow for some variability in shape, the absolute values of these waves were raised to a power *p* randomly varying between 0.75 and 1.25, according to:

$$A = |2sin(ft)|^p \qquad \text{(S4)}$$

After the power transform, signals were transformed back to their original sign, so that the signals were alternating positive and negative again, after which the reshaped sinusoids were concatenated. The power transform creates sinusoids that have a slightly more curved shape. Finally, these simulated respiratory oscillations were added to the simulated input (MABP) and output (CBFV) signals.

NIRS signals

For simulating NIRS signals, the OxyHb signal was obtained in the same way as the CBFV signal, including similar phase differences and gain function compared to MABP but with 10 times lower amplitude, and with additional transit time effects (see below). We thus assume that OxyHb and CBFV signals are both pre-arteriolar signals. HHb signals were created from the OxyHb signal, with phase shifts similar to those between MABP and CBFV for frequencies between 0.01 and 0.2 Hz, and with additional transit time effects (see below). Next, two variants of the HHb signals were constructed. First, a negated version of the HHb signal was created, by multiplying all values by -1.

This adds an additional 180 degree phase difference to the HHb signal for all frequencies, which simulates the 'washout' effect in case of only oscillations in blood flow without blood volume oscillations. Second, an in phase HHb signal was created, which is not negated, and relates to oscillations in blood volume. Transit time effects were added to the HHb signal, by constructing time shifted versions of the HHb signal, with time shifts that varied from 0.1 second to 3.0 seconds, in 0.1 s increments. This range was chosen to include normal capillary transit times that are known from previous experiments[11,12]. We also considered the possibility of no transit time effects. This has been suggested to occur in the case of blood volume changes[3], and we simulated this effect by setting the transit time to 0 s. As HHb oscillations have been observed to be lower in amplitude compared to OxyHb oscillations, we introduce a constant damping factor of 0.33 to be present between OxyHb and HHb oscillations, in the form of an additional gain function with a value of 0.33 for all frequencies.

This results in roughly 10 times lower power in the frequency domain for HHb compared to OxyHb[5]. The sampling rate was set to 250 Hz. An overview of the signal generation procedure and an example of the simulated data can be found in Fig S2.

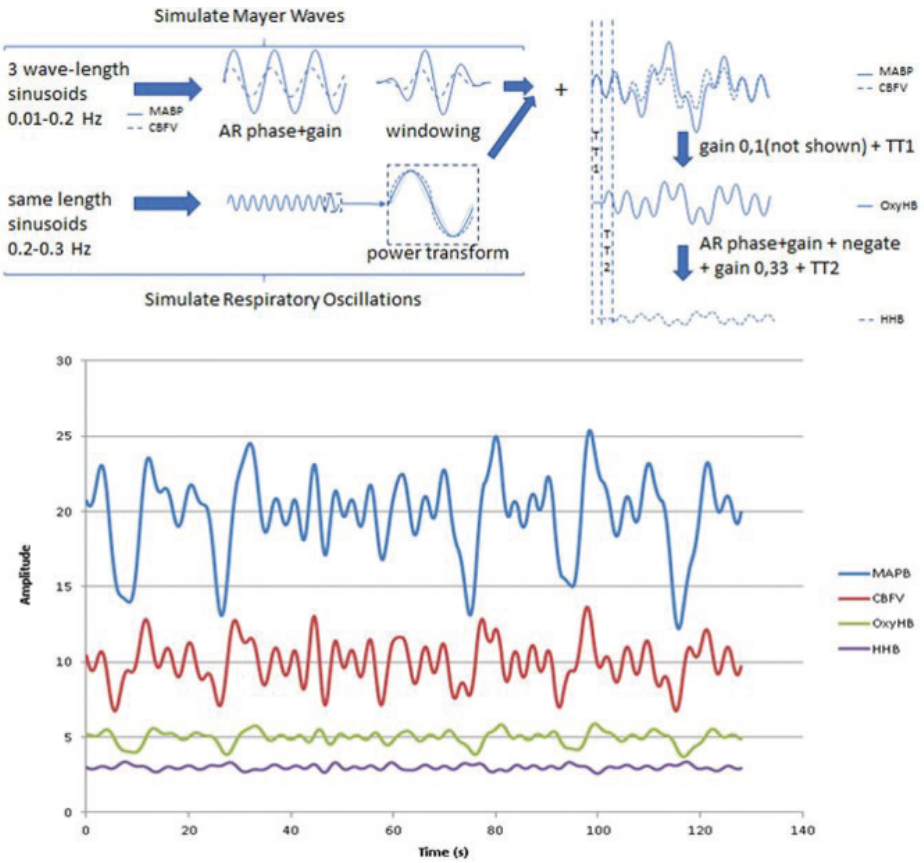

Figure S2 | Details of the signal generation procedure and an example of simulated data. Simulated Mayer waves and respiratory induced MABP oscillations were added to create a MABP signal. To create a CBFV signal, autoregulation induced phase shift and gain functions were applied. To create an OxyHb signal, CBFV was shifted by a transit time (TT1), and a gain function (0,1) was applied. From the OxyHb signal, an HHb signal was created by applying autoregulation induced phase shift and gain, transit time (TT2), and a second gain function (0,33) to simulate passage of OxyHb through the brain tissue. The washout effect was simulated by negating the OxyHb signal.

Table S1 | Reference TFA results for the simulated data

	Mean values		
Frequency Band	*VLF*	*LF*	*HF*
MABP-CBFV			
Gain (cm.s^{-1} /mmHg)	0,23	0,68	1
Phase (°)	62	26	0
MABP-OxyHb			
Gain(umol.l^{-1}/mmHg)	0,02	0,07	0,1
Phase (°)	62	26	0
CBFV-OxyHb			
Gain(umol.l^{-1}/ cm.s^{-1})	0,005	0,048	0,1
Phase (°)	0	0	0
OxyHb-HHb			
Gain(umol.l$^{-1/}$ umol.l^{-1})	0,07	0,22	0,33
Phase (°)	62	26	0

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Part 2: Simulation Experiment: Analysis of the simulated data

Simulation Experiment: Results of the analysis of the simulated data

We analyzed the simulated data with TFA and evaluated if the transit time and autoregulation effects can be reliably identified by our analysis based on the constant time lag plus constant phase shift model. We determined to which degree errors in the transit time and autoregulation estimates were present after applying the correction for transit time effects and blood flow and blood volume oscillations (TT-BF/BV correction). We performed two main analyses:

1. TFA analysis of the simulated data for all transit times ranging between 0.1 to 3.0 s, assuming 100% blood flow oscillations.
2. TFA analysis of the simulated data for different percentages of blood flow and blood volume oscillations, for a fixed transit time of 1.0 s.

TFA analysis of the simulated data for all transit times (0.1 to 3.0 s)

For analysis, the CARNET recommend settings were used. Signals were cut into segments of 100 seconds with 50% overlap, resulting in 5 segments per analysis, for a total data length of 5 minutes. Table S2 shows the results of the TFA analysis for all predefined transit times (0.1 – 3.0 s) after TT- BF/BV correction. Note that the error for the transit time and Y axis intercept and for all gain values is very low. For phase, the error in the HF and LF band is also very low, but for the VLF band, some error is present.

TFA analysis of the simulated data for different percentages of blood flow and blood volume oscillations

For analysis, the CARNET recommend settings were used. Signals were cut into segments of 100 seconds with 50% overlap, resulting in 5 segments per analysis, for a total data length of 5 minutes. To investigate the effect of different proportions of blood flow and blood volume oscillations, we used antiphase output signals with a transit time of 1 s to simulate blood flow oscillations, and in-phase signals with a transit time of 0 s to simulate blood volume oscillations. The percentage of time that blood volume oscillations occurred was set at 0%, 20%, 40%, 60%, 80% and 100% by replacing the corresponding number of segments in the output signal with in-phase signals (i.e 40% blood volume oscillations means 2 segments with in-phase output signals, and 3 with antiphase output signals). We evaluated if the error in transit time estimates was affected by different percentages of blood volume oscillations, and if the percentage of blood volume oscillations could be correctly retrieved from by our analysis.

Table S3 shows the results of the TFA analysis for different percentages of blood volume oscillations. Note that the error in TT (BF) is very low for blood volume oscillation percentages up to 60%. At 80% some error is present.

Table S2 | Results of the simulation experiment: TFA results after TT-BF/BV correction. For the MABP-CBFV comparison, only 1 TFA was performed since there are no transit time effects for this signal combination. For the Oxy Hb-HHb comparison, 30 TFA were performed for transit times (TT) 0.1 through 3.0 s in 0.1 s increments: therefore, the mean ±SD is given for the 30 analyses. Note that the error is very low for the LF and HF bands, but some error is present for the VLF band.

		Phase difference (degrees)			**Gain (cm/s*mmHg^{-1})**			**Linear Fit data**	
	Comparison	*VLF*	*LF*	*HF*	*VLF*	*LF*	*HF*	*TT (s)*	*Y axis intercept (degree)*
Reference	MABP-CBFV	62	26	0	0.23	0.68	1	0	0
Measured	MABP-CBFV	61	31	1	0.22	0.56	0.97	0.02	4.1
Error	MABP-CBFV	1	5	1	0.01	0.12	0.03	0.02	4.1
Reference	OxyHb-HHb	62	26	0	0.07	0.22	0.33	0.1-3.0	180
Measured (TT 0.1-3.0)	OxyHb-HHb	53.2 ± 0.5	29.4 ± 0.1	0 ± 0	0.07 ± 0.0	0.18 ± 0.0	0.32 ± 0.0	1.5 ± 0.9	179 ± 0.3
Error (TT 0.1-3.0)	OxyHb-HHb	8.7 ± 0.5	3.5 ± 0.1	0 ± 0	0.00 ± 0.0	0.03 ± 0.0	0.00 ± 0.0	0.0 ± 0.01	1.2 ± 0.3

Table S3 | Results of the simulation experiment: Transit time and blood volume (BV) oscillation estimates for different combinations of percentages of blood volume (BV) oscillations (0 s TT) and blood flow oscillations (1 s TT). Note that the error in TT (BF) is very low for blood volume oscillation percentages up to 60%. At 80% some error is present. The error for the estimated %BV is between 0 and 6 %.

% BV oscillations	Simulated data TT (s) %		Estimated mean TT (s)	Y axis Intercept	Estimated % BV	TT (BF)	TT (BF) error
	0 s %	1 s %					
0	0	100	1	181.7	0	0.99	0.01
20	20	80	0.86	155.1	14	1	0
40	40	60	0.64	115.4	36	1	0
60	60	40	0.37	68.2	62	0.98	0.02
80	80	20	0.15	28.6	84	0.94	0.06
100	100	0	0.01	2.1	99	*	*

PART 3: PROPOSED COUPLING BETWEEN THE OXY-HB-HHB TFA RESULTS AND THE MICROVASCULAR ANATOMY

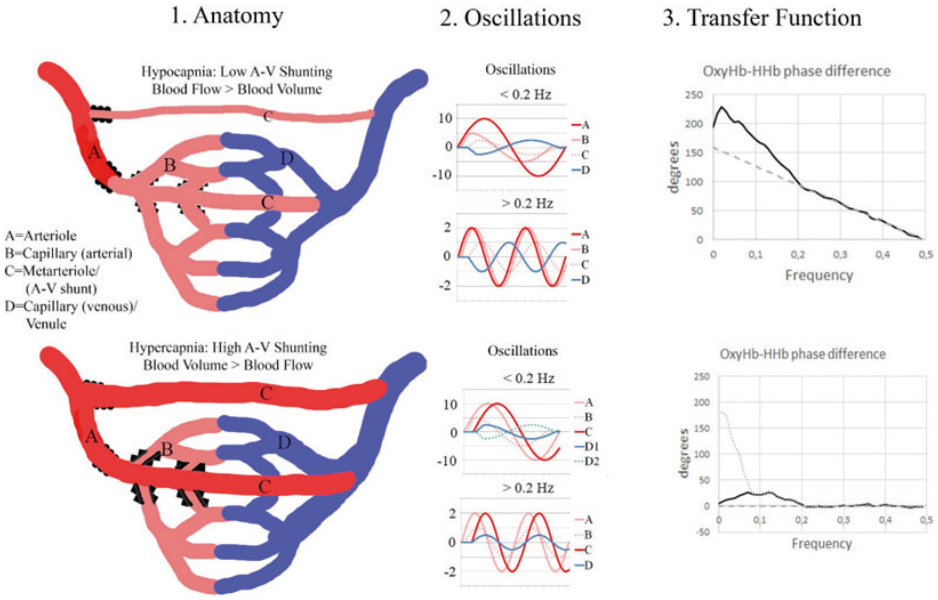

Figure S3 | Proposed coupling between the OxyHb-HHb TFA results and the microvascular anatomy.

1. Anatomy (left panel): Dense colours indicate the dominant oscillatory component, and pale colours indicate other oscillatory components that contribute less to the signals. Small black hemi-circles indicate the site of contraction of arteriolar muscle and small black triangles indicate the site of the pre-capillary sphincters. A high degree of contraction is indicated with larger symbols. During hypocapnia arterioles contract while pre-capillary sphincters relax. The reverse occurs during hypercapnia, which results in recruitment and dilation of A-V shunts and of postcapillary venous structures.

2. Oscillations (middle panel): During hypocapnia, the dominant oscillatory OxyHb component comes from the arterioles (A), autoregulation leads to damping and phase shift of slow oscillations, but not of faster oscillations in OxyHb (B), A-V shunts contribute little to the OxyHb signal, but will be delayed as the result of transit time (C: dotted line) and blood flow changes are prominent which results in the washout effect with signal reversal for HHb (D). During hypercapnia, the dominant oscillatory OxyHb component shifts to the A-V shunts, with less damping (C). Arteriolar (A) and capillary components (B) contribute less to the OxyHb signal, but capillary components (B) are damped, and also phase shifted for slow oscillations by the action of the pre-capillary sphincters. As a result of dilation of postcapillary venous structures the HHb signal is not reversed (D1) and is now synchronous with the dominant oscillatory OxyHb component (C) for faster frequencies, while for slower frequencies phase shifts can still occur. For very slow and high amplitude oscillations in the VLF (D2), the washout effect may still be present, as the capacity for dilation of postcapillary venous structures may be exceeded.

3. Transfer Function (right panel): The dominant oscillatory components will determine the TFA results. During hypocapnia, transit time effects are present which are visible as a linear decrease pattern in the HF band in the OxyHb-HHb phase difference plot, from which the mean transit time can be determined. During hypercapnia, the linear trend will be approach 0 due to an increase in

synchronous oscillations due to blood volume changes. Phase differences can still occur for frequencies <0.2 Hz as a result of residual autoregulation activity, and due to maintained blood flow effects for very slow (<0.07 Hz) oscillations (fine dotted line in the lower panel).

From a system analysis perspective, the system has a predominantly serial function profile during hypocapnia, while during hypercapnia a predominantly parallel function profile is present.

Part 4: Group delay: a runners example

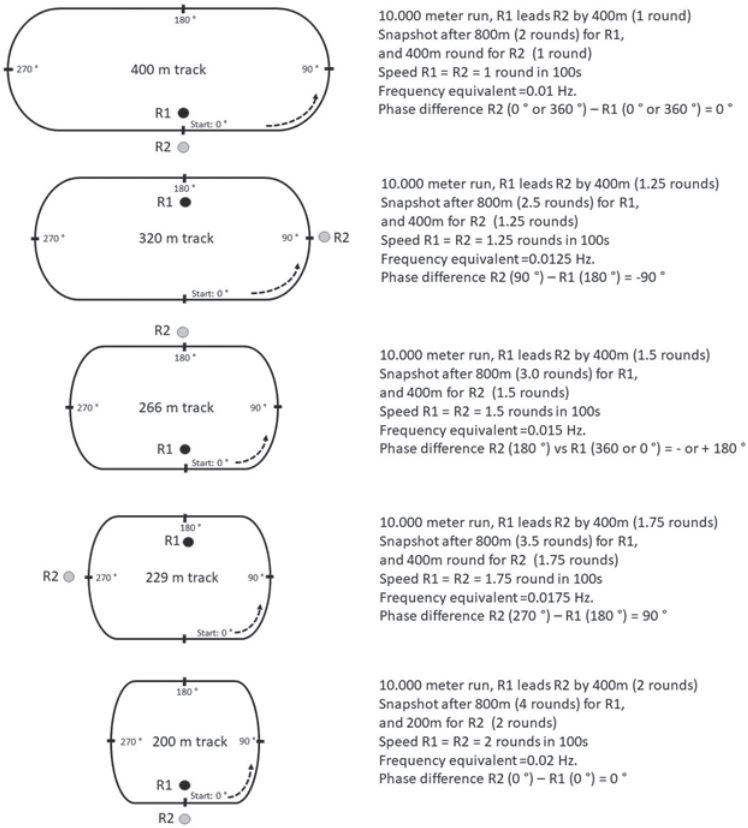

Figure S4 | Example of group delay:

1. Consider two runners, R1 and R2, running during a 10.000 m run contest.

2. R2 is very confident and gives R1 a head start of 400 m. Therefore, R1 leads R2 by 400 m.

3. However, after the start of the race, both runners have a constant speed of 400 m per 100 seconds, and this remains constant throughout the race. Therefore the 400 m lead that R1 has over R2 also remains constant during the entire race.

4. Now consider the events depicted in the figure S4. Five different scenarios are depicted, with the exact settings as described above, but with different track lengths. After a fixed interval of 800 meters for R1 and 400 meters for R2, a snapshot of the situation is presented. This will illustrate the phenomenon of group delay: a constant time difference (100s) produces a different phase difference between the input (R1) and output (R2) signal for different tracks (frequencies).

5. If we plot the phase difference between R2 and R1 vs frequency, we see a linear trend in this plot, with phase wrap around at 0,015 Hz.

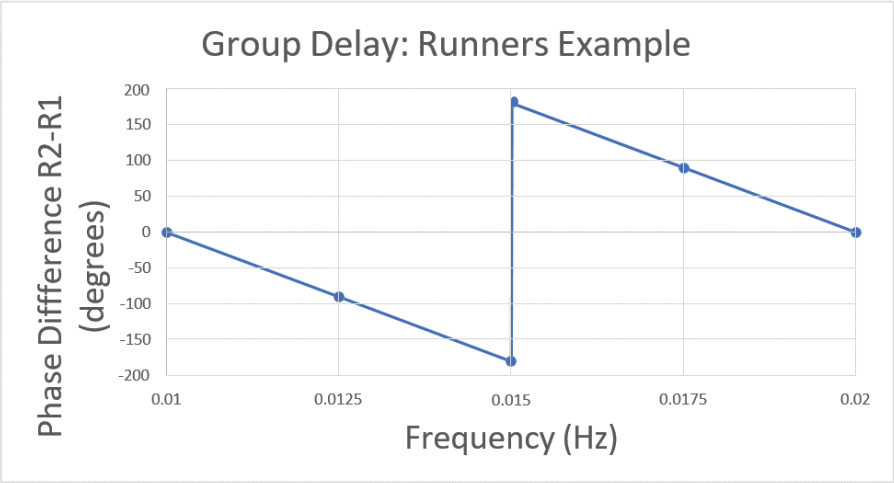

Figure S5 | Phase difference between R2 and R1 vs frequency, illustrating the group delay phenomenon

This plot also illustrates the danger of interpreting the sign of the phase difference as evidence that one signal is leading the other: the phase difference may be positive or negative depending on the frequency that is examined. To determine which signal is leading the other, one must rely of the sign of the slope of the phase difference plot: a negative slope means R1 leads R2, and a positive slope indicates R2 leads R1. This strategy is valid only in passively conducting serial systems (i.e. modification by an active system such as cerebral autoregulation will distort the linear phase plot).

Please note that positive or negative phase depends on how this is defined in the software package, and that differences exist between software packages. In our software, phase difference is calculated as output phase -input phase. (CBFV-MABP, and HHb-OxyHb).

we can retrieve the transit time from this plot by using equation 2:

$$TT\ \frac{\varphi(f_i)xy - \varphi(f_j)xy}{f_i - f_j \cdot 360} = \frac{90 - 0}{0.0175 - 0.02 \cdot 360} = 100\ s$$

Replace the different tracks with frequencies, R1 with OxyHb, R2 with HHb, and the delay between R1 and R2 with the cerebral transit time, in order to interpret group delay in terms of NIRS variables.

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8

Cerebral Autoregulation Assessment Using the Near Infrared Spectroscopy 'NIRS-Only' High Frequency Methodology in Critically Ill Patients: a Prospective Cross-Sectional Study

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ABSTRACT

Impairments in cerebral autoregulation (CA) are related to poor clinical outcome. Near infrared spectroscopy (NIRS) is a non-invasive technique applied to estimate CA. Our general purpose was to study the clinical feasibility of a previously published 'NIRS-only' CA methodology in a critically ill intensive care unit (ICU) population and determine its relationship with clinical outcome. Bilateral NIRS measurements were performed for 1–2 h. Data segments of ten-minutes were used to calculate transfer function analyses (TFA) CA estimates between high frequency oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) signals. The phase shift was corrected for serial time shifts. Criteria were defined to select TFA phase plot segments (segments) with 'high-pass filter' characteristics. In 54 patients, 490 out of 729 segments were automatically selected (67%). In 34 primary neurology patients the median (q1–q3) low frequency (LF) phase shift was higher in 19 survivors compared to 15 non-survivors (13° (6.3–35) versus 0.83° (−2.8–13), $p = 0.0167$). CA estimation using the NIRS-only methodology seems feasible in an ICU population using segment selection for more robust and consistent CA estimations. The 'NIRS-only' methodology needs further validation, but has the advantage of being non-invasive without the need for arterial blood pressure monitoring.

1. INTRODUCTION

Impaired cerebral autoregulation (CA) contributes to a poor clinical outcome in several acute neurological insults (events) such as traumatic brain injury [1], out of hospital cardiac arrest [2] and to the development of delayed cerebral ischemia in subarachnoid hemorrhage [3]. CA impairment has been observed in other critically ill patients like those with sepsis or septic shock and has been shown to be associated with sepsis-associated delirium [4]. However, it is unknown whether this is an indication of systemic hemodynamic failure, (focal) end-organ cerebral damage or more a combination of both. Excursions of arterial blood pressure (ABP) below the lower limit of CA and not absolute ABP were independently associated with postoperative acute kidney injury in cardiac surgery patients [5]. CA monitoring might be a novel method for precise guiding of ABP targets in critically ill patients with a diversity of clinical diagnoses [6].

Near infrared spectroscopy (NIRS) is a non-invasive technique to study cerebral hemodynamics and CA status. In the time domain, the correlation between slow waves in ABP and NIRS-based regional oxygen saturation (rSO_2) can be calculated as CA trend measures [7]. In the frequency domain, transfer function analysis (TFA) is a common CA methodology which is historically applied using transcranial Doppler (TCD) and ABP recordings over shorter time periods compared to time domain analysis. However, there are only limited reports on TFA using low frequency sampling NIRS devices as used for time domain analysis [8]. In 2018, Elting et al. developed a 'NIRS-only' methodology that allows CA estimations by studying the relationship between 50 Hz oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) concentration differences in the very low (VLF) and low frequency (LF) range [9]. The phase shifts in these CA frequency ranges were corrected for the capillary transit time (TT blood flow) and the cerebral blood flow/volume ratio (%BF), using the high frequency (HF) range. The correction was applied to correct for the non-CA related 'group delay' and 'washout' phenomenon. Both at rest and during hypocapnia/hypercapnia, the corrected NIRS phase shifts showed comparable changes in CA status to those measured with TCD and ABP in healthy subjects. In contrast to TCD, NIRS is easy to use, user independent and therefore suitable for a larger population who might benefit from cerebral monitoring. In addition, the 'NIRS-only' methodology does not require continuous (invasive or non-invasive) ABP recordings.

An important requirement for reliable CA estimation is that sufficient slow ABP oscillations are present during the recording period [10]. In comatose patients, spontaneous slow oscillations may be limited due to sedation, analgesia and

hemodynamic management [11]. The Cerebrovascular Research Network (CARNet) recommends a minimum duration of five minutes for reliable CA estimations with TCD recordings [8]. Zhang et al. showed that after seven minutes of spontaneous ABP oscillations, the TCD-based CA-parameters became stable in an intensive care unit (ICU) population [12].

In this prospective study, the general purpose was to study the clinical feasibility of the 'NIRS-only' CA methodology in a critically ill ICU population. The feasibility aims included: (1) developing an automated data processing method. We defined criteria to automatically select data segments for interpretable LF-phase shift estimation and (2) evaluating the clinical applicability by calculating the variability of the LF-phase shift between and within patients. Finally, we studied the relationship between LF-phase shift and the six-month clinical outcome.

2. MATERIALS AND METHODS

Details about the methodology are described in Supplementary File S1. This was a single center, prospective cross-sectional study that was conducted between June 2018 and March 2020. Recruited patients were admitted to the ICU of an academic teaching hospital. The measurement protocol was approved by the local ethical committee (METC Maastricht 16-4-243). The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines [13] (Supplementary Table S1).

2.1. Participants

Inclusion criteria were (1) critically ill adult patient (≥18 years and no intention to withdraw treatment), (2) comatose or sedated (Richmond agitation and sedation scale of −4 or −5), (3) intubated and ventilated patient and (4) the ability to measure within 48 h after ICU admission. Excluded patients had (uni- or bilateral) frontotemporal skin hematoma (due to difficulties with obtaining NIRS signals), frequent cardiac arrythmias (mainly atrial fibrillation) or no written informed consent by a lawful representative. The informed consent procedure was in accordance with the declaration of Helsinki's ethical guidelines [14]. Patients were recruited during daytime when a member of the research team was available. We did not perform a sample size calculation beforehand as there was no literature on 'NIRS-only' CA-assessment in critically ill patients at that time.

2.2. Near infrared spectroscopy (NIRS) Measurements

NIRS measurements (Portalite, Artinis Medical Systems, Elst, The Netherlands) were performed bilaterally on the frontotemporal regions simultaneously (intended total duration measurement: 1 h) in the period June 2018 until June

2019. This was changed to unilateral, consecutive measurements (intended duration total measurement: 2 h) onwards due to severe issues with crosstalk between the simultaneously acquired NIRS signals. Changes in oxyHb and deoxyHb concentrations were computed using the modified Lambert-Beer law and updated at 50 Hz. During the measurement, nursing interventions (like turning and suctioning) as well as major changes in medication and ventilator settings were limited to a minimum, if the clinical situation allowed.

2.3. Data Collection

For each patient, we collected the patient and admission characteristics. The six-month Glasgow Outcome Scale Extended (GOSE) was collected as clinical outcome parameter by telephone interview. In addition, we collected continuous (50 Hz) physiological data: ABP (mmHg), heart rate (HR, min^{-1}), electrocardiogram (ECG, μV), end tidal carbon dioxide ($EtCO_2$, kPa), peripheral oxygen saturation (SpO_2, %) and body temperature (°C). This was collected from the Intellivue Philips bedside monitor (Philips MX800, Eindhoven, The Netherlands). OxyHb (μM) and deoxyHb (μM) concentration differences were collected with Oxysoft at 50 Hz recording software (version: 3.0.103.3, Artinis Medical Systems, Elst, The Netherlands). All the (neuro) physiological signals were stored in the research software ICM+® (Cambridge Enterprise, Cambridge, UK).

2.4. Data Preparation

All stored data were exported from ICM+ software to plain text files and imported in MATLAB (Release 2019b, The MathWorks, Inc., Natick, MA, USA). NIRS data was first visually inspected, and artifacts were removed (details on the applied methodology can be found in Supplementary Figure S1). Then, the data was stored in ten-minute data segments per patient and imported into a custom made LabVIEW program (LabVIEW 2015, National Instruments, Austin, TX, USA) calculating the CA-estimates (Section 2.4.1) as used in Elting et al. [9]. Sufficiently slow ABP oscillations are required for a reliable CA assessment [10]. The amount of slow ABP and resulting slow oxyHb and deoxyHb oscillations were quantified by the Power Spectral Density (PSD).

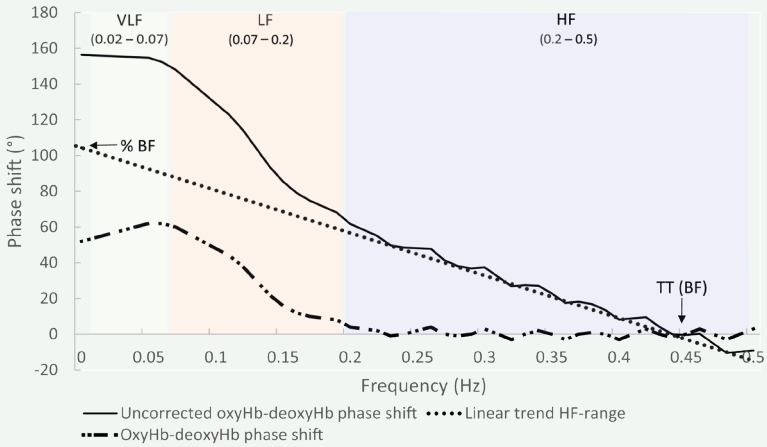
2.4.1. Transfer Function Analysis (TFA)

TFA was applied in concordance with the CARNet recommendations for TFA [8]. In addition, Box 1 describes the 'NIRS-only' methodology for phase shift correction. The following outputs were obtained for each frequency range of interest: very low frequency (VLF 0.02–0.07 Hz), low frequency (LF 0.07–0.2 Hz) and high frequency range (HF 0.2–0.5 Hz): coherence, gain, corrected phase shift (referred to as 'phase shift' in the remaining text) and uncorrected phase shift. The TT and %BF were obtained per segment. In addition, the

phase shift values per individual frequency bin (i.e., per 0.01 Hz frequency bin) were obtained. The latter was used to construct the TFA phase plot (0.01–0.5 Hz) and stored for later use (see Section 2.4.2).

Box 1 | NIRS-only methodology

In the NIRS-only methodology, the transfer function analysis (TFA) phase shifts between oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) are corrected for phase shifts caused by two physiological factors not related to cerebral autoregulation (CA) effects. First, a constant microvascular transit time (TT blood flow, referred to as TT in the main text) effect, resulting in different phase shifts for different frequencies ('group delay phenomenon'). Second, the 'washout effect', expressed as the ratio between slow changes in blood flow (BF) and blood volume (BV), results in phase shifts (BV expressed as the percentage of BF oscillations, %BF) [9]



Intact CA

TFA-phase shift plot showing the high-pass filter principle (i.e., higher phase shift for lower frequencies). An example is shown here in the figure

Impaired CA

TFA-phase shift plot showing low phase shifts (around zero) for all frequencies (i.e., 'flat line', not shown in this figure).

* Schematic representation of the TFA phase shift plot. The different curves show (1) the uncorrected oxyHb—deoxyHb phase shift (solid line), (2) the best linear fit on the phase shifts in the high frequency (HF) range, called HF trend line (dotted straight line), and the corrected oxyHb—deoxyHb phase shift (dashdotted line). Phase shift correction is performed by subtracting the extrapolated linear HF trend line from the uncorrected phase shifts over the very low frequency (VLF) and low frequency (LF) ranges. %BF is determined by the y-axis intercept of the linear HF trend line.* The TT(BF) is determined by the x-axis intercept of the linear HF trend line. *measure of cardiac complications).

* calculations described in Elting et al. [9].

2.4.2. Selection of Transfer Function Analysis (TFA) Segments

In addition to the CARNet TFA recommendations for data processing, we formulated criteria to select ten-minute TFA phase shift data segments (referred to as segments in the remaining text) based on the assumptions given in Table 1. Because segment selection might entail the risk of selection bias, we compared common physiological ICU parameters and the mean PSD of ABP and NIRS between the 'in'- and 'excluded' segments. After segment selection, for the 'included' segments the model output variables, the mean ABP values and PSD values (ABP, oxyHb and deoxyHb) of the 'included' segments were averaged per patient and per hemisphere (with standard deviations (SD) as a measure for within-patient variability). In addition, other physiological data (like HR and $EtCO_2$) were averaged per patient over the entire recording period (i.e., without data segment selection and artifact removal) (See Supplementary File S2).

2.5. Statistical Analysis

Data are presented as median and interquartile range (q1–q3) for continuous variables and frequencies (%) for categorical variables. First, we described the cohort including the number of 'included' and 'excluded' segments. Second, we described and compared clinical outcome groups regarding patient demographics, clinical variables, NIRS data length and data quality. Third, we compared 'included' and 'excluded' segments regarding signal characteristics (i.e., mean PSD results (oxyHb, deoxyHb and ABP) and physiological variables). Fourth, we compared clinical outcome groups regarding CA estimates and PSD. Fifth, we repeated the analysis for patients with a primary neurological admission diagnosis. Each patient was represented by the hemisphere with the worst CA—which was defined by the lowest LF-phase shift—in case bilateral NIRS measurements were available.

The statistical relationship between dichotomized clinical outcome and the LF-phase shift was evaluated using the Mann–Whitney U test. To assess the influence of potential confounders, multivariable logistic regression was performed. Although no effect of age on CA phase shift has been found in the literature [15], age was included, being a strong predictor of outcome after ICU admission. Six-month clinical outcome was used as the dependent variable and the variables age, acute physiology and chronic health evaluation (APACHE) IV score and measurement time after ICU admission as independent variables. A p-value < 0.05 was considered as statistically significant. All statistical analyses were performed in R (version 4.0.3; R Core Team, Vienna, Austria) [16].

Table 1 | Transfer function analysis phase plot criteria for segment selection. A detailed rationale for the automated ten-minute TFA phase plot data segment selection (segment) is provided in Supplementary File S2.

Assumptions	Criteria to Exclude a Segment	Reference
(I) The physiological high-pass filter characteristics of CA are observed in the VLF and LF range; (II) Reliable correction for serial time effects using the HF data (correction for TT and %BF) is performed [9].	Correction for TT and %BF was not possible, i.e., no HF trend line was available.	[9], Box 1, Supplementary Figure S2, Supplementary Table S2
	A negative mean VLF and/or LF-phase shift of <−10° was present.	[8]
	Mean VLF and/or LF-phase shift values of >180° or <−180° (likely caused by persistence of 'phase wrap around') were present.	[8], Supplementary Table S2
	<33% of the frequency bins in the VLF + LF or the HF-range had a coherence value above the significance threshold (meaning <6 bins available for the VLF + LF range and <10 bins for the HF range).	Figure S3

%BF = percentage blood flow oscillations; CA = cerebral autoregulation; HF = high frequency; LF = low frequency; TT = microvascular transit time; TFA = transfer function analysis; VLF = very low frequency.

3. RESULTS

We measured eighty-six critically ill sedated/comatose patients with a variety of admission diagnoses (Supplementary Table S3). The patient and segment selection flowchart is shown in Figure 1. For four patients no informed consent was given. We excluded the whole recordings of 23 patients during the first period of our study due to practical and technical issues (mainly crosstalk between the NIRS optodes, details in Figure 1). This led to a protocol change to avoid crosstalk. Fifty-nine patients with 727 segments were available for the TFA. Application of the (automated) selection of segments, resulted in 490 segments (67%) in fifty-four patients. On average four segments (q1–q3 2–7) were available per patient. The final study population consisted of predominantly middle-aged male patients of whom 63% (n = 34) had a primary neurological diagnosis (Table 2). The six-month mortality rate was 46% (n = 29 survivors versus n = 25 non-survivors). Six patients died between ICU discharge and planned follow-up. The survivors were on average younger compared to the non-survivors (49 (q1–q3 40–57) versus 71 (q1–q3 59–77) years old), had lower APACHE IV scores (65 (q1–q3 41–94) versus 102 (q1–q3 72–120) and were measured later (44 (q1–q3 20–84) versus 22 (q1–q3

13–45) hours) after ICU admission (Table 3). There were no clinically relevant physiological differences between the groups during the measurement period (Supplementary Table S4).

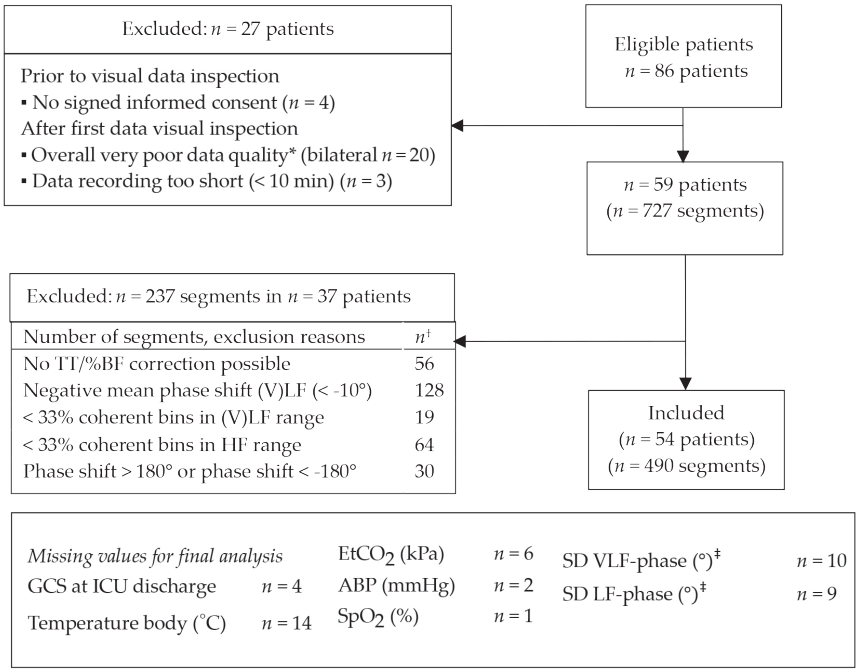


Figure 1 | Study flow chart. Each box (right side) shows the remaining number of patients and remaining number of segments. For each patient a different number of segments is available. * Overall poor data quality e.g., crosstalk, no beat-to-beat pulsatility, multiple-artifacts. † The numbers do not count to the number of 'excluded' segments, because each segment can have more than one reason for exclusion. ‡ No SD could be calculated, as the patient is represented by only one segment. ABP = arterial blood pressure; BF = blood flow oscillations; $EtCO_2$ = end tidal carbon dioxide; GCS = Glasgow coma scale; HF = high frequency range; (V) LF = (very) low frequency range; SD = standard deviation; SpO_2 = peripheral oxygen saturation; TFA = transfer function analysis; TT = microvascular transit time.

Table 2 | Patient characteristics dichotomized for six-month mortality.

Median (q1–q3)	Total (n = 54)	Survivors (n = 29)	Non-Survivors (n = 25)
Age (years)	58 (43–72)	49 (40–57)	71 (59–77)
Sex, male, n (%)	46 (85)	22 (76)	24 (96)
Admission diagnosis, primary neurological *, n (%)	34 (63)	15 (52)	19 (76)
Admission APACHE IV score	84 (51–111)	65 (41–94)	102 (72–120)
SOFA score (on day of measurement)	9 (6–10)	8 (6 -10)	10 (7–11)
Length of ICU stay (days)	12 (6–17)	15 (6.2–20)	8.4 (5.9–15)
Days on mechanical ventilation	7.2 (2.9–12)	8.5 (2.9–14)	7.2 (3.6–11)
Mortality at ICU discharge, n (%)	19 (34)	0	19 (76) ‡
GCS at ICU discharge †, n (%)			
GCS score 3–5	1 (1.9)	0	1 (4)
GCS score 6–8	1 (1.9)	0	1
GCS score 9–12	8 (15)	7 (25)	1
GCS score 13–15	21 (39)	19 (72)	2
GOSE at 6 months, n (%)			
Favorable outcome, GOSE 5–8	25 (46)	25 (86)	0
Unfavorable outcome, GOSE 2–4	4 (7.4)	4 (14)	0
Mortality GOSE 1	25 (46)	0	25 (100)

* Primary neurological diagnoses include: traumatic brain injury, cardiac arrest, acute stroke, status epilepticus and meningitis (see Supplementary Tables S4–S8). † The number of missing GCS at ICU discharge values are for survivors n = 3 and non-survivors n = 1. ‡ Six patients died between ICU discharge and six months follow-up. Admission diagnoses of these patients were: acute stroke (n = 2), respiratory insufficiency (n = 3) and hemorrhagic shock (n = 1). APACHE IV = acute physiology and chronic health evaluation IV; GCS = Glasgow coma scale; GOSE = Glasgow outcome scale extended; ICU = intensive care unit; SOFA= sequential organ failure assessment; TBI= traumatic brain injury.

Table 3 | Near infrared spectroscopy data length and quality dichotomized for six-month mortality. The results of the unilateral hemispheric measurement are reported, i.e., the hemisphere with the worst cerebral autoregulation estimate (lowest LF-phase shift for an individual).

Median (q1–q3)	Total (n = 54)	Survivors (n = 29)	Non-Survivors (n = 25)
Bilateral measurements, n (%)	40 (74)	19 (54)	21 (84)
Start measurement after ICU admission (h)	29 (16–77)	44 (20–84)	22 (13–45)
Duration bedside recording (min)	77 (59–130)	71 (68–59)	79 (63–125)
Artifact free NIRS recording (min) *	61 (47–121)	54 (53–46)	67 (48–122)
NIRS data removed † (%)	9.5 (2–26)	11 (2.9–27)	8.8 (1.6–17)
Number of segments per patient *	4 (2–7)	4 (2–6)	5 (2–7)

* Discrepancy between artifact free NIRS recordings and number of ten-minute TFA phase plot segments is due to the requirement of ten contiguous minutes to be selected as a data segment. † The removed NIRS data (before data processing) as a percentage of the recorded data. LF = low frequency; ICU = intensive care unit; NIRS = near infrared spectroscopy; q1–q3 = interquartile range; TFA = transfer function analysis.

3.1. Selection of Transfer Function Analysis (TFA) Segments

Signal characteristics between 'included' segments (n = 490 in 54 patients) and 'excluded' segments (n = 237 segments in 37 patients) are compared in Supplementary Table S5. The percentage of raw oxyHb and deoxyHb signal artifact removal was similar between the groups ('included' 8.2% (q1–q3 1.4–17) versus 'excluded' 9% (q1–q3 2.3–30) segments). Both the mean PSD-oxyHb LF and PSD-ABP LF were higher for the 'included' segments ('included' PSD-oxyHb LF 0.03 (q1–q3 0.01–0.076) versus 'excluded' 0.012 (q1–q3 0.005–0.027) μM^2/Hz; mean PSD-ABP LF ('included' 3.9 (q1–q3 1.0–14) versus 'excluded' 1.6 (q1–q3 0.4–3.6) $mmHg^2$/Hz segments). There were no differences for the other physiological variables.

3.2. Cerebral Autoregulation (CA) Parameters

Figure 2 shows two examples of the TFA phase shift plot of a segment: one segment with the interpretation of an intact CA ('high-pass filter' configuration and LF-phase shift of 19°, Figure 2A) and one segment with the interpretation of an impaired CA (almost 'flat line' configuration and LF-phase shift of 2°, Figure 2B). The median LF-phase shift of the study population was 12° (q1–q3 2.2–34). The coherence, remaining model output variables and the mean PSD results are summarized in Supplementary Tables S6 and S7. The TFA LF-phase shift values dichotomized for six-month mortality are given in Figure 3A. There was no significant difference between survivors and non-survivors (survivors 20° (q1–q3 6.7–34) versus non-survivors 6.2° (q1–q3 0.51–27),

p = 0.118, n = 54). The within-patient LF-phase shift variability is shown in Supplementary Figure S4. Median LF-phase shift SD was 6.5° (q1–q3 3.5–14) with comparable results between the groups (survivors 8.3° (q1–q3 4–15) versus non-survivors 5.9° (q1–q3 2.9–9.3)).

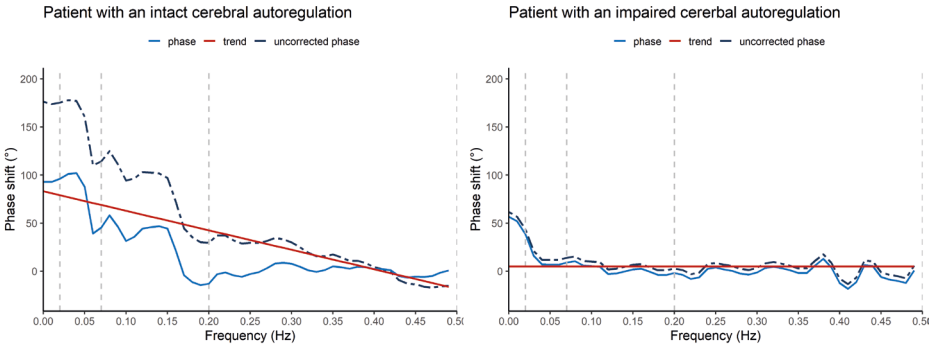


Figure 2 | TFA-phase shift plot examples in two patients (ten-minute segment) of intact/impaired CA estimations. (**A**) shows a segment with a 'high pass' filter concept configuration and TFA VLF and LF numbers assuming working CA (mean LF-phase shift 19°). (**B**) shows a segment with a 'flat line' with minimal HF correction. No 'high-pass' filter principle configuration is seen and VLF and LF-phase shift numbers are close to zero (mean LF-phase shift 2°), assuming impaired CA. The dashed dark blue curve is the uncorrected phase shift computed for the frequency range 0.01–0.5 Hz. The lighter blue line is the phase shift computed after subtraction of the red linear HF trend line from the uncorrected phase shift. The dashed vertical grey lines delineate the frequency ranges for the VLF (0.02–0.07 Hz), LF (0.07–0.2 Hz) and HF (0.2–0.5 Hz) range. CA = cerebral autoregulation; deoxyHb = deoxyhemoglobin; HF = high frequency range; LF = low frequency range; oxyHb = oxyhemoglobin; TFA = transfer function analysis; VLF = very low frequency range.

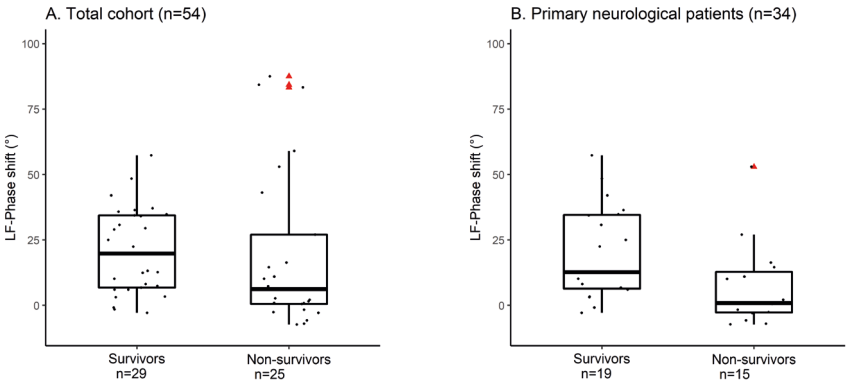


Figure 3 | Low frequency phase shift dichotomized for six-month mortality. The boxplots in (**A**) show for the total cohort no significant difference between survivors and non-survivors for the LF-phase shift (survivors 20° (q1–q3 6.7–34) versus non-survivors 6.2° (q1–q3 0.51–27), p = 0.118, n = 54). Three outliers (Δ in the non-survivor group (LF-phase shift > 75°) were identified. These three patients had the admission diagnosis: respiratory insufficiency (n = 2) and hemorrhagic shock (n = 1). (**B**) shows the boxplots for patients with a primary neurological admission diagnosis. A significant difference between survivors and non-survivors for the LF-phase shift (survivors 13° (q1–q3 6.3–35) versus non-survivors 0.83° (−2.8–13), p = 0.0167, n = 34) is presented. The outlier (Δ in the non-survivor group (LF-phase shift = 52°) was a multi-trauma patient with only mild brain injury involvement who was intubated because of respiratory insufficiency. deoxyHb = deoxyhemoglobin; LF = low frequency range; oxyHb = oxyhemoglobin; q1–q3 = interquartile range; Δ = data outlier.

3.3. Primary Neurological Admission Diagnosis

Thirty-four patients had a primary neurological admission diagnosis. The physiological and CA measures are described in Tables S8–S12. The LF-phase shift was significantly higher in survivors (survivors 13° (q1–q3 6.3–35) versus non-survivors 0.83° (q1–q3 2.8–13), p = 0.0167, Figure 3B), indicating a more preserved CA in survivors compared to non-survivors. This relationship remained significant after correction for age, APACHE IV score and measurement time after ICU admission in the multivariate model. Per 10° lower phase shift a significant increase in mortality was found (adjusted Odds Ratio (OR) of 0.27, 95%—confidence interval (95%-CI) 0.10–0.78, p = 0.015)). For the variable age (keeping the other predictors constant) a significant positive relationship with mortality was found (adjusted OR of 1.16, 95%-CI 1.01–1.33, p = 0.032). No significant independent relationship with mortality was found for APACHE IV score (p = 0.614) and measurement time after ICU admission (p = 0.218) (Supplementary Table S13).

4. DISCUSSION

In this prospective single center observational study, we tested for the first time in critically ill and sedated/comatose patients our non-invasive methodology that uses high frequency cerebral oxyHb and deoxyHb NIRS signals to estimate CA. We upgraded the methodology by adding criteria to select segments for more robust and consistent CA estimations in individual patients. An estimation of CA could be provided in more than 90% of our patients (n = 54) with acceptable within-patient variability of the LF-phase shift, leaving around forty minutes of data available for the analysis per patient. Even after adoption of our bedside measurement protocol in 2019, 33% of the segments had to be excluded. In 34 patients with a primary neurological admission diagnosis, a significant and independent relationship with six-month mortality was found.

4.1. Data segment Selection

Although in this 'NIRS-only' methodology no continuous ABP recordings are required, sufficient hemodynamic oscillations are needed to challenge the cerebrovascular network. Although many maneuvers—like thigh cuffs or squad stands—have been tested successfully to induce ABP oscillations, they can be dangerous or impractical for critically ill patients [17]. Although CA-estimates that correlated with clinical outcome have been calculated in the time domain using spontaneous ABP oscillations, these measurements required long recordings and ABP-monitoring [18,19]. Data from multiple research sites suggested that when using TCD recordings of around five minutes, a mean PSD ABP LF of at least 10 $mmHg^2/Hz$ is required for reliable frequency domain CA estimations in healthy awake subjects [10]. Comparing the 'in'- and 'excluded' segments in our study population supports that limited spontaneous ABP oscillations might explain periods with poor signal-to-noise ratio in our sedated patients and warrants the need for additional criteria for data selection. Being a 'NIRS-only' methodology, we formulated NIRS-based criteria making use of (1) the TFA-based 'high-pass filter' characteristic of dynamic CA and (2) the applied correction for serial time shifts between the oxyHb and deoxyHb signals through the capillaries (Box 1, Table 1). The CA concept can be described as a 'high-pass' filter with active altering of the lower frequency oscillations in the cerebral signals [8,20]. Most TFA CA papers report averaged values per frequency range. We decided to construct the TFA phase plot of all segments and reviewed from these plots the interpretability of the obtained phase shift values in the VLF, LF and HF range. We translated this into a set of criteria that can be applied in an automated way (Supplementary File S1).

4.2. Clinical Interpretation

The advantage of our 'NIRS-only' methodology is that it provides an easy way to measure CA that can be applied in different clinical situations (hospital wards, operating room but also outpatient clinic). In the current study, we evaluated the methodology in a critically ill sedated/comatose ICU population. Several studies showed that impaired CA in critically ill patients is related to poor clinical outcome [1,21]. We were able to replicate these findings for 34 patients with a primary neurological patient admission diagnosis. Interestingly, for the whole ICU study population, the LF-phase shift was low (12° (q1–q3 2.2–34)). So far, our 'NIRS-only' methodology has been applied in only two small studies [9,22]. In eleven healthy subjects, the baseline LF-phase shift was between 30° and 40° and decreased to values around 20° during hypercapnia. In a sepsis model in eleven healthy subjects, the baseline LF-phase shift values of 16.2° (q1–q3 3.0–52.6) decreased to 3.9° (q1–q3 2.0–8.8) after endotoxin infusion. Zhang et al. obtained the CA status in neurological ICU patients using ABP and TCD recordings and found an average LF-phase shift of about 30° in twenty patients [12]. This might suggest that in our critically ill and sedated/comatose population with high disease severity scores, the CA status was somehow impaired in general. Another factor that might explain the lower LF-phase shift values is, that the patients in our study were represented by the 'worst' CA hemisphere.

4.3. Limitations

Our study has several limitations that need to be addressed. Although the NIRS technique is easy to apply on the forehead, there are several issues that limits its application (even in sedated/comatose patients). Firstly, artifacts and crosstalk in particular (due to simultaneous, bilateral measurements). Unique for our NIRS device compared to other commercially available devices is that it collects high frequency raw data of 50 Hz. Noisy signals or artifacts are therefore clearly visible in the pulsating oxyHb and deoxyHb signals. For example, we noticed an artifact (of ~4.5 Hz) on top of the per heart-beat oscillations which was explained by crosstalk between the optodes. This artifact disturbed the TFA due to its high amplitude, and broad and varying frequency content. For this reason, we had to exclude whole patient recordings in a large number of patients and had to change our measurement protocol from bilateral, simultaneous to unilateral, consecutive measurements. The latter limits the comparison of both hemispheres over time. Regarding the crosstalk, incorporating asynchronous data sampling can solve the crosstalk problem. The influence of the pre-processing (artifact removal) was not evaluated formally, but it is recommended to remove artifacts (preferably in an automated way), as this results in incorrect high coherence values between both NIRS signals [8]. Secondly, there is controversy about the exact measurement depth

of the NIRS technology and the degree to which the signals are influenced by skin or bone tissue [23]. We used the deepest recording loop of our device, but without the option to correct for more superficial light absorption. Thirdly, we did not use another (non-invasive) brain monitoring technique to compare our results with. TCD is often used as a reliable technique to estimate CA in the frequency domain, but usually allows only short recordings. Our 'NIRS-only' methodology was previously compared with TCD results in healthy subjects which is reassuring [9], but the recent modifications (Supplementary Table S2) and data segment selection option justify a new comparison. In addition, we did not compare our results with a model including ABP signals. A NIRS model using a slightly different HF-range correction for serial time trends was previously studied in awake patients with (mild) cognitive and in healthy subjects. They studied the relationship between ABP and oxyHb [24]. It might be interesting to compare our results with those retrieved from ABP—oxyHb calculations. Fourthly, our outcome analysis and results are hampered by the short recordings (forty minutes on average), the high mortality rates and the majority of patients having a primary neurological admission diagnosis. This limits the generalizability of our findings. In addition, the outcome analysis is likely affected by other pathophysiological processes during the ICU stay. However, the relationship of LF-phase shift with outcome in primary neurological patients was independent from disease severity, age and measurement time. Fifthly, we experienced difficulties with some digital signal processing steps. As an example, two of the data selection criteria are directly related to the phase wrap around phenomenon. Phase wrap around is a complex data processing problem in TFA phase shift calculations, as for phase calculations the inverse tangent is computed and the inverse tangent cannot differentiate between π (180°) and 2π (360°) radians. Therefore, CARNet recommends removing phase shift values showing wrapped phases [8]. In our software we applied methods to adjust automatically for phase wrap around (Supplementary Table S2), but phase wrap was not always recognized. We therefore restricted the phase shift values to the range [−180°–180°] and removed mean negative (V)LF phase shift values (<−10°) computed per segment [8]. The arbitrary −10° threshold was chosen to accept small calculation errors for patients with total CA impairment. Another example that likely has affected our data is the effect of mechanical ventilation on our applied BF/BV and TT correction, as the ventilation rate is within the HF range. The positive pressure ventilation influenced the HF trend line estimation in some segments quite dramatically. Future studies should investigate more in-depth into the effect of mechanical ventilation on phase shifts between oxyHb and deoxyHb and on our 'NIRS-only' CA methodology.

Sixthly, the unexpected difference between the groups at the start of the measurement might have resulted from a recruitment selection bias. However, in our multivariate outcome model we corrected for this potential confounder (Supplementary Table S13). Lastly, the measurement timing for nineteen patients was outside our intended 48 h window (35%) after ICU admission. Although this might have affected our results, for a feasibility study this protocol violation might be of less importance.

4.4. Future Perspectives

Our results show that the 'NIRS-only' methodology seems applicable on the ICU when taking data processing, data selection criteria and limitations of the NIRS technology into account. Future studies are required for the validation of our modifications and selection criteria in larger study populations and should investigate more in-depth the effect of certain interventions like mechanical ventilation on the CA estimation. The methodology should also be tested with signals from other available NIRS devices. Furthermore, the performance of our methodology should be investigated in longer recordings to monitor the CA status over time.

5. CONCLUSIONS

CA estimation using the 'NIRS-only' methodology seems feasible in critically ill sedated/comatose patients after incorporation of methodological improvements and automated data segment selections for more robust and consistent CA estimations. We found an independent and significant correlation between LF-phase shift and six-month mortality in patients with a primary neurological admission diagnosis. CA estimation without the need for continuous ABP measurement ('NIRS-only' methodology) is an attractive option to be (continuously) informed about the individual CA status.

Supplementary Materials

The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/cells11142254/s1. Table S1: STROBE Statement—checklist of items that should be included in reports of observational studies; File S1: Extra information about the applied Methodology; Figure S1: Artefact removal algorithm; Table S2: 'NIRS-only' methodology modifications with respect to Elting et al. [1]; Figure S2: Examples of linear polynomial high frequency range fit; File S2: Transfer function analysis phase shift plot segment selection; Figure S3: Threshold for the number of coherent bins; Table S3: Patient clinical admission diagnosis dichotomized for six-month mortality; Table S4: Physiological variables during the bedside measurement dichotomized for six-month mortality; Table S5: Characteristics of 'included' versus

'excluded' segments; Table S6: Power spectral density results dichotomized for six months mortality; Table S7: Cerebral autoregulation parameters (TFA estimates) results dichotomized for six-month mortality; Table S8: Patient characteristics dichotomized for six-month mortality for primary neurological diagnosis; Table S9: NIRS data length and quality dichotomized for six-month mortality for primary neurological diagnosis; Table S10: Frequency analysis dichotomized for six-month mortality for primary neurological diagnosis; Table S11: Cerebral autoregulation parameters dichotomized for six-month mortality for primary neurological diagnosis; Table S12: Physiological variables during the bedside measurement dichotomized for six-month mortality for primary neurological diagnosis; Figure S4: Within patient variability for the low frequency phase shift (n = 54); Table S13: Multivariate logistic regression model for primary neurological diagnosis (n = 34). References [25,26] are cited in the supplementary materials.

Author Contributions

Conceptualization, M.J.H.A. and J.W.J.E.; Data curation, J.T.; Formal analysis, J.T. and N.E.; Funding acquisition, I.C.C.v.d.H., M.J.H.A. and J.W.J.E.; Investigation, J.T., N.E., M.B., K.D.J.B. and A.P.L.; Methodology, J.T., N.E., K.D.J.B., S.M.J.v.K., M.J.H.A. and J.W.J.E.; Project administration, M.J.H.A. and J.W.J.E.; Resources, I.C.C.v.d.H., M.J.H.A. and J.W.J.E.; Software, N.E. and J.W.J.E.; Supervision, M.J.H.A. and J.W.J.E.; Validation, J.T. and N.E.; Visualization, J.T., N.E., M.J.H.A. and J.W.J.E.; Writing—original draft, J.T., N.E., M.J.H.A. and J.W.J.E.; Writing—review and editing, J.T., N.E., M.B., K.D.J.B., A.P L., S.M.J.v.K., I.C.C.v.d.H., M.J.H.A. and J.W.J.E. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Maastricht University Center Maastricht (protocol code METC Maastricht 16-4-243, 16-10-2020).

Informed Consent Statement

Informed consent was obtained from all subjects or legal representatives involved in the study.

Data Availability Statement
Data is contained within the article or supplementary material.

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Conflicts of Interest
The authors declare no conflict of interest.

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SUPPLEMENTARY DATA

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APPENDIX A. EXTRA INFORMATION ABOUT THE APPLIED METHODOLOGY

A.1 Data collection

For each patient, we collected the following patient and admission characteristics: age, sex, admission diagnosis, Acute Physiology And Chronic Health Evaluation IV (APACHE IV) score at admission, Sequential Organ Failure Assessment (SOFA) score on the measurement day, ICU length of stay and the number of days on mechanical ventilation. Close to the measurement, the following variables were retrieved from laboratory or arterial blood gas analysis results: partial oxygen tension (PaO_2, kPa), partial carbon dioxide tension ($PaCO_2$, kPa), the PaO_2 / FiO_2 ratio (mmHg/%), and hemoglobin concentrations (mM). In addition, the Glasgow Coma Scale (GCS) at ICU discharge (from discharge letter or nursing chart), the ICU mortality (from discharge letter), and the six-month Glasgow Outcome Scale Extended (GOSE) by telephone interview were collected as clinical outcome parameters.

A.2 Arterial blood pressure monitoring

The arterial blood pressure (ABP) was monitored invasively in the arteria radialis or femoralis and in most patients zeroed at (right) heart level. In traumatic brain injury (TBI) patients with intracranial pressure monitoring, the ABP was zeroed at the foramen of Monroe level to be able to calculate the cerebral perfusion pressure

A.3 High frequency NIRS monitoring

The Portalite NIRS has an emitter of infrared (IR) light and three receivers for the IR light. The distance between the emitter and the receivers determines the depth that the light transfers through the (brain)tissue. The Portalite measures at three distances (superficial, intermediate, and deepest loop). We used the deepest loop (largest inter-optode distance of 40 mm) for our analyses. The largest inter-optode distance increased the likelihood of measuring brain tissue. Age-related pathlength scattering correction was applied for the age range 17-50 years [1]. In contrast to other commercial NIRS devices, the Portalite collects high-frequency (50Hz) data. For the NIRS-only methodology, a NIRS device with oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) signals with at least a sampling frequency of 1 Hz is needed so frequencies up to 0.5 Hz can be reliably measured. Via a custom-made ICM+ Portalite module, these high frequency NIRS data were transferred in real-time from the NIRS recording Oxysoft software (version: 3.0.103.3; Artinis Medical Systems, Elst, The Netherlands) to the ICM+ software.

A.4 Power spectral density analysis

Sufficient slow ABP fluctuations are required for a reliable CA assessment [2]. The amount of slow ABP, oxyHb and deoxyHb fluctuations was quantified by the Power Spectral Density (PSD) over detrended ABP, oxyHb, deoxyHb-traces using Welch's method: 100 second windows, 50% window overlap, and a Hanning window. The ABP signals were pre-processed automatically with the removal of segments with ABP values < 0 mmHg, systolic ABP values > 200 mmHg, or data gaps > 0.2 sec (mainly caused by zeroing, flushing, or manipulation of the arterial line). After that, the mean PSD for the very low frequency (VLF) and low frequency (LF) range for ABP, oxyHb, and deoxyHb was determined per patient.

A.5 Transfer function analysis

The relationship between oxyHb (input) and deoxyHb (output) in the different frequency ranges was studied by TFA [3]. The frequency ranges of interest are the very low frequency (VLF 0.02 - 0.07 Hz), the low frequency (LF 0.07 - 0.2 Hz), and the high frequency range (HF 0.2 - 0.5 Hz). From this analysis, the parameters coherence, gain, and phase shift are retrieved to represent different aspects of CA. In short, in the frequency domain, coherence is a measure of the linear relation between the signals (unitless), the gain is the amplification factor between the in-and output signals (unitless), and the phase shift is the time shift between the signals with the same frequency (in degrees (◦)) [4].

Table A1 | Strengthening the Reporting of Observational studies in Epidemiology (STROBE) - checklist of items that should be included in reports of observational studies.

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract.	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found.	1
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported.	1-2
Objectives	3	State specific objectives, including any prespecified hypotheses.	2
Methods			
Study design	4	Present key elements of study design early in the paper.	2
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection.	2-3
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls. *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants.	2
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed. *Case-control study*—For matched studies, give matching criteria and the number of controls per case.	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	3,4,5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group.	3 and 5
Bias	9	Describe any efforts to address potential sources of bias.	4

Table A1 | Strengthening the Reporting of Observational studies in Epidemiology (STROBE) - checklist of items that should be included in reports of observational studies. (continued)

	Item No	Recommendation	Page No
Study size	10	Explain how the study size was arrived at.	2
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why.	4 and 5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding.	5
		(*b*) Describe any methods used to examine subgroups and interactions.	5
		(*c*) Explain how missing data were addressed.	AP. A4
		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy.	NA
		(e) Describe any sensitivity analyses.	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5-6
		(b) Give reasons for non-participation at each stage	5-6
		(c) Consider use of a flow diagram	6
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6-7
		(b) Indicate number of participants with missing data for each variable of interest	6
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	7

Table A1 | Strengthening the Reporting of Observational studies in Epidemiology (STROBE) - checklist of items that should be included in reports of observational studies. (continued)

	Item No	Recommendation	Page No
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	7 and 8
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done - e.g. analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10-11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10
Generalisability	21	Discuss the generalisability (external validity) of the study results	10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	12

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies [5].

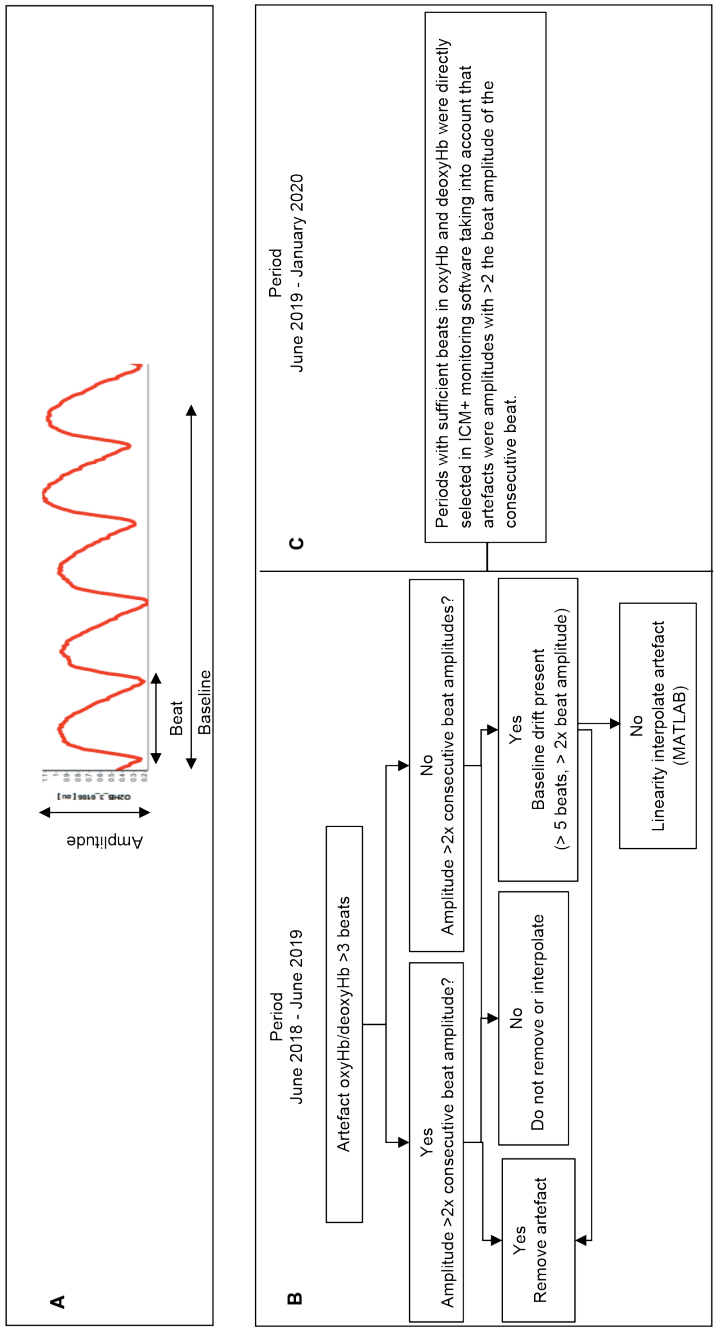

Figure A1 | Artefact removal algorithm. (A) A period of five beats of the 50 Hz oxyHb signal. The beats are reflections of heart beats. Artefact removal was performed differently in the two measurement periods. **(B)** For the first period, sample numbers of artefacts in the oxyHb and deoxyHb signal were notated in a Microsoft Excel workbook by inspecting the imported data in LABVIEW. Subsequently, artefacts were removed or interpolated using the Excel workbook information in combination with a MATLAB algorithm. **(C)** In the second period (after the protocol change), periods with sufficient beats in the oxyHb and deoxyHb signals were selected directly in the monitoring software ICM+ taking into account the artefact criteria from period one. Artefacts in period 2 were the result of frequent ectopic heart beats in critically ill patients or manipulation of the optodes). deoxyHb = deoxyhemoglobin; oxyHb = oxyhemoglobin.

Table A2 | NIRS-only methodology modifications with respect to Elting et al. (2018)

Modification	Description
Automated Phase wrapping correction	In contrary to the 'manual' unwrapping correction in the previous model [6], the unwrapping was in the current study 'automated' with the inbuilt 'unwrap phase' function in LABVIEW. This function compares the phase shifts of two consecutive frequency bins. If the difference in phase shift is larger than 180°, 360° was added to the phase shift of the latter bin: If $\lvert \phi_{n-\ n+1} \rvert$ >180°: $\phi_{n+1} \leftarrow \phi_{n+1}$ +360° with ϕ_n = phase shift difference at position n and ϕ_{n+1} = phase shift difference at position n + 1 frequency bin. However, if the first frequency bin was phase wrapped (i.e. ϕ is close to -180°), the phase shift in all the following frequency bins were incorrectly changed into values around -180°. To correct for this, 180°was added to the phase shifts in all frequency bins when then mean of the phase shifts was below a threshold of -90°.
Y intercept wrap limit	A setting to additionally correct for wrapped phases. Default setting:, -180°. This setting was functional in case the 'phase wrap limit mean' was not sufficient to correct for phase wrap. By using this setting, the calculations for TT(BF), ϕ%BF and y-intercept corrects also for the phase wrap
Slope min, Slope max, Intercept min, Intercept max,	Settings to add restrictions to the HF-trendline estimation. These settings can be set e.g. to avoid a HF-trendline with an unphysiological positive slope. Default settings: slope min: infinite, maximum: 0°, intercept minimum: 0°, intercept maximum: 180°). For the current analysis, we additionally evaluated the effect of small positive slopes of the HF-trendline (to avoid too strict application of our segment selection). In case of small positive slopes, no phase shift correction was done and the uncorrected phase shift was provided. Small slopes were defined as a threshold < 0.3º /bin. This corresponds to a maximal change in phase shift of 9º. In case the HF-trendline slope of was larger than this threshold, no phase shift values were provided. Two examples of this applied criterion are given in Figure A2. When no HF-trendline correction was applied, the model assumes that BV oscillations dominates BF oscillations. Therefore, the TT(BF) cannot be defined, but assumed to be very close to zero (equation 4 in ref [6]).

BV = blood volume; BF = blood flow; F = high frequency; TT BF) = capillary transit time (resulting from blood flow oscillations only).

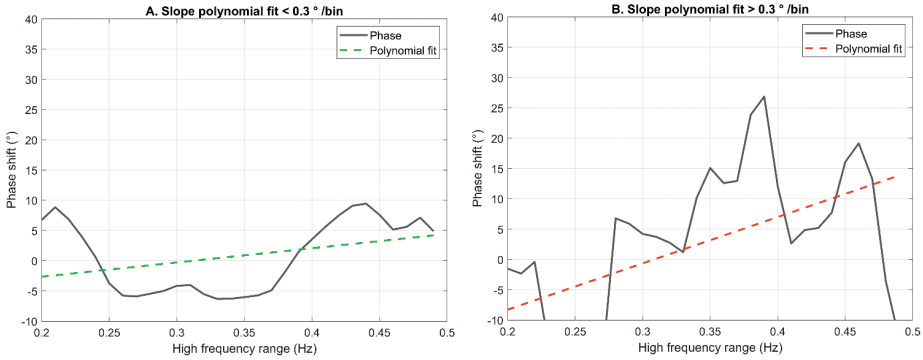

Figure A2 | Examples of the linear polynomial high frequency range fit. The high frequency (0.2 - 0.5 Hz) range (x-axis) and the phase shift between oxyHb and deoxyHb concentration differences (y-axis). **(A)** This example shows the slope of the fitted linear polynomial less than 0.3º /bin (uncorrected phase shift values for the (very) low frequency ranges were used) and **(B)** shows an example for which the slope of the linear polynomial increases with more than 0.3º /bin (no phase shift values were provided. Segment was not used for outcome analysis). See further explanation in Table A2.

APPENDIX B. TRANSFER FUNCTION ANALYSIS PHASE SHIFT PLOT SEGMENT SELECTION

The transfer function analysis (TFA) phase shift plots were computed over ten minute data segments (segments). The four selection criteria for physiologically interpretable TFA phase shift plots are described below.

Criterion I. For the serial transit time - blood flow/blood volume (TT-BF/BV) correction, a linear fit over the phase shift values in the high frequency (HF)-range is used (HF-trendline). Segments with a significant positive slope for the linear HF-trendline were excluded (Figure A2). The motivation is that a clear positive slope indicates a negative transit time between oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb), which entails that oscillations in deoxyHb (mainly venous microvasculature) occur ahead of oscillations in oxyHb (mainly arterial microvasculature). We regard this as very unlikely. It is most probable that the significant positive slope is the result of motion artefacts and device noise, that affect the HF-trendline and no reliable correction in the methodology can be applied. Smaller positive HF-trendlines were treated differently (see Table A2 and Figure A2).

Criterion II. For the very low frequency (VLF)- and low frequency (LF)-range segments with negative mean phase shift results (< -10º) were excluded , This was applied to all VLF- and LF-range frequencies (< 0.2 Hz) for consistency, whereas removal of all negative phase shift values <0.1 Hz is recommended by The Cerebrovascular Research Network (CARNet) [3]. The occurrence of

small negative phase shift values (0 > ϕ > -10º) was interpretated as impaired cerebral autoregulation.

Criterion III. Phase shift values above >180º or < -180º were excluded to account for wrap around that was not detected by our extensive automated algorithm. The removal of phases wrap around is in accordance with the CARNet recommendations [3]. (Table A2 explains details about the automated phase wrap correction).

Criterion IV. A minimal number of bins with a coherence above the (calculated) significance threshold was determined. The smaller the number of allowed missing bins per frequency range (Figure A3) , the larger the change in number of excluded segments. However, a more stringent threshold on the minimal number of allowed missing bins per frequency range naturally leads to the exclusion of more segments. Figure A3 displayed the trade-off between minimal number of bins and number of excluded segments . A threshold of 66% was determined as this resulted in low exclusion of additional segments (5.8%, 30/520 segments), and yielded at least six bins for the VLF- plus LF-range and ten bins for the HF-range.

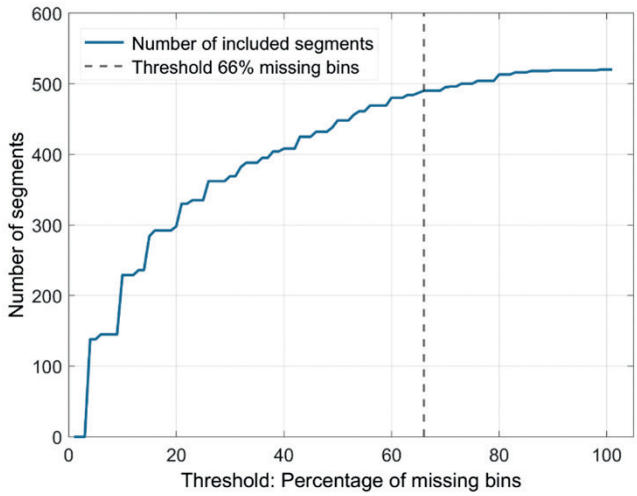

Figure A3 | Threshold for the number of coherent bins. The trade-off between number of missing bins (%) (x-axis) and the number of included segments (y-axis). The graph shows the number of excluded segments after applying criteria I, II, III (Appendix B). A higher threshold (x-axis) result in more included than excluded segments. The number of excluded segments for a threshold of 0% allowed no segments. A threshold of 66% (dotted line) is used, resulting in the inclusion of 490 of 520 segments.

Table A3 | Patient clinical admission diagnosis dichotomized for six-month mortality

Median (q1-q3)	**Total (*n* = 54)**	**Survivors (*n* = 29)**	**Non-survivors (*n* = 25)**
Admission clinical diagnosis, n (%)			
Traumatic brain injury	13 (24)	10 (34)	3 (12)
Cardiac shock	1 (1.9)	1 (3.4)	0
Meningitis	1 (1.9)	1 (3.4)	0
Status epilepticus	1 (1.9)	0	1 (4)
Respiratory insufficiency	7 (13)	1 (3.4)	6 (24)
Acute Stroke	9 (17)	2 (6.9)	7 (28)
Post-surgical observation	2 (3.7)	1 (3.4)	1 (4)
Septic shock	2 (3.7)	2 (6.9)	0
Cardiac arrest	10 (19)	6 (21)	4 (16)
General (non-TBI) trauma	3 (5.6)	3 (10)	0
Hemorrhagic shock	4 (7.4)	1 (3.4)	3 (12)
Upper airway obstruction due to lymphoma	1 (1.9)	1 (3.4)	0

TBI = traumatic brain injury; q1-q3 = interquartile range

Table A4 | Physiological variables during the bedside measurement dichotomized for six-month mortality. The results of the unilateral hemispheric measurement period are reported, i.e. of the hemisphere with the worst cerebral autoregulation estimate (lowest LF-phase shift for an individual).

Median (q1 - q3)	**Total (*n* = 54)**	**Survivors (*n* = 29)**	**Non-survivors (*n* = 25)**
MAP (mmHg) – segments*	76 (71 - 85)	77 (71 - 84)	78 (70 - 88)
Heart rate (min^{-1})	79 (65 - 88)	82 (72 - 96)	77 (62 -85)
$EtCO_2$ (kPa) ‡	4.1 (3.7 - 4.7)	4.4 (4.0 - 4.8)	4.0 (3.5 - 4.3)
SpO_2 (%)§	97 (95 - 98)	97 (96 - 98)	96 (95 - 98)
Body temperature (°C) ‖	36.8 (36.1 - 37.2)	37 (36.4 - 37.5)	36.7 (35.8 - 37.1)
FiO_2 (%)	35 (26 - 40)	30 (25 - 40)	40 (30 – 50)
During measurement			
PaO_2 (kPa)	11.6 (9.7 - 13.4)	11.5 (9.9 - 13.4)	11.6 (9.5 -13.2)
$PaCO_2$ (kPa)	4.9 (4.4 - 5.6)	5.1 (4.7 - 5.4)	4.9 (4.3 - 5.7)
PaO_2 / FiO_2 ratio (mmHg/%)	240 (187 -328)	262 (225 - 337)	202 (142 - 270)
Hemoglobin (mM)	6.6 (5.7 - 8.2)	6.9 (5.9 - 8.1)	6.5 (5.7 - 8.2)

* The number of missing MAP values for non-survivors *n* = 2.
‡ The number of missing $EtCO_2$ values for survivors *n* = 2 and for non-survivors *n* = 4.
§ The number of missing SpO_2 values for survivors *n* = 1.
‖ The number of missing body temperature values for survivors is *n* = 9 and for non-survivors *n* = 5.
$EtCO_2$ = end tidal carbon dioxide; FiO_2 = oxygen fraction; MAP = mean arterial blood pressure; $PaCO_2$= partial carbon dioxide pressure; PaO_2 = partial oxygen pressure; SpO_2 = peripheral oxygen; q1 - q3 = interquartile range.

Table A5 | Characteristics of 'included' and 'excluded' segments

Median (q1 - q3)	**Total segments (*n* = 727)**	**Included segments* (*n* = 490)**	**Excluded segments* (*n* = 237)**
Physiological values			
MAP (mmHg) – segments†	78 (71 - 87)	77 (69 - 85)	78 (71- 87)
Heart rate (min^{-1})	80 (65 - 92)	80 (65 - 92)	79 (66 - 95)
$EtCO_2$ (kPa) §	4.1 (3.7 - 4.6)	4.2 (4.0 - 4.8)	4.0 (3.5 - 4.5)
During measurement			
PaO_2 (kPa)	11.9 (10 - 13.3)	11.9 (9.8 - 13.9)	11.6 (10.5 - 12.7)
$PaCO_2$ (kPa)	4.9 (4.4 - 5.4)	4.9 (4.4 - 5.4)	5.0 (4.7 - 5.4)
Hemoglobin, (mM)	6.4 (5.6 - 8.2)	6.6 (5.7 - 8.3)	6.2 (5.4 - 6.9)
Frequency analysis			
Mean PSD – oxyHb ($\mu M^2/Hz$) ‖			
VLF (0.02 – 0.07 Hz)	0.31 (0.11 - 0.56)	0.34 (0.16 - 0.55)	0.20 (0.07 - 0.63)
LF (0.07 – 0.2 Hz)	0.022 (0.008 - 0.058)	0.03 (0.01 - 0.076)	0.012 (0.005 - 0.027)
Mean PSD – deoxyHb ($\mu M^2/Hz$) ‖			
VLF (0.02 – 0.07 Hz)	0.035 (0.016 - 0.07)	0.035 (0.016 - 0.069)	0.036 (0.15 - 0.08)
LF (0.07 – 0.2 Hz)	0.003 (0.002 - 0.008)	0.003 (0.002 - 0.009)	0.002 (0.001 - 0.005)
Mean PSD ABP ($mmHg^2/Hz$) ‖			
VLF (0.02 – 0.07 Hz)	18 (7.1 - 46)	22 (7.9 - 55)	15 (5.6 - 30)
LF (0.07 – 0.2 Hz)	2.5 (0.7 - 9.4)	3.9 (1.0 - 14)	1.6 (0.4 - 3.6)

Table A5 | Characteristics of 'included' and 'excluded' segments (continued)

Median (q1 - q3)	**Total segments (*n* = 727)**	**Included segments* (*n* = 490)**	**Excluded segments* (*n* = 237)**
Data overview			
Duration bedside recording (min)	125 (79 - 150)	123 (75 - 151)	132 (114 - 212)
Artefact free NIRS recording (min)	117 (66 -136)	115 (60 - 135)	125 (87 - 175)
NIRS data removed‡ (%)	8.8 (1.6 - 19)	8.2 (1.4 - 17)	9 (2.3 - 30)

* One patient can participate in both groups.
† The number of missing MAP values is for the included category *n* = 42 segments and for the excluded category *n* = 19 segments.
§ The number of missing $EtCO_2$ values are for the included category *n* = 92 segments and for the excluded category *n* = 29 segments.
‖ The number of missing oxyHb and deoxyHb values is for both in- and excluded 4 segments as for the frequency analysis, only data with ABP, oxyHb and deoxyHb signals available were included.
‡ The removed NIRS data (before data processing) as percentage of the recorded data.
ABP = arterial blood pressure; deoxyHb = deoxyhemoglobin; LF = low frequency; oxyHb = oxyhemoglobin; PSD = power spectral density; q1 - q3 = interquartile range; VLF = very low frequency.

Table A6 | Power spectral density results dichotomized for six months mortality. In this table the results of the unilateral hemispheric measurement are reported, i.e. of the hemisphere with the worst cerebral autoregulation estimate (lowest LF-phase shift for an individual).

Median (q1-q3)	Total (*n*= 54)	Survivors (*n*= 29)	Non-survivors (*n*= 25)*
Mean PSD – oxyHb (μM^2/Hz)			
VLF (0.02 – 0.07 Hz)	0.39 (0.16 - 0.74)	0.44 (0.16 - 0.88)	0.34 (0.13 - 0.48)
LF (0.07 – 0.2 Hz)	0.02 (0.009 - 0.05)	0.02 (0.008 - 0.05)	0.03 (0.01 - 0.05)
Mean PSD – deoxyHb (μM^2/Hz)			
VLF (0.02 – 0.07 Hz)	0.04 (0.02 - 0.06)	0.05 (0.02 - 0.06)	0.03 (0.01 - 0.06)
LF (0.07 – 0.2 Hz)	0.003 (0.001 - 0.006)	0.003 (0.001 - 0.004)	0.004 (0.002 - 0.008)
Mean PSD ABP ($mmHg^2$/Hz)			
VLF (0.02 – 0.07 Hz)	19 (8.1 - 45)	19 (12 - 45)	12 (4 - 44)
LF (0.07 – 0.2 Hz)	2.2 (0.9 - 6.5)	2.9 (1.1 - 5.6)	1.8 (0.26 - 9.4)

*ABP data of two patients was missing. Therefore, the two patients were excluded for the PSD analysis, as the PSD batch analysis was only done in patients with all signals available (ABP, oxyHb, and deoxyHb. ABP = arterial blood pressure; deoxyHb = deoxyhemoglobin; LF = low frequency range; oxyHb = oxyhemoglobin; PSD = power spectral density; q1-q3 = interquartile range; VLF = very low frequency range.

Table A7 | Cerebral autoregulation parameters (TFA estimates) results dichotomized for six-month mortality. In this table the results of the unilateral hemispheric measurement are reported, i.e. of the hemisphere with the worst cerebral autoregulation estimate (lowest LF-phase shift for an individual).

Median (q1-q3)	**Total (*n*= 54)**	**Survivors (*n*= 29)**	**Non-survivors (*n*= 25)**
Coherence			
VLF (0.02 – 0.07 Hz)	0.55 (0.43 - 0.68)	0.53 (0.47 - 0.65)	0.57 (0.41 - 0.78)
LF (0.07 – 0.2 Hz)	0.7 (0.51 - 0.86)	0.62 (0.45 - 0.76)	0.77 (0.65 - 0.87)
HF (0.2 – 0.5 Hz)	0.72 (0.57 - 0.86)	0.74 (0.57 - 0.81)	0.7 (0.59 - 0.87)
Gain			
VLF (0.02 – 0.07 Hz)	0.26 (0.17 - 0.34)	0.24 (0.17 - 0.34)	0.28 (0.19 - 0.34)
LF (0.07 – 0.2 Hz)	0.28 (0.24 - 0.34)	0.24 (0.24 - 0.38)	0.28 (0.24 - 0.32)
Phase shift ()			
VLF (0.02 – 0.07 Hz)	39 (10 - 100)	49 (9 - 115)	35 (10 - 64)
LF (0.07 – 0.2 Hz)	12 (2.2 - 34)	20 (6.7 - 34)	6.2 (0.51 - 27)
Phase shift () - SD			
VLF (0.02 – 0.07 Hz)*	14 (7 - 22)	14 (5.4 - 19)	13 (7.7 - 25)
LF (0.07 – 0.2 Hz)†	6.5 (3.5 - 14)	8.3 (4 -15)	5.9 (2.9 - 9.3)
TT‡ (sec)	1.3 (0.89 - 1.6)	1.3 (1.1 - 1.1)	1.0 (0.83 - 1.3)
%BF (%)	8.8 (2.8 - 27)	9 (0.8 - 27)	8.5 (3.3 - 23)

* The number of missing SD-VLF-phase shift values: survivors *n*= 7 patients, non-survivors *n*= 3 patients. † The number of missing SD-LF-phase shift values: survivors *n*= 6 patients, non-survivors *n*= 3 patients.
‡ The number of TT could not be defined because of predominantly blood volume oscillations. Survivors *n*= 5 patients, non-survivors *n*= 2 patients.
BF = percentage blood flow oscillations; HF = high frequency; q1 - q3 = interquartile range; LF = low frequency; TT = capillary transit time; VLF = very low frequency.

Table A8 | Patients characteristics dichotomized for six-month mortality for patients with primary neurological diagnosis

Median (q1-q3)	**Total (*n* = 34)**	**Survivors (*n* = 19)**	**Non-survivors (*n* = 15)**
Age (years)	56 (41 - 72)	43 (40 - 56)	72 (60 - 77)
Sex, male, *n* (%)	28 (82)	13 (68)	15 (100)
Admission diagnosis, *n* (%)			
Traumatic brain injury	13 (38)	10 (53)	3 (20)
Cardiac arrest	10 (29)	6 (32)	4 (27)
Acute stroke	9 (26)	2 (11)	7 (47)
Meningitis	1 (2.9)	1 (5.2)	0
Status epilepticus	1 (2.9)	0	1 (6.7)
APACHE IV	93 (42 - 115)	56 (22 - 97)	110 (92 - 129)
SOFA (day of measurement)	9 (7 - 10)	9 (7 - 10)	9 (7 - 11)
Length of ICU stay (days)	11 (5.3 - 19)	11 (5.5 - 21)	8.1 (4.3 - 15)
Days on mechanical ventilation	6.4 (2.1 - 12)	10 (2.5 - 13)	5.6 (2.1 - 10)
Outcome			
Mortality at ICU discharge, *n* (%)	13 (38)	-	11 (74)
GCS at ICU discharge, n (%)*			
GCS score 4-5	1 (3)	0	1 (6.7)
GCS score 6-8	1 (3)	0	1 (6.7)
GCS score 9-12	5 (15)	5 (26)	0
GCS score 13-15	13 (38)	13 (68)	0
GOSE at 6-month, *n* (%)			

Table A8 | Patients characteristics dichotomized for six-month mortality for patients with primary neurological diagnosis (continued)

Median (q1-q3)	**Total (*n* = 34)**	**Survivors (*n* = 19)**	**Non-survivors (*n* = 15)**
Favorabel outcome,GOSE (5 - 8)	15 (44)	15 (79)	-
Unfavorable outcome,GOSE (2- 4)	4 (12)	4 (21)	-
Mortality, GOSE 1	15 (44)	19 (0)	15 (100)

*The number of missing GCS values for survivors *n* = 1. APACHE IV = acute physiology and chronic health evaluation; GCS = glasgow coma scale; GOSE = Glasgow outcome score extended; ICU = intensive care unit; SOFA = sequential organ failure assessment; q1 - q3 = interquartile range.

Table A9 | NIRS data length and quality dichotomized for six-month mortality in patients with primary neurological diagnosis. In this table the results of the unilateral hemispheric measurement period are reported, i.e. of the hemisphere with the worst cerebral autoregulation estimate (lowest LF-phase shift for an individual**).**

Median (q1 - q3)	**Total (*n* = 34)**	**Survivors (*n* = 19)**	**Non-survivors (*n* = 15)**
Bilateral measurements, *n* (%)	23 (68)	11 (58)	12 (80)
Start measurement after ICU admission (h)	24 (14 - 62)	40 (16 - 71)	22 (11 - 50)
Duration bedside recording (min)	102 (61 - 140)	94 (60 - 144)	115 (73 - 132)
Artefact free NIRS recording (min)*	78 (48 - 124)	68 (46 - 114)	89 (52 - 126)
NIRS data removed† (%)	13 (5.6 - 28)	11 (6.4 - 28)	16 (5.1 - 28)
Number of segments per patient	4 (2 - 9)	4 (2 - 8)	6 (3 - 8)

*Discrepancy between artifact free NIRS recordings and number of ten-minute TFA segments is due to the requirement of ten contiguous minutes to be selected as a data segment.
†The removed NIRS data (before data processing) as percentage of the recorded data.
ICU = intensive care unit; LF = low frequency; NIRS = near infrared spectroscopy; q1 - q3 = interquartile range.

Table A10 | Frequency analysis dichotomized for six-month mortality for patients with primary neurological diagnosis. The results of the unilateral hemispheric measurement are reported, i.e. of the hemisphere with the worst cerebral autoregulation estimate (lowest LF-phase shift for an individual).

Median (q1 - q3)	**Total (*n* = 34)**	**Survivors (*n* = 19)**	**Non-survivors (*n* = 15)**
Mean PSD – oxyHb ($\mu M^2/Hz$)			
VLF (0.02 – 0.07 Hz)	0.42 (0.15 - 0.89)	0.51 (0.15 - 0.91)	0.35 (0.13 - 0.46)
LF (0.07 – 0.2 Hz)	0.02 (0.012 - 0.05)	0.02 (0.008 - 0.05)	0.04 (0.02 - 0.05)
Mean PSD - deoxyHb ($\mu M^2/Hz$)			
VLF (0.02 – 0.07 Hz)	0.04 (0.02 - 0.06)	0.04 (0.02 - 0.06)	0.03 (0.009 - 0.05)
LF (0.07 – 0.2 Hz)	0.003 (0.001 - 0.005)	0.003 (0.001 - 0.004)	0.004 (0.002 - 0.006)
Mean PSD - ABP ($mmHg^2/Hz$)			
VLF (0.02 – 0.07 Hz)	32 (13 - 80)	31 (16 - 54)	38 (9.9 - 89)
LF (0.07 – 0.2 Hz)	3.6 (1.5 - 8.0)	3.3 (1.5 - 5.6)	4.9 (1.5 - 9.4)

ABP = arterial blood pressure; deoxyHb = deoxyhemoglobin; LF = low frequency; oxyHb = oxyhemoglobin; PSD = power spectral density; VLF = very low frequency; q1 - q3 = interquartile range.

Table A11 | Cerebral autoregulation parameters dichotomized for six-month mortality for patients with primary neurological diagnosis. The results of the unilateral hemispheric measurement are reported, i.e. of the hemisphere with the worst cerebral autoregulation estimate (lowest LF-phase shift for an individual).

Median (q1 - q3)	**Total (*n* = 34)**	**Survivors (*n* = 19)**	**Non-survivors (*n* = 15)**
Coherence			
VLF (0.02 - 0.07 Hz)	0.6 (0.45 - 0.79)	0.61 (0.49 - 0.73)	0.59 (0.40 - 0.82)
LF (0.07 - 0.2 Hz)	0.76 (0.52 - 0.88)	0.68 (0.44 - 0.83)	0.85 (0.75 - 0.90)
HF (0.2 - 0.5 Hz)	0.75 (0.63 - 0.88)	0.73 (0.57 - 0.84)	0.80 (0.70 - 0.92)
Gain			
VLF (0.02 - 0.07 Hz)	0.24 (0.17 - 0.30)	0.24 (0.17 - 0.34)	0.24 (0.19 - 0.29)
LF (0.07 - 0.2 Hz)	0.27 (0.24 - 0.33)	0.27 (0.24 - 0.33)	0.27 (0.24 - 0.31)
Phase shift (°)			
VLF (0.02 – 0.07 Hz)	34 (6 - 76)	49 (7.7 - 122)	33 (6 - 57)
LF (0.07 – 0.2 Hz)	10 (0.59 - 27)	13 (6.3 - 35)	0.83 (-2.8 - 13)
Phase shift – SD (°)			
VLF* (0.02 – 0.07 Hz)	8.4 (5.5 - 17)	7.2 (5.1 - 14)	13 (7.2 - 24)
LF† (0.07 – 0.2 Hz)	5.6 (3.2 - 13)	6.5 (3.8 - 14)	3.8 (2.9 - 7.4)
TT‡ (s)	1.3 (0.86 - 1.6)	1.4 (1.1 - 2.0)	0.95 (0.82 - 1.3)
%BF (%)	5.7 (1.5 - 22)	5.1 (0.7 - 25)	6.2 (2.9 - 15)

* The number of missing SD-VLF phase values (only one data segment was available) is for the survivors *n* = 5 and for non-survivors *n* = 3.
† The number of missing SD-LF phase values for survivors *n* = 4 and for non-survivors *n* = 3.
‡ The TT could not be defined because of predominantly blood volume oscillations for survivors *n* = 3 and for non-survivors *n* = 1.
%BF = percentage blood flow oscillations; HF = high frequency; LF = low frequency; SD = standard deviation; TT = capillary transit time; VLF = very low frequency; q1 - q3 = interquartile range.

Table A12 | Physiological variables during the bedside measurement dichotomized for six-month mortality for patients with primary neurological diagnosis. The results of the unilateral hemispheric measurement period are reported, i.e. of the hemisphere with the worst cerebral autoregulation estimate (lowest LF-phase shift for an individual).

Median (q1 - q3)	**Total (*n* = 34)**	**Survivors (*n* = 19)**	**Non-survivors (*n* = 15)**
MAP (mmHg) – segments	79 (69 - 88)	77 (72 - 85)	83 (68 - 90)
Heart rate (min^{-1})	73 (61 – 87)	67 (58 - 81)	82 (72 – 97)
$EtCO_2$ (kPa)[‡]	4 (3.7 - 4.7)	4.3 (3.9 - 4.8)	3.8 (3.4 – 4.7)
SpO_2 (%) [§]	97 (96 - 98)	97 (96 - 99)	97 (96 - 98)
Body temperature (°C) [‖]	36.8 (36.3 - 37.2)	37.1 (36.5 - 37.9)	36.7 (35.9 -36.9)
FiO_2 (%)	32 (25 - 40)	30 (25 - 37)	40 (28 - 52)
During measurement			
PaO_2 (kPa)	12.1 (10.6 - 13.3)	12.0 (10.4 - 13.3)	12.1 (11.1 - 13.8)
$PaCO_2$ (kPa)	4.9 (4.4 - 5.4)	4.9 (4.6 - 5.4)	4.9 (4.3 - 5.8)
PaO_2 / FiO_2 ratio (mmHg/%)	251 (219 - 360)	255 (236 - 360)	225 (150 - 345)
Hemoglobin (mM)	7.4 (6.3 – 8.3)	7.3 (6.3 – 8.6)	7.5 (6.2 – 8.2)

[‡] The number of missing $EtCO_2$ values are for survivors *n* = 1 and for non-survivors *n* = 1.
[§] The number of missing SpO_2 values is for survivors *n* = 1.
[‖] The number of missing body temperature values is for survivors *n* = 7 and for non-survivors *n* = 2.
$EtCO_2$ = end tidal carbon dioxide; FiO_2 = oxygen fraction; MAP = mean arterial blood pressure; $PaCO_2$= partial carbon dioxide pressure; PaO_2 = partial oxygen pressure; q1 - q3 = interquartile range; SpO_2 = peripheral oxygen saturation.

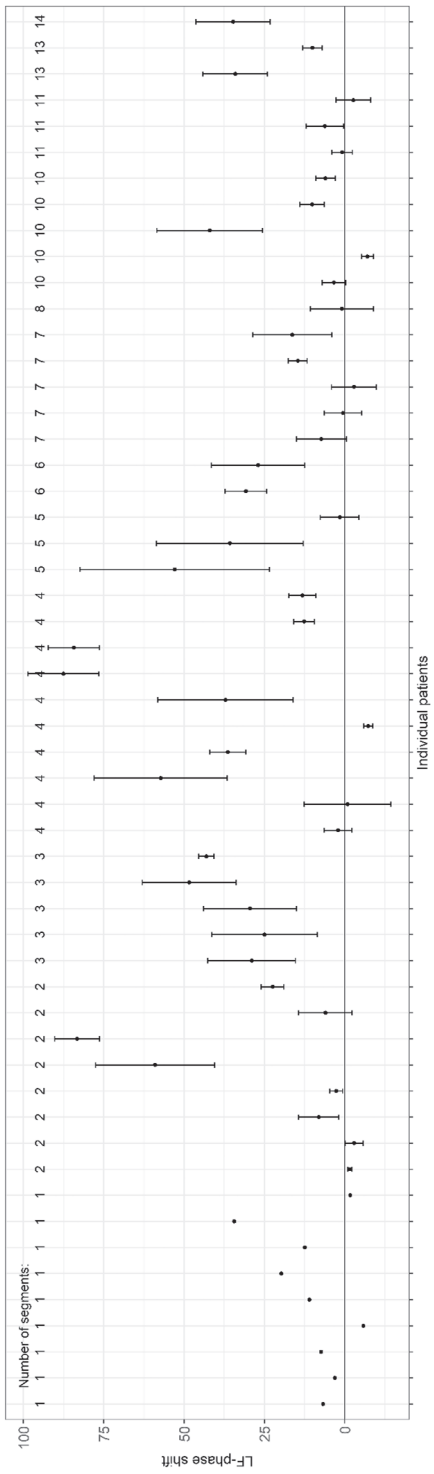

Figure A4 | Within patient variability for the low frequency phase shift (n = 54). For each patient (x-axis) the LF-phase shift and SD of the worst hemisphere (lowest LF-phase shift for an individual) (y-axis) is shown. The number of included segments is shown on top. From left to right the number of segments per patient increases, ranging from 1 until 14 segments. The within patient variability seems independent from the number of segments. Nine patients were presented by one segment and therefore no SD was available. The median SD for n = 45 patients was 6.5° (3.5 - 14) (Table A7). deoxyHb = deoxyhemoglobin; LF = low frequency ; oxyHb = oxyhemoglobin ; SD = standard deviation.

Table A13 | Multivariate logistic regression model for patients with primary neurological diagnosis (n = 34)

Independent variable	Adjusted OR (95% CI)	*p*-value
LF-phase shift (/10º)	0.27 (0.10 - 0.78)	0.015
Age (years)	1.16 (1.01 - 1.33)	0.032
APACHE IV	1.00 (0.97 - 1.04)	0.614
Measurement time after ICU admission (h)	1.51 (0.78 - 2.90)	0.218

APACHE IV = acute physiology and chronic health evaluation IV ; CI = confidence interval ; ICU= intensive care unit; LF = low frequency; OR = odds ratio.

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PART IV
LONG-TERM OUTCOME

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9

Long-Term Follow-Up of Critically Ill Traumatic Brain Injury Patients: From Intensive Care Parameters to Patient and Caregiver-Reported Outcome

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(submitted)

ABSTRACT

Traumatic brain injury (TBI) is associated with a high social and financial burden due to persisting (severe) disabilities. The consequences of TBI after Intensive Care Unit (ICU) admission are generally measured with global disability screeners such as the Glasgow Outcome Scale-Extended, which may lack precision. In order to improve outcome measurement after brain injury, a comprehensive clinical outcome assessment tool called the Minimal Dataset for Acquired Brain Injury (MDS-ABI) was recently developed. The MDS-ABI covers twelve life domains (demographics, injury characteristics, comorbidity, cognitive functioning, emotional functioning, energy, mobility, self-care, communication, participation, social support, and quality of life), as well as informal caregiver capacity and strain. In this cross-sectional study, we administered the MDS-ABI during long-term follow-up home visits to explore the relationship between dichotomized severity of TBI and long-term outcome. Our objectives were to 1) summarize demographics, clinical characteristics, and long-term outcome of formerly ICU admitted TBI patients and their informal caregivers and 2) compare differences between long-term outcomes patients with mild-moderate TBI and severe TBI based on Glasgow Coma Scale (GCS) scores at admission. Participants were former patients (n=52) of a Dutch university hospital who had been admitted between six months and five years prior to the study, as well as their informal caregivers (n=45). Hospital records were evaluated, and the MDS-ABI was administered during a home visit. On average, 3.2 years after their TBI, 62% of the patients were cognitively impaired, 62% reported elevated fatigue, and 69% experienced restrictions in ≥2 participation domains (most frequently work or education and going out). Informal caregivers generally felt competent to provide necessary care (81%), but 31% experienced a disproportionate caregiver burden. All but four patients lived at home independently, often together with their informal caregiver (81%). Although the mild-moderate TBI group and the severe TBI group had significantly different clinical trajectories, there were no persisting differences between the groups for patient or caregiver outcomes at follow-up. As a large proportion of the patients experiences long-lasting consequences beyond global disability or independent living, clinicians should implement a multi-domain outcome set such as the MDS-AB to follow up on their patients. Future research needs to identify admission predictors (other than GCS scores) that are related to (multi-domain, multi-perspective) unfavorable outcome to which clinical decision-making in ICU departments can be adjusted.

INTRODUCTION

Traumatic brain injury (TBI) is associated with a high social and financial burden due to persisting and often severe disabilities in young and older people (1). In case of severe TBI or multi-trauma, patients are admitted to the Intensive Care Unit (ICU) (2), where their level of consciousness is commonly assessed using the Glasgow Coma Scale (GCS). The GCS is one of the most commonly used indices for primary injury severity (3) and therefore is an important determinant for prognostication and clinical course (4). After the acute phase, the short-term functional outcome of TBI is frequently assessed using ordinal classification systems of global neurological disability (5) such as the Glasgow Outcome Scale – Extended (GOSE) (6) or Disability Rating Scale (DRS)(7). Due to their screening-like set-up, these instruments seem straightforward to apply but may lack precision (8), especially when total scores are dichotomized into favorable versus unfavorable for group-level evaluations. Several studies investigated overall TBI outcome with instruments other than disability screeners (9–13), such as measures of post-concussion symptoms or quality of life, or measures aimed at single-domain outcomes, such as cognitive functioning or return to work. However, none of these studies comprehensively evaluated long-term, multi-domain outcomes.

To improve the accuracy of clinical outcome assessment after TBI, it has been recommended to use standardized, comprehensive measurement instruments (14,15). These instruments can eventually assess treatment effectiveness or be implemented in outcome prediction models. Therefore, in 2019, we developed a minimal dataset for standardized, multi-domain outcome measurement for all types of acquired brain injury (MDS-ABI) (16). The MDS-ABI contains clinician/researcher-, patient- and proxy-reported measurement instruments on twelve outcome domains (demographics, injury characteristics, comorbidity, cognitive functioning, emotional functioning, energy, mobility, self-care, communication, participation, social support, and quality of life), as well as instruments for measuring outcomes for the informal caregiver of a person with TBI, such as caregiver capacity and strain. The MDS-ABI was considered relevant in measuring the outcomes of ABI along the full spectrum of life domains by clinicians and people with brain injury (17) and can therefore be considered a feasible and comprehensive tool to measure long-term outcome after brain injury.

As the MDS-ABI has never been applied to an ICU TBI population, this cross-sectional single-center study aimed to explore the long-term outcome of a TBI ICU population using the MDS-ABI. The objectives of our study were (1) to summarize demographics, clinical characteristics, and long-term outcome

of TBI patients and their informal caregivers and (2) to compare long-term outcomes between patients with mild-moderate TBI and severe TBI based on GCS. Since lower GCS scores are associated with unfavorable global outcomes of TBI (18,19), we hypothesize that patients with lower GCS admission scores have lower long-term outcome levels in the MDS-ABI domains (e.g., independent living, cognitive functioning, and societal participation). We also expect that patients with lower GCS scores at admission have different care trajectories (e.g., more often receive intracranial pressure monitoring (ICP) and intubation), and are less likely to be discharged home from the hospital.

MATERIALS AND METHODS

Design

The current study is a cross-sectional study investigating the long-term consequences of TBI in former ICU patients and their informal caregivers. The study is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (20) (Table S1 of the Supplemental Data). In addition, this study was approved by the local Medical Ethical Committee (azM/UM) (reference number 2020-1598).

Participants

TBI patients were eligible for participation when they had been admitted to the ICU of the MUMC+ -an academic teaching hospital and neurosurgical referral center - between six months and five years prior to the screening date. Eligible participants were identified based on the Acute Physiology And Chronic Health Evaluation IV (APACHE IV) score (21) in their Electronic Patient Record (EPR). After filtering for APACHE IV diagnostic categories reflecting head injury (22) (Table S3 of the Supplemental Data), the resulting EPRs were screened for the presence of TBI. TBI was defined as a confirmed diagnosis of TBI reported in the EPR by the treating physician. Participants (both TBI patients and their informal caregivers) had to be alive, at least 18 years old at the time of screening, willing and able to give consent, have sufficient proficiency in the Dutch or English language based on the judgment of the researchers, and living in the Netherlands or within a 200 km range from the hospital. Patients diagnosed with neurodegenerative diseases such as Alzheimer's and/or Parkinson's disease (based on EPRs and eligibility screening) were excluded from the current study. Informal caregivers were people close to the patient, such as a partner or other relative, friend, or neighbor. Due to the explorative nature of this study, we did not perform a sample size calculation. However, we intended to include as many patients and caregivers as available within the five years period.

Data collection

Potential participants were identified by a medical research assistant (BD) who screened the EPRs. A member of the medical ICU team phoned the eligible patients and requested permission to be contacted for study participation. Upon consenting, their contact details were disclosed to the executive research assistant (JK), after which the candidates were further informed about the study. When they agreed to participate, a home visit was scheduled with the participant, during which the informed consent form was signed, and all instruments were administered once by JK. Furthermore, medical data collected during the ICU admission were drawn from their medical records by BD and JT. If applicable, informal caregivers provided separate informed consent. They completed the questionnaires pertaining to caregiver capacity and caregiver burden in a separate room from the patient or on their occasion, after which they returned the forms to the research institute via mail.

Injury and clinical characteristics

Clinical data, which were collected as part of regular patient care, were extracted from the EPRs and entered manually into an electronic case report form (CASTOR EDC (23)). Specific data included age at ICU admission, TBI etiology, primary brain injury severity based on the GCS, defined as the highest GCS pre-ICU admission (i.e., at the trauma scene or after resuscitation in the emergency room), other brain injury severity characteristics, neurosurgical interventions, ICP measurement, and duration of ICU and hospital stay. A detailed description of all medical data included in this study is available in Table S2 (Supplemental Data).

Long-term outcomes

Long-term outcomes were measured during the home visit with the MDS-ABI (16,17). The MDS-ABI is divided into four parts. Part A was completed by the researcher in consultation with the patient and consists of previous injury information (date and type of previous brain injuries), information on the performance of activities of daily living, communication abilities, and a cognitive screening test. Part B was completed by the patient and consisted of demographic and patient-reported questionnaires. Part C contained proxy-reported questions about the patient and was completed by an informal caregiver. Part D is also completed by the informal caregiver of the patient and contains self-reported questionnaires on caregiver characteristics, perceived caregiver capacity, and caregiver burden. All domains and the included measurement instruments that are part of the MDS-ABI, including

cut-off values, are specified in Table 1. Detailed information about the content and background of the MDS-ABI were outlined in previous studies (16,17,24).

Table 1 | Domains and measurement instruments in the MDS-ABI.

Domain	Operationalization	Cut-off for impairment	ICF level [43]
Part A: Researcher reported			
Injury characteristics	Date of most recent brain injury Type of most recent brain injury Date of previous brain injuries Type of previous brain injuries Duration of hospital stay Discharge destination		Body structures & functions
Cognitive functioning	MoCA	< 26	Body structures & functions
Communication	Screening question		Body structures & functions
Comorbidity Screening question			Body structures & functions
Functional independence	Barthel Index		Activities & participation
Part B: Patient-reported			
Demographic characteristics	Age Gender Education Living situation		Personal factors
Emotional functioning	HADS Anxiety Depression	≥ 8 ≥ 8	Body structures & functions
Energy and fatigue	FSS	≥ 4	Body structures & functions
Societal participation	USER-P Frequency Restrictions Participation		Activities & participation
Social support	Screening question		Environmental factors

Table 1 | Domains and measurement instruments in the MDS-ABI. (continued)

Domain	Operationalization	Cut-off for impairment	ICF level [43]
Part C: Proxy-reported (informal caregiver)			
Demographic characteristics	Age Gender Living situation		Personal factors
Emotional functioning	NPI-Q		Body structures & functions
Fatigue	Screening question		Body structures & functions
Social support	Screening question		Environmental factors
Societal participation	Screening questions		Activities & participation
Part D: informal caregiver			
Demographic data of caregiver	Age Gender Relation to person with ABI Living situation		Environmental factors
Caregiver sense of competence	Screening question		Environmental factors
Caregiver burden	CSI	≥7	Environmental factors

Note: ICF, International Classification of Functioning, Disability and Health; MoCA, Montreal Cognitive Assessment; HADS, Hospital Anxiety and Depression Scale; FSS = Fatigue Severity Scale; USER-P; Utrecht Scale for Evaluation of Rehabilitation – Participation; NPI-Q, Neuropsychiatric Inventory – Questionnaire; CSI, Caregiver Strain Index.

Statistical analysis

We explored our main aim using descriptive analyses to summarize the demographic and injury-related characteristics of the sample and assess their long-term functioning. First, continuous variables were reported as Means (SD) or medians (IQR) depending on the normality of the distributions based on Shapiro-Wilk tests and the inspection of histograms. Continuous variables were reported as frequencies and percentages. In line with our second objective, we divided patients into mild (GCS 13-15), moderate (GCS 9-12), and severe (GCS 3-8) (4,25,26). Mild and moderate groups were merged to enable a more balanced comparison between groups (mmTBI, *n*=23; severe TBI, *n*=29). We used χ^2 tests or Fisher's exact tests to analyse group differences in categorical outcomes in the case of one or more cells with an expected count of <5. Independent t-tests or Mann-Whitney U tests for non-normally distributed variables were used for continuous outcomes. In case of missing data, we reported the number of data points available for each variable of interest. A selection bias analysis was performed to compare the basic characteristics of included patients and surviving, excluded patients. The analyses were performed using IBM SPSS version 24.0 (27) and R-statistics (version 4.1.2; R-Core Team) (28). Alpha was set at 0.05.

RESULTS

Sample characteristics

In total, 163 patients with TBI were admitted to the ICU between January 2016 and April 2021 (Figure 1). A total of 65 (40%) patients died, of whom 54 patients died during ICU admission. A total of 32 (20%) patients fulfilled the exclusion criteria or could not be reached, leading to the inclusion of 52 (32%) patients and 45 informal caregivers. Most included patients were classified as sTBI (n=29, 56%).

Demographic and injury-related characteristics of patients are presented in Table 2. The mean age at ICU admission was 45 years (SD=17). Most patients were male (60%). The most frequently reported TBI etiologies were cycling accident (33%) or fall from a height (>2 m) (21%). Ten percent of the patients had sustained a previous brain injury. There were no significant differences between the mmTBI and sTBI groups regarding demographics or injury-related characteristics.

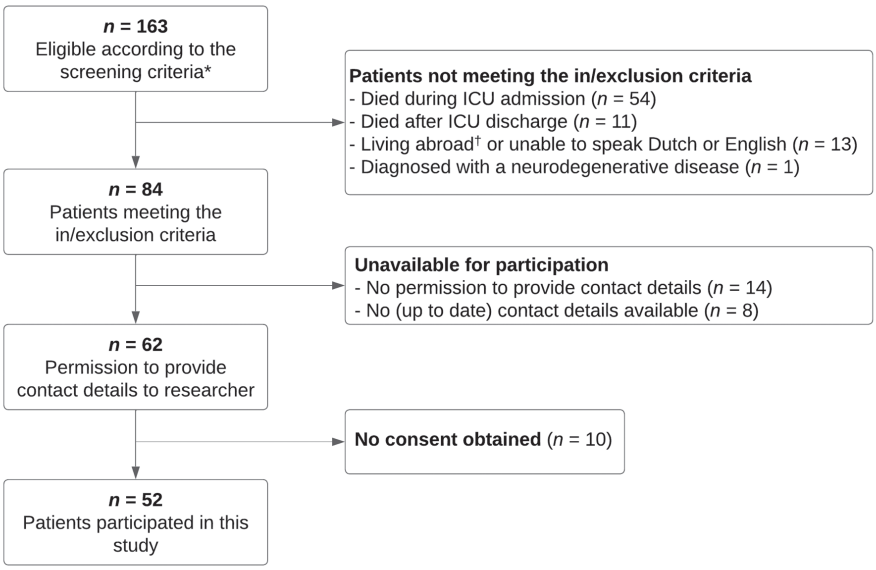

Figure 1 | Flow chart of patient inclusion.

Note: *Screening criteria: TBI, adult, admitted to the ICU between January 2016 and April 2021; †Abroad is defined as not living in The Netherlands and a maximum distance of 200 kilometers around Maastricht; ICU, intensive care unit.

Clinical characteristics

Clinical care and course characteristics are displayed in Table 3. Thirty-five (67%) patients received ICP monitoring, of which most were classified as sTBI (n=26, 90%). mmTBI patients had a shorter ICU stay (median=5 days (IQR=2-14)) than sTBI patients (median=11 days (IQR=5.5-18)), $p<0.05$ and, consequently, a shorter hospital stay (median=12 days (IQR=6.5-22) vs. 28 days (IQR=13-36)). Moreover, GCS at ICU discharge was higher for the mmTBI group (median=15 (IQR =14-15)) than the sTBI group (median=13 (IQR = 11-15)), $p<0.05$. Patients with mmTBI were discharged home directly more frequently (n=15, 68%) than patients with sTBI (n=8, 28%). There were no differences between groups for the remaining clinical characteristics.

Table 2 | Patient characteristics

		Total (*n* = 52)		Mild/moderate patients (*n* = 23)		Severe TBI patients (*n* = 29)	
Variable	***n***	n % / M (SD) / Med (range)	*n*	n % / M (SD) / Med (range)	*n*	n % / M (SD) / Med (range)	*p*
Demographic characteristics							
Age in years at inclusion	52	47.75 (16.9)	23	52.0 (18.2)	29	44.4 (15.3)	.259
Age in years at ICU admission	52	44.56 (17.2)	23	49.0 (18.8)	29	41.0 (15.1)	.103
Gender (male)	52	31 (59.6%)	23	14 (60.9%)	29	17 (58.6%)	.870
Years of education	48	15.5 (4.1)	21	15.3 (4.7)	29	15.0 (3.6)	.177
Injury characteristics							
Etiology	52	7 (13%)	23	4 (17%)	29	3 (10%)	.747
Fall < 2m		11 (21%)		3 (13%)		8 (28%)	
Fall > 2 m		7 (13%)		2 (8.7%)		5 (17%)	
Car accident		17 (33%)		9 (39%)		8 (28%)	
Bicycle accident		5 (9.6%)		2 (8.7%)		3 (10%)	
Scooter or motor		3 (5.8%)		2 (8.7%)		1 (3.4%)	
Pedestrian hit by a car		2 (3.8%)		1 (4.3%)		1 (3.4%)	
Other							
Previous brain injury (yes)	50	5 (10%)	21	4 (19%)	29	1 (3.4%)	.148
Comorbidity (screening question, yes)	51	17 (33.3%)	22	7 (31.8%)	29	10 (34.5%)	.842

Note. ICU, intensive care unit; SD, standard deviation; TBI, traumatic brain injury; Med, median

Table 3 | Medical characteristics (ICU)

		Total (*n* = 52)		Mild and Moderate TBI (*n* = 23)		Severe TBI (*n* = 29)	
Variable	***n***	n % / M (SD) / Med (range)	n	n % / M (SD) / Med (range)	n	n % / M (SD) / Med (range)	*p*
Initial assessment							
Pupil reactivity	52	46 (88%)	23	22 (96%)	29	24 (83%)	.431
Both reactive		3 (5.8%)		1 (4.3%)		2 (6.7%)	
One reactive		3 (5.8%)		0 (0%)		3 (10%)	
None							
GCS score total (initial)	52	8 (2-12)	23	12 (10 – 14)	29	6 (5-7)	**<0.001**
GCS score (initial)*	52	8 (15%)	23	8 (35%)	17	0 (0%)	**<0.001**
Mild TBI		15 (29%)		15 (65%)		0 (0%)	
Moderate TBI		29 (56%)		0 (0%)		29 (100%)	
Severe TBI							
GCS motor score	52	5 (3-5)	21	6 (5-6)	27	4 (2-4)	**<0.001**
Marshall CT-score	52	3 (5.7%)	23	2 (8.7%)	29	1 (3.4%)	.159
I Diffuse injury		33 (63%)		14 (61%)		19 (66%)	
II Diffuse injury		2 (3.8%)		1 (4.3%)		1 (3.4%)	
III Diffuse injury		2 (3.8%)		1 (4.3%)		1 (3.4%)	
IV Diffuse injury		5 (9.6%)		0 (0%)		5 (17%)	
V Evacuated mass lesion		7 (7.7%)		5 (22%)		2 (6.9%)	
VI non-evacuated mass lesion							
Multitrauma†	52	27 (52%)	23	10 (44%)	29	17 (59%)	.420
Intoxication, yes	35	11 (31%)	17	4 (24%)	18	7 (39%)	.539

Table 3 | Medical characteristics (ICU) (continued)

		Total (*n* = 52)		Mild and Moderate TBI (*n* = 23)		Severe TBI (*n* = 29)	
ICU stay							
Primary surgery	52		23		29		.161
Craniotomy		2		0		2 (6.9)	
Craniectomy		3		0		3 (10.3)	
Secondary surgery	52		23		29		1.00
Craniotomy		0		0		0	
Craniectomy		1		1		0	
ICP monitoring (yes)	52	35 (67.3%)	23	9 (39.1%)	26	26 (100%)	<0.001
Max ICP value during the first week, mmHg	35	20 (10)	9	26 (9.6)	26	18 (10)	.069
Delay injury – ICU admission, hr	52	2.5 (2-3)	23	3 (2-3)	29	2 (2-3)	.855
Duration of ICU stay, days	50	9 (3-17)	23	5 (2-14)	27	11 (5.5-18)	<0.05
Intubation, yes	52	45 (87%)	23	16 (70%)	29	29 (100%)	<0.001
Duration intubation, days	42	6 (3-14)	15	3 (1-15)	27	8 (3.5-13)	.197
Hospital stay, days	42	20 (9.2-35)	20	12 (6.5-22)	22	28 (13-36)	<0.05
GCS ICU discharge	52	15 (12-15)	23	15 (14-15)	29	13 (11-15)	<0.05
Discharge destination	51		22		29		.004
Home		23 (45.1%)		15 (68.2%)		8 (27.6%)	
Rehabilitation centre		26 (51%)		6 (27.3%)		20 (69.0%)	
Geriatric rehabilitation centre		1 (2%)		1 (4.5%)		-	
Nursing home		1 (2%)		-		1 (3.4%)	

Note: ICU, intensive care unit; GCS, Glasgow coma scale; ICP, intracranial pressure; Marshall CT-score, Marshall computer tomography score; TBI, traumatic brain injury; *The highest GCS score assessed before ICU admission. Mild (GCS 14-15), moderate (GCS 9-14), severe (GCS (3-8) † Multi-trauma was defined as an injury that requires hospital admission within its right (49).

Long-term outcomes

Patients

The long-term outcome of the patients is presented in Table 4. The mean time between TBI and the administration of the MDS-ABI was 3.2 years (SD=1.5). All but four patients lived independently (92%). Most patients lived together with others (37% with a partner, 33% with their partner and children, 4% with children, and 15% with others). A third of the patients (33%) was affected by a comorbid health condition.

Concerning cognitive functioning, the majority (62%) of the patients scored below the cut-off on the Montreal Cognitive Assessment (MoCA). Scores on the Barthel Index were high (median=20/20). Nine patients (17%) scored above the cut-off on the anxiety subscale of the Hospital Anxiety and Depression Scale (HADS), and six patients (12%) scored above the cut-off level on the HADS depression subscale. On average, caregivers reported that their relatives with TBI showed psychiatric problems in two out of twelve domains of the Neuropsychiatric Inventory – Questionnaire (NPI-Q) (IQR=2-10). Most patients (62%) reported elevated fatigue levels on the Fatigue Severity Scale (FSS) (proxy-reported fatigue: 71%). Regarding communication, 37% of the patients had problems expressing themselves, and 17% had difficulties understanding others (verbally or non-verbally). Regarding societal participation, 46% of the patients experienced restrictions in ≥2 out of 11 participation domains. Patients most frequently reported restrictions in the domains of household duties (39%) and mobility (39%). Caregivers estimated that their relatives experienced restrictions in daily life situations in 16 instances (37%) and social restrictions in 15 instances (36%). Most patients (92%) experienced sufficient support from their surroundings (proxy-reported support: 82%).

There were no differences regarding long-term outcome between the mmTBI and sTBI group, except for the total severity of problems on the NPI-Q for psychiatric symptoms, which was higher for the mmTBI group (Median=10 (IQR=3.5-12.5)) compared to the sTBI group (Median=3 (IQR=1-4.8), p=.010)).

Caregivers

In Table 5, the characteristics and outcomes of caregivers of patients with TBI are summarized. On average, caregivers were 52.4 years old (SD=13.0), less often male (31%), and most often the spouse of the patient (66%). Most primary caregivers cohabited with the patient (81%). Regarding caregiver duties, most informal caregivers (81%) felt competent to perform tasks associated with caring for the patient. However, 31% scored above the cut-off level on the caregiver strain index (CSI). There were no differences in characteristics or outcome between caregivers of the mmTBI and the sTBI group.

Table 4 | Long-term outcome

		Total (N = 52)		Mild and Moderate TBI (n = 23)		Severe TBI (n = 29)	
Variable	**N**	**n % / M (SD) / Med (range)**	**N**	**n % / M (SD) / Med (range)**	**N**	**n % / M (SD) / Med (range)**	***p***
Self or clinician-reported							
Type of residence	52		23		29		.845
Independently		48 (92.3%)		21 (91.3%)		27 (%)	
Nursing home		1 (1.9%)		-		1 (3.4%)	
Residential psychiatric setting		1 (1.9%)		1 (4.3%)		-	
With parents		2 (3.8%)		1 (4.3%)		1 (3.4%)	
Living situation	52		23		29		.777
Alone		6 (11.5%)		3 (13.0%)		3 (5.9%)	
With partner		19 (36.5%)		10 (43.5%)		9 (47.1%)	
With partner and child(ren)		17 (32.7%)		7 (30.4%)		10 (29.4%)	
With children		2 (3.8%)		1 (4.3%)		1 (5.9%)	
With others		8 (15.4%)		2 (8.7%)		6 (11.8%)	
Living independently (yes)	52	48 (92.3%)	23	21 (91.3%)	29	27 (93.1%)	1.000
Comorbidity (screening question, yes)	51	17 (33.3%)	22	7 (31.8%)	29	10 (34.5%)	.842
Cognitive functioning (MoCA; 0-**30**)	52	25 (23-27)	23	25 (21-27)	29	25 (23.5-27.5)	.126
Proportion impaired (<26)		32 (61.5%)		16 (69.6%)		16 (55.2%)	.289
ADL independence (Barthel Index; 0-**20**)	52	20 (20-20)	23	20 (19-20)	29	20 (20-20)	.579
Emotional functioning (HADS)	52		23		29		.845
Anxiety (**0**-21)		6.4 (4.4)		6.5 (4.3)		6.3 (4.6)	1.000
Proportion impaired (≥8)		9 (17.3%)		7 (20.0%)		2 (11.8%)	.678
Depression (**0**-21)		5.1 (4.5)		5.2 (4.1)		5.0 (4.8)	1.000
Proportion impaired (≥8)		6 (11.5%)		3 (13.0%)		3 (10.3%)	
Energy and fatigue (FSS; **0**-7)	52	4.3 (1.3)	23	4.8 (1.2)	29	4.0 (1.4)	.475
Proportion impaired (≥4)		32 (61.5%)		18 (78.3%)		14 (48.3%)	.161

Table 4 | Long-term outcome (continued)

		Total (N = 52)		Mild and Moderate TBI (n = 23)		Severe TBI (n = 29)	
Communication difficulties – expressing (screening question, yes)	52	19 (36.5%)	23	11 (47.8%)	29	8 (27.6%)	.132
Communication difficulties – understanding (screening question, yes)	52	9 (17.3%)	23	6 (26.1%)	29	3 (10.3 %)	.161
Societal participation (USER-P)							
Frequency (0-**100**)	52	30.6 (13.3)	23	28.2 (13.8)	29	32.6 (12.7)	.256
Restrictions (0-**100**)	52	87.4 (57.6-87.4)	23	79.2 (66.7-100)	29	93.3 (74.3-100)	.365
Proportion with restrictions	52	36 (69.2%)	23	18 (78.3%)	29	18 (78.3%)	.170
on ≥2 domains	52		23		29		.451
Satisfaction (0-**100**)/Quality of Life		68.1 (22.6)		63.3 (19.7)		71.9 (24.3)	
Perceived social support (screening question, sufficient)	51	47 (92.2%)	23	22 (95.7%)	28	25 (89.3%)	.383
Proxy-reported							
Emotional functioning (NPI-Q)							
Total number of problems	45	2 (1-4.5)	20	2.5 (0.3-5.8)	25	2 (1-3.5)	.412
Total severity of problems	33	4 (2-10)	13	10 (3.5-12.5)	20	3 (1-4.8)	**.010**
Fatigue (screening question, yes)	45	32 (71.1%)	20	15 (75.0%)	25	17 (68.0%)	.607
Daily life restrictions (screening question, yes)	43	16 (37.2%)	19	8 (42.1%)	24	8 (33.3%)	.555
Social restrictions (screening question, yes)	42	15 (35.7%)	18	6 (33.3%)	24	9 (37.5%)	.780
Experienced support (screening question, sufficient)	45	37 (82.2%)	20	18 (90.0%)	25	19 (76.0%)	.269

Note. MoCA, Montreal Cognitive Assessment; NPI-Q, Neuropsychiatric Inventory Questionnaire. Bold scores in score ranges represent the most desirable outcome.

Table 5 | Caregiver characteristics and outcome

Variable	N	Total (N = 52)	N	Mild and Moderate TBI (n = 23)	N	Severe TBI (n = 29)	*p*
Caregiver demographic characteristics							
Age in years	45	52.4 (13.0)	28	52.5 (15.7)	17	52.4 (10.8)	.990
Male Gender	45	14 (31.3)	20	8 (40.0)	25	6 (24.0)	.249
Relationship to person with ABI	44		20		24		.482
Spouse		29 (65.9%)		14 (70.0%)		15 (62.5)	
Parent		8 (18.2%)		2 (10.2%)		6 (25.0)	
Sibling		1 (2.3%)		-		1 (4.2)	
Child		4 (9.1%)		3 (15.0%)		1 (4.2)	
Other		2 (4.5%)		1 (5.0%)		1 (4.2)	
Cohabiting with person with ABI	43	35 (81.4%)	19	15 (78.9%)	24	20 (83.34)	1.000
Caregiver outcomes							
Caregiver sense of competence (screening question, yes)	45	42 (80.8)	20	20 (100.0)	25	22 (88.0)	.242
Caregiver burden (CSI; **0**-13)	45	5 (3-7)	20	5 (3-7.8)	25	4 (2.5-7)	.603
Proportion impaired (≥7)		14 (31.1)		7 (35.0)		7 (28.0)	.614
Neuropsychiatric problems (NPI-Q, perceived burden)	34	5 (2-12)	14	10 (2.8-14.8)	20	3 (2-6.8)	.051

Note. CSI, caregiver strain index; NPI-Q,Neuropsychiatric Inventory Questionnaire. Bold scores in score ranges represent the most desirable outcome

.

DISCUSSION

This study aimed to 1) explore the characteristics and long-term outcome of former ICU patients with TBI and their informal caregivers and 2) assess differences in outcomes between two groups of estimated brain injury severity as classified by the initial GCS. Among patients who survived their TBI, we found high levels of cognitive impairment (62%), fatigue (62%), and participation restrictions (46%). Informal caregivers generally felt competent to provide necessary care (81%), even though 31% of these caregivers experienced a disproportionate caregiver burden. Despite that a third of the patients was affected by a comorbid health condition, all but four lived at home independently, often together with their informal caregiver (81%). When comparing surviving mmTBI patients with sTBI patients, we found between-group differences in clinical characteristics but not long-term outcomes.

Group-level outcomes and differences between severity groups

On a group level, our results are in accordance with previous studies on the consequences of TBI. The most apparent long-term difficulties were in the domains of cognition and fatigue, which is consistent with the literature (29,30) and may reflect the interrelatedness of cognitive impairment and fatigue after TBI (31) and their impact on daily life (32,33). Moreover, the level of societal participation (frequency, restrictions, and satisfaction) is similar to that of other patients with acquired brain injury or similar disabilities (34). We found high levels of independence in activities of daily living, and almost all patients could live at home independently, which is consistent with an earlier study on functional outcomes after moderate to severe TBI (8). Living at home independently is often associated with patient empowerment and lower societal cost (35), and could therefore be considered a favorable outcome. However, independent living of people with disabilities leads to increased hours of care for the informal caregiver, which is related to a higher caregiver burden (36). Moreover, research suggests that successful community integration extends beyond functional independence (37). Therefore, the MDS-ABI may be of added value for outcome measurement after TBI as it captured impairments, limitations, and restrictions throughout various life domains of patients and their informal caregivers, which would go unnoticed when outcomes are evaluated on the level of global functional alone.

Regarding differences between the mmTBI and sTBI group, we found that the clinical trajectory differed as a function of injury severity. The initial GCS, as measured at the trauma scene or at hospital admission, is a well-established injury severity score for outcome prognostication and an important determinant for ICP monitoring in TBI patients (38). Unsurprisingly, patients in the sTBI

group received ICP monitoring more frequently, accompanied by a higher incidence of intubation (39) and a prolonged ICU and hospital stay than patients without ICP monitoring. However, the fact that long-term outcomes did not differ between different levels of injury severity among TBI survivors contradicted our hypothesis and can have a number of explanations. Firstly, although brain injury severity is a known predictor of mortality and disability (19) and is part of frequently used prognostic models (40)(41), its actual prognostic value remains a matter of debate (8). Moreover, previous research indicated that disability is not necessarily related to how patients experience their post-TBI quality of life (42). This may partly be explained by the so-called 'disability paradox', in which patients with more severe injuries experience a higher quality of life because they feel lucky to be alive (43). Secondly, previous research found that injury characteristics (e.g., injury severity) only account for a small proportion of the variance in long-term self-reported outcomes such as participation and quality of life among TBI patients (44,45) and that neuropsychological predictors (e.g. coping style) need to be taken into account as well.

Another explanation for the lack of differences in outcome between mmTBI and sTBI patients may lie in the fact that the current study only included patients who survived the ICU admission. As a result, the patients who died at the ICU (and who probably had the most severe TBI) were left out if this comparison. Moreover, the initial GCS may not have been a reliable estimate of injury severity in our sample. Even though, in general, mild TBI does not necessitate ICU admittance (46), this study found a significant proportion of the TBI patients to be classified as mild TBI. Therefore, it is reasonable to assume that these patients initially exhibited a high level of consciousness but secondarily deteriorated or had other indications for ICU-admittance (e.g., severe facial trauma or multi-trauma monitoring), despite being conscious. This may also be reflected by the relatively high number of ICP monitoring (39%) in the mmTBI group. Moreover, as alcohol and drug intoxications are common in TBI patients, initial GCS assessment may be influenced by the sedative effects of these substances (47). Recently, Akerlund et al. proposed a novel clustering of endotypes of ICU-admitted TBI patients based on the GCS combined with systemic metabolic stress profiles (48). The authors found that a cluster of patients with moderate TBI based on GCS alone but with a deranged metabolic profile had a worse outcome than patients who would classify as severe TBI but had a normal metabolic profile. This illustrates that injury severity after TBI may need to be based on a profile of numerous clinical variables instead of GCS alone.

Strengths and limitations

This study was the first to use the MDS-ABI for measuring the long-term outcome of TBI patients once admitted to the ICU. In doing so, we provided a complete overview of the long-term consequences of TBI from different angles (objective testing, patient-reported, and caregiver-reported outcomes) throughout several life domains. As the MDS-ABI provides information on outcomes beyond the level of clinician-rated disability, it can be a valuable addition to the frequently used screening instruments for functional outcome.

There are several limitations to the current study. First, our study was restricted by its retrospective single-center design. The administration of the GOSE is not considered standard practice at the MUMC+, and scores were only sporadically available for the patients in our sample. Consequently, we could not incorporate the short-term outcomes as measured with the GOSE (typically administered after 6 months) in our study. Second, the inclusion of patients might have been affected by selection bias because we selected patients retrospectively based on APACHE-IV scores, which may not have identified all true TBI patients. In addition, ten patients who initially agreed to participate eventually declined participation because of practical reasons (e.g., being unavailable for a home visit) or disease-related reasons (e.g., a home visit turned out to be too strenuous on the patient), but selection bias analysis revealed no differences between in and excluded patients on basic demographic and injury-related variables. Nevertheless, only patients who survived their TBI could be included in this follow-up study, which has markedly influenced our estimates of long-term outcomes in this particular group and may affect the generalizability of our findings to the TBI population. Third, the results from our study may have been influenced by confounders not included in our study, such as pre-injury functioning, although the mmTBI and sTBI groups were similar on the level of demographic characteristics. Finally, no multiple testing correction was performed, and our analyses may lack statistical power to detect differences between groups, as we did not perform a sample size calculation.

Implications for future research and clinical practice

This study showed that the MDS-ABI is a feasible tool for collecting information on the long-term functioning of TBI patients admitted to the ICU, and their informal caregivers. The MDS-ABI offers insight into multi-domain outcomes and provides information on the consequences of TBI that extend beyond functional independence. Consequently, it may be a promising tool for the follow-up of formerly ICU-admitted TBI patients to enhance the timely identification of the widespread consequences of TBI, and steer individualized and specific rehabilitation strategies.

Future large-scale prospective studies should implement multi-domain outcome sets, such as the MDS-ABI, to study the long-term consequences of TBI in more depth, and evaluate the effectiveness of rehabilitation treatment. Moreover, future research needs to be aimed at the relationship between the results of established screening tools for functional outcomes and outcomes as measured with the MDS-ABI. This information, in turn, can inform clinical decision-making in ICU departments and shape treatment in subacute and chronic phases of TBI.

CONCLUSIONS

This study showed that TBI patients report cognitive, emotional, and communicative problems, experience fatigue, and are limited in social participation even years after being admitted to the ICU. Despite these difficulties, almost all patients live at home independently during follow-up. Informal caregivers of these patients generally feel competent to provide the necessary care, although levels of care-related burden are high. To comprehensively monitor the consequences of TBI that extend beyond global disability or level of independence, it seems of particular interest for clinicians to implement a multi-domain outcome set, such as the MDS-ABI, to follow up on their patients and adjust their treatments accordingly.

Author statements

Anne-Fleur Domensino: conceptualization, methodology, formal analysis, investigation, writing – original draft, writing - review & editing, project administration. Jeanette Tas: conceptualization, methodology, formal analysis, investigation, writing – original draft, writing - review & editing, project administration. Babette Donners: investigation, writing - review & editing, project administration. Joyce Kooyman: investigation, writing - review & editing, project administration. Iwan C.C. van der Horst: supervision, writing - review & editing. Roel Haeren: writing - review & editing, supervision. Marcel J.H. Aries: methodology, writing - review & editing, supervision. Caroline van Heugten: methodology, writing - review & editing, supervision, project administration.

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Transparency, rigor and reproducibility summary

This study was not formally registered because the study was registered internally after ethical approval, and there was no incentive to register the study externally. The analysis plan was not formally pre-registered, but the lead author certifies that the analysis plan was pre-specified. A sample size of 100 subjects was planned based on the availability of 300 prior TBI ICU admissions. The actual sample size was 52 subjects (because of an actual number of 163

TBI ICU admissions). Data collection was performed by investigators blinded to relevant participant characteristics such as pre-defined group membership. Data analyses were performed by investigators who were aware of the relevant characteristics of the participants. Data were labelled using codes that were not linked to participant identifying information. Data were acquired between March 2021 and July 2021. Data were analyzed using SPSS Statistics and R-statistics. Clinical data and long-term outcome data resulting from the MDS-ABI were analyzed separately. The time required for data acquisition was 5 months. The time required for preprocessing and analysis was 5 months. All equipment and software used to perform acquisition and analysis are widely available from IBM and www.r-project.org. The key inclusion criteria (e.g., primary diagnosis or prognostic factor) are established standards in the field. The primary clinical outcome measure is an emerging standard in the field. Information on the validity of the instruments included in the MDS-ABI is available here: 10.1186/s12955-020-01286-3. The statistical tests used were based on the assumptions of normality. Implications of possible violations of these assumptions include nonparametric alternatives that had to be used. The sample sizes and degrees of freedom reflect the number of independent measurements (i.e., the number of individual participants). The number of participants included in each analysis is displayed in Table 2-5. Due to the explorative nature of this study, no correction for multiple testing was used. External validation studies are ongoing. De-identified data from this study are not available in a public archive. De-identified data from this study will be made available (as allowable according to institutional IRB standards) by emailing the corresponding author as of 01-01-2023. There is no analytic code associated with this study. The authors agree to provide the full content of the manuscript on request by contacting the corresponding author.

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SUPPLEMENTARY MATERIAL

Table S1 | STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2/3
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	5-6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7

Table S1 | STROBE Statement—checklist of items that should be included in reports of observational studies (continued)

	Item No	Recommendation	Page No
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	8
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy	n/a
		(*e*) Describe any sensitivity analyses	n/a
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	9
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9
		(b) Indicate number of participants with missing data for each variable of interest	9-11
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	n/a
Outcome data	15*	Cohort study—Report numbers of outcome events or summary measures over time	n/a
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	n/a
		Cross-sectional study—Report numbers of outcome events or summary measures	9-11

Table S1 | STROBE Statement—checklist of items that should be included in reports of observational studies (continued)

	Item No	Recommendation	Page No
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(b) Report category boundaries when continuous variables were categorized	9-11
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	n/a
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	14
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	n/a

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Table S2 | Medical variables collected from the electronic patient records.

Group	Variables
General patient characteristics	Age at ICU admission,
Admission brain injury severity by the GCS	Highest GCS pre-ICU admission (i.e. at the trauma scene or after stabilization on the emergency room)
Other injury severity characteristics	Etiology, pupil reactivity, Marshall computerized tomography (CT)-score, multi-trauma presence
ICU stay characteristics	Primary or secondary craniectomy or craniotomy, intubation, maximum intracranial pressure (ICP) (extracted from the hourly reported value in the EPR during the first week).
Duration	Estimated delay between time of injury and ICU admission, duration ICU stay, duration that the patient was intubated, duration of the patient's hospital stay.
Clinical outcome	GCS at ICU discharge
Clinical outcome CRASH score (corticosteroid randomization after significant head injury)	The CRASH score is an admission clinical outcome prediction score that is validated for a GCS ≤ 14. The CRASH score is computed from the variables: Included patient characteristics are: country, age, GCS, pupil reactivity, major extra cranial injury, CT-scan (presence of petechial hemorrhage, Obliteration of the third ventricle or basal cisterns, Subarachnoid bleeding, midline shift, Non-evacuated hematoma). Two outcome prediction scores are given for 14-day mortality and 6-months unfavorable outcome (GOS 1-3) [1] [2].
IMPACT (International Mission for Prognosis and Analysis of Clinical Trials in TBI)	The IMPACT score is an admission clinical outcome prediction score that is validated for moderate to severe TBI. Included patient characteristics in the prognostic models: Core model: age, GCS motor score, and pupillary reactivity; Core + CT model: additional Marshall CT-score and secondary insults (hypoxia, hypotension); Core + CT + laboratory model: additional haemoglobin and glucose values. Two prediction scores are given for 6-months mortality and 6-months unfavourable outcome (GOS 1-3) [3].

GCS, Glasgow coma score ; GOS, Glasgow outcome score ; ICU, intensive care unit, Y/N, yes/no.

Table S3 | APACHE IV diagnosis categories

198. Chest/face trauma	419. Chest/multiple trauma, surgery for
199. Chest/multiple trauma	424. Extremity/face trauma, surgery for
204. Extremity/face trauma	425. Extremity/multiple trauma, surgery for
205. Extremity/multiple trauma	426. Face only trauma, surgery for
206. Face only trauma	427. Face/multiple trauma, surgery for
207. Face/multiple trauma	428. Head (CNS) only trauma, surgery for
208. Head (CNS) only trauma	429. Head/abdomen trauma, surgery for
209. Head/abdomen trauma	430. Head/chest trauma, surgery for
210. Head/chest trauma	431. Head/extremity trauma, surgery for
211. Head/extremity trauma	432. Head/face trauma, surgery for
212. Head/face trauma	433. Head/multiple trauma, surgery for
213. Head/multiple trauma	434. Head/pelvis trauma, surgery for
214. Head/pelvis trauma	435. Head/spinal trauma, surgery for
215. Head/spinal trauma	437. Pelvis/face trauma, surgery for
217. Pelvis/face trauma	443. Spinal/face trauma, surgery for
219. Pelvis/multiple trauma	444. Spinal/multiple trauma, surgery for
223. Spinal/face trauma	
224. Spinal/multiple trauma	
225. Trauma medical, other	
418. Chest/face trauma, surgery for	

The APACHE diagnosis from the EPR database were extracted to define patients with traumatic brain injury [4]. APACHE = Acute Physiology And Chronic Health Evaluation ; EPR = electronic patient records

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2 "CRASH Head Injury Prognostic Models: web based calculator." http://www.crash.lshtm.ac.uk/Risk calculator/index.html (accessed Jan. 01, 2022).

3 A. I. R. Maas *et al.*, "IMPACT Recommendations for Improving the Design and Analysis of Clinical Trials in Moderate to Severe Traumatic Brain Injury," *Neurotherapeutics*, vol. 7, no. 1, pp. 127–134, 2010, doi: 10.1016/j.nurt.2009.10.020.

4 Stichting NICE, "Stichting NICE Datadictionary," 2022. https://stichting-nice.nl/dd/#Data Dictionary-full-en.pdf&pdf.

10

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Neuromonitoring is available for a selection of the neurocritical care patients. In this thesis we focused on research towards 'precision' medicine. Examples of precision medicine are the integration of cerebral multimodality monitoring (MMM) signals, individualized treatment targets using cerebral autoregulation (CA) monitoring information, and a refined outcome assessment. In this thesis, we investigated these aspects in neurocritical ill, mainly traumatic brain injury (TBI) patients admitted to the intensive care unit (ICU). A schematic representation of the link between the chapters is presented in **Figure 1**. First, the main findings of the individual studies are summarized. After that, we put neuromonitoring in a broader perspective by discussing general hallmarks that determine the feasibility of neuromonitoring in clinical studies and by discussing time- versus frequency analysis for CA monitoring. Furthermore, we discuss different perspectives for CA-assessment. Finally, we outline the future perspectives of CA-guided perfusion therapy, CA monitoring using near-infrared spectroscopy, and outcome assessment.

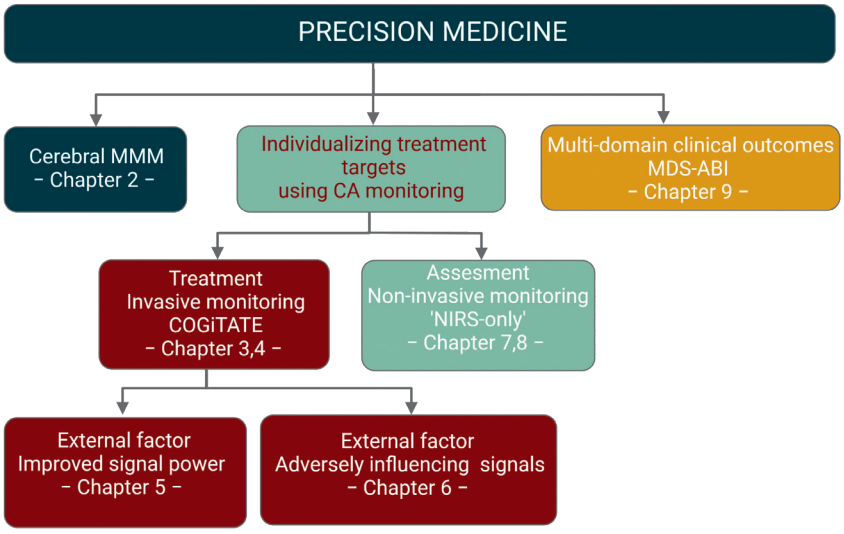

Figure 1 | Aspects of precision medicine addressed in this thesis. The figure is a simplified schematic representation of the link between the chapters. In individual chapters multiple aspects of precision medicine are addressed. CA, cerebral autoregulation; MDS-ABI, Minimal Dataset for Acquired Brain Injury; MMM, multimodality monitoring; near-infrared spectroscopy. Created with BioRender.com

10.1 SUMMARY OF THE INDIVIDUAL CHAPTERS

In **Chapter 2**, we present an overview of MMM studies by studying the application of continuous or daily updated monitoring modalities in critically ill acute brain injury patients. First, we systematically searched adult MMM studies between 2015 - 2022, as Le Roux et al. provided five year's projections regarding MMM in 2014 [1]. Then, we summarized the monitoring setting, study setting, clinical characteristics and clinical outcome and reported our observations. First, we found that MMM was mainly applied in TBI patients and that multimodality in most cases (52%) implicated a bimodal application. Second, most studies had a small sample size and an observational design. Third, the intervention studies used a wide variety of 20 different interventions in a limited number of intervention studies (44 studies). Based on these observations, we concluded that MMM studies are heterogenous in study design and setting which hampers conclusions about patient benefit. Nevertheless, the MMM-guided intervention studies showed in seven out of nine studies an improved clinical outcome which strengthens the belief in this application.

In **Chapters 3-4**, we studied in a multi-center randomized controlled trial the feasibility and safety of CA-guided perfusion therapy by targeting the 'optimal' cerebral perfusion pressure (CPPopt) in 60 patients with TBI and intracranial pressure (ICP) monitoring. CPPopt is the CPP value with the best-preserved individual CA-status. We randomized 28 patients to the control group (CPP 60-70 mmHg, standard treatment) and 32 patients to the intervention group (targeting CPPopt). In the intervention group, CPP was 46.5% (1st – 3rd quartile, 41.2 – 58) of the time concordant (± 5 mmHg) with the CPP target value. Compared to the estimated percentage of 36% from retrospective data, there was a significantly increased percentage of time with a CPP concordant with the CPP target (p<0.001). In addition, the intracranial hypertension therapy intensity level (TIL) scores between both groups were similar without differences in (serious) adverse events or organ dysfunction parameters. Therefore, targeting a six-times daily updated CPPopt value is feasible and safe. This encourages a prospective intervention trial powered by clinical outcomes.

In **Chapters 5-6**, we studied external factors influencing monitoring signals in patients with TBI and ICP monitoring. Sufficient slow arterial blood pressure (ABP) oscillations are required for reliable CA-estimations. In **Chapter 5**, we applied an innovative – adapted from an animal model - methodology to induce slow ABP oscillations in 10 patients. For 30 minutes, we applied a repeated (1/min) ventilator sigh to generate positive end-expiratory pressure (PEEP)

oscillations that induced slow ABP waves. After that, we studied the effect on the CA measure, the pressure reactivity index (PRx). Between the baseline and induced PRx period, the PRx-standard deviation (SD) decreased from the PRx period of 0.25 (1st – 3rd quartile, 0.22 – 0.30) to the induced PRx period of 0.14 (1st – 3rd quartile, 0.09 – 0.17) (p = 0.006) without other clinically relevant physiological changes. A reduced PRx variability might improve CA-guided perfusion management by reducing the time to find the 'optimal' CPP in individual patients. Larger studies with prolonged periods of PEEP-induced oscillations are required before taking it to routine use. In **Chapter 6**, we reported about the observation of repeated in- and decreases in the ICP, ABP signals, and, consequently, the pressure reactivity index (PRx). This observation resulted from the alternating (in- and deflating) anti-decubitus bed mattress and may adversely affect the CA-estimation.

In **Chapters 7-8**, we studied a model for non-invasive CA-estimations. Previous studies investigated non-invasive transcranial Doppler (TCD) monitoring by studying the transfer function analysis (TFA) between arterial blood pressure (ABP) and cerebral blood flow velocity (CBFV) [2,3]. We studied a non-invasive near infrared spectroscopy '(NIRS)-only' model for CA-estimations by studying the relationship between high frequency (50 Hz) oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) and compared our results with TFA ABP - CBFV results. It was hypothesized that a correction was required to convert the serial microvascular oxyHb - deoxyHb system back to the parallel ABP- CBFV system. Therefore, we added a phase shift correction to exclude non-CA related (i.e. related to microvascular characteristics) phase shifts. This included the correction for blood flow/blood volume oscillations and capillary transit time (BF/BV-TT). We simulated and quantified the relationship between changes in BF/BV-TT and the effect on phase shift differences. In addition, three physiological stages were compared within 15 healthy subjects for NIRS and TCD monitoring modalities to study the dynamic CA: baseline, mild hypocapnia (cyclic deep breathing instructions) and hypercapnia (cyclic deep breathing plus inhalation of 8% CO_2). A comparison between ABP - CBFV and oxyHb – deoxyHb TFA results showed an interclass correlation coefficient for mild hypocapnia on the left side of 0.73 and the right-side 0.70 (**Chapter 7**). Note: an interclass correlation coefficient of 0.60 to 0.74 is considered as good [4].

In **Chapter 8**, we evaluated our results in a cohort study using NIRS monitoring data in 54 patients admitted to the ICU who were critically ill comatose and sedated. In addition, we improved the 'NIRS-only' model and added an automated TFA (phase shift) data segment selection methodology to increase the robustness and consistency of the TFA phase shift results. We evaluated the model results using a multivariate logistic regression model using the

phase shift in the low-frequency range (LF) as a predictor of clinical outcome after six months. A phase shift close to zero indicate an impaired CA-status, whereas high phase shifts up to 180 degrees indicates an intact CA-status. The introduced data segment selection methodology improved the robustness and consistency of the phase shift by excluding the following segments automatically: (1) segments without BF/BV-TT correction; (2) segments with negative mean phase shifts, (3) segments with low (<33%) coherent bins; (4) segments with phase shift values >180 or <180 degrees. Furthermore, we showed, in critically ill patients with a primary neurological diagnosis, an independent relationship between mortality and LF phase shift difference: (LF phase shift in survivors (13° (1st – 3rd quartile, 6.3 – 35) and non-survivors (0.83° 1st – 3rd quartile, -2.8 – 13), p = 0.0167). Although the improved model seems a promising approach to be (continuously) informed about the individual CA status without the need for ABP monitoring, future studies are required to validate our results.

Finally, in **Chapter 9,** we explored a refined clinical outcome assessment tool. In a cross-sectional study, we applied the Minimal Dataset for Acquired Brain Injury (MDS-ABI) in an ICU TBI population. On average 3.2 years after the brain injury, 52 patients were assessed and interviewed by a neuropsychologist during a home visit. According to the MDS-ABI, 62% of the former patients were cognitively impaired, 62% reported elevated fatigue, and 69% experienced restrictions in ≥2 participation domains (most frequently, work or education and going out). Caregivers generally felt competent to provide necessary care (81%), but 31% experienced a disproportionate caregiver burden. Regarding injury severity, there were no significant differences between the mild/moderate and severe TBI patients. For future research towards precision medicine, a multi-domain outcome set, such as the MDS-ABI, seems essential to evaluate the efficacy of new individualized therapies.

10.2 GENERAL DISCUSSION: The feasibility of neuro-monitoring in clinical studies

Clinical neuromonitoring studies are challenging as they include a combination of hallmarks that substantially contributes to the success of a study. This starts with a dedicated clinical care. After that, the main hallmarks are suitable devices for data collection, appropriateness of the study design, eligibility of patients for neuromonitoring studies, availability of outcome measures, and families for the consent procedure. These hallmarks must function independently and in combination with each other. Each hallmark will be discussed and are shown in **Figure 2**.

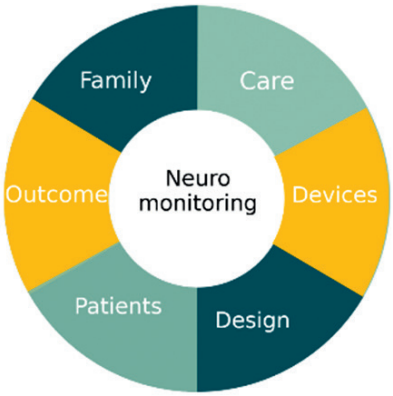

Figure 2 | Hallmarks of feasibility for neuromonitoring studies

10.2.1 Clinical care

An ICU is hectic with professionals from several disciplines caring for patients. Literature shows that patients submitted to specialized neurocritical care units have an improved outcome compared to those submitted to the general ICU [5]. Improvements in the outcome of patients were shown, e.g., by a reduction in mortality and a shorter length of stay. The improved outcome was explained by specialized care, greater adherence to protocols, use of neuromonitoring, and a more conservative approach to withdrawal of care [6]. In the current thesis (**Chapter 5-6, 8-9**), the studies were performed in a general ICU with, on average, 33 beds and approximately 1.5 patients per nurse (during the day) [7]. Moreover, no specialized neuro ICUs exist in the Netherlands. Therefore, with the increasing complexity of care, there is a lack of routine expected for treating those patients in a general ICU, which may reduce the feasibility of neuromonitoring studies in those centers.

Either centralizing neurocritical care between hospitals or introducing novel technologies might overcome this. The financially most attractive option might be to centralize neurocritical care in a selection of university hospitals. These units can afford advanced cerebral multimodality monitoring for each patient that improves neurocritical care and increases the benefits of a multidisciplinary approach. Alternatively, improved neurocritical care for a general ICU might focus on the visibility and adherence of the clinical protocol, e.g., by technological advances such as evaluating the protocol using collected neuromonitoring data. Simple calculations could inform about the care given (e.g., percentage of high/low ICP, CPP, $EtCO_2$, the amount of environmental noise).

10.2.2 Devices (data collection)

As shown in **Chapter 2**, we identified 11 neuromonitoring devices that update the data regularly during the day or continuously. However, the individual signals are complex to interpret as the measurement location may not always be known or representative of the severity of the clinical condition, and critical thresholds are not always known. For example, ICP monitoring using a microsensor is seen as a global measure of intracranial pressure, but local gradients are missed [8]. In addition, there is still no agreement about the contribution of skin perfusion and measurement location of the NIRS signals. Furthermore, artifacts due to interference with other devices might further complicate the interpretation of the signals, as we showed in **Chapter 6**. Finally, the devices are often stand-alone devices. In other words, devices are not combined with monitoring software or the electronic patient records. Therefore, only monitoring software - such as ICM+ - can collect (a selection of) signals from different monitoring devices [9]. This hampers an integrated data approach, including medication and other patient interventions, whereas an integrated data approach could be the key to precision medicine [10]. Therefore, companies should improve their technical support, combine technologies in existing devices, and provide data integration tools.

10.2.3 Study design

Three types of clinical neuromonitoring studies were performed in this thesis: a randomized controlled intervention trial (RCT) (**Chapters 3-4**), a pre-/post intervention study (**Chapter 5**), and an observational cohort study (**Chapters 7**). Observational cohort studies for CA monitoring seem the least appropriate design for CA monitoring as the number of confounders is large in the ICU (e.g., medication, medical history, comorbidities, duration of ICU stay). Therefore, a large number of patients is required to perform those studies. When monitoring is applied for research purposes only, the data collection might therefore become time-consuming. On the other hand, the outcome measure for a pre-/post intervention study is much easier, as a change in monitoring results can be used as an outcome measure (**Chapter 5**). The main advantage of an RCT is that confounders are present in both study groups. However, mainly one research question is answered during the study. Although sub-analyses are often performed, they might be underpowered. Overall, each design has advantages and disadvantages. Knowing the limitations of the design for a particular question on forehand using study protocols and structured reporting guidelines [11] reduces anticipated pitfalls or mistakes and increases the interpretation of the results.

10.2.4 Outcome measures

In this thesis, CA monitoring has been studied. However, little is known about the functioning of the CA [12]. The myogenic activity is unrelated to the central nervous system [13,14] and is mainly located in the pial arterioles causing vasoconstriction and vasodilatation by changes in Ca^{2+} concentration. What the underlying signal is that triggers the vessels to initiate the contraction, and hence depolarization of the cells are largely unknown [12]. Impairments in CA are related to a sympathetic catecholamine storm, such as the release of IL-6 that impairs the CA [15] but much is unknown. Therefore, caution should be taken by studying the causal relationship between CA monitoring and clinical outcomes. This thesis reports the clinical outcome as a secondary endpoint in two clinical neuromonitoring studies. In **Chapter 4**, we showed for the intervention group indications for an improved six-months outcome compared to the control group. In **Chapter 8**, we showed higher phase shift values (indicative of better working CA) for patients who survived after six months compared to non-survivors. However, the CA is a single marker in a forest of (patho-) physiological processes such as, diffusion impairments, mitochondrial dysfunction and spreading depolarization. Therefore, considering other neuromonitoring signals might increase the understanding of causal relations between CA and clinical outcome [16].

10.2.5 The patients

TBI is recognized as a systemic disease due to multi-trauma injuries and neurological control system impairments, or high-intensity treatments that might impair other organs such as the kidneys [10]. These other impairments could affect the signals and hence contaminate signal analysis. For example, cardiac arrhythmias effects TCD and NIRS signals and hence the transfer function analysis **(Chapter 8).** In addition, patients with an internal autonomic oscillator effecting the ABP and subsequent the ICP signal. This affected the determination of the transmission of PEEP oscillations to the ABP signal **(Chapter 5)**. Furthermore, therapies affect the signals indirectly or directly. To illustrate, Major et al. found that increasing the fraction of inspiratory oxygen (FiO_2%) on the ventilator effects the electrocorticography (ECoG) electrodes due to the initiation of redox reactions [17]. Also, the role of vasopressors, sedation, and analgesia and their effect on the CA is not fully understood. For example, phenylephrine resulted in a different sex response. In males, it impaired the CA, whereas, in females, it improved the CA functioning [18]. Again, data integration and studies on the relationship between e.g., medication and CA might increase the understanding of the CA mechanism.

10.2.6 Family

The last hallmark of the feasibility of neuromonitoring studies is the willingness to participate in studies. Since acute brain injury patients are often comatose and sedated, they are unable to consent to the study participation. Alternatively, a relative represent the patient for study participation consent. We show in **Chapter 4** a delay between ICU admission and the start of the study of about 14 hours. Therefore, so-called deferred informed consent procedures for study participation should be considered for comatose patients with acute brain injuries and the family being in shock [19]. Delaying the start of interventions or the start of the monitoring decreases the feasibility and (possible) effectiveness of neuromonitoring studies for CA assessment and related therapies.

10.3 GENERAL DISCUSSION: time versus frequency analysis for cerebral autoregulation assessment

For CA analysis is no 'golden' standard available [3]. In this thesis, we studied two CA analysis approaches in the time (**Chapters 4-6**) and frequency (**Chapters 7-8**) domain. For invasive ICP monitoring, time-domain Pearson correlation coefficient analysis (PRx) is the most commonly applied methodology. For non-invasive NIRS and TCD monitoring both time- and frequency domain analysis have been applied, but we only studied frequency domain analysis. However, in the field of neuromonitoring are different frequency ranges recommended for CA research. In general, time domain analysis uses different ranges compared to frequency domain analysis. Since we studied both domains, we discuss the main conceptual differences and clinical applicability of the different frequency ranges. In addition, **Figure 3** shows different frequency ranges for the CA monitoring combinations applied in our studies or discussed in this thesis.

10.3.1 Frequency range of interest

The frequency range of interest for PRx is 0.003 - 0.05 Hz, whereas the Cerebrovascular Research Network (CARNet) TFA recommendations advocate the frequency ranges: very-low-frequency (VLF) 0.02 - 0.05 Hz, LF 0.05 - 0.2 Hz, and high frequency (HF) 0.2 - 0.5 Hz. The overlap between both measures is only for the frequencies 0.02 - 0.05 Hz. Furthermore, Fraser et al. demonstrated that 0.017 Hz is the optimum frequency for CA monitoring assessment, and he showed that no CA information is present for frequencies >0.03 Hz [20]. Although the PRx frequency range includes this optimum frequency, the CARNet recommendations do not include this frequency [21].

CARNet recommends the ranges with limited evidence but chose commonly used ranges [22,21]. The lower threshold of 0.02 Hz was chosen because the relationship between ABP and CBFV is increasingly non-linear for lower

frequencies, whereas TFA assumes a linear relationship between in- and output signals [21,23]. Therefore, lower frequencies are less reliable for CA research using TFA. However, there are arguments against this reasoning, as the CA is acknowledged as a non-linear system. Therefore, low coherence values (<0.5) could also implicate that an intact CA is measured [3]. To reduce the effect of non-linearity in the system, induced slow ABP oscillations can be applied [24].

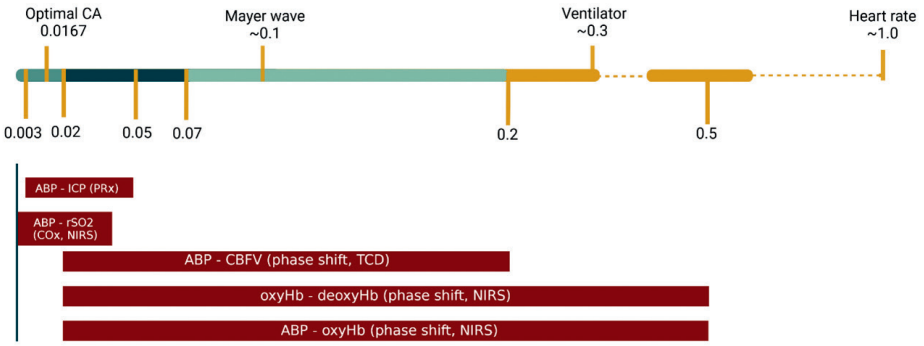

Figure 3 | Frequency ranges for different methodologies and relationships discussed in this thesis. The time domain analysis includes ABP-ICP (PRx) [25] (**Chapters 4-6**) and ABP-NIRS (COx) [26]. The frequency domain analysis includes ABP- CBFV (phase shift TCD) [2] (**Chapter 7**), oxyHb-deoxyHb (phase shift, NIRS) (**Chapter 7- 8**), and ABP - NIRS oxyHb (phase shift, NIRS) [27]. The optimal CA frequency according to Fraser et al. [28]. The units are in Hertz. ABP, arterial blood pressure; CA, cerebral autoregulation; CBFV, cerebral blood flow velocity; COx, cerebral oximeter index; ICP, intracranial pressure; NIRS, near-infrared spectroscopy; oxyHb, oxyhemoglobin; deoxyHb, deoxy-hemoglobin; PRx, pressure reactivity index; TCD, transcranial Doppler. Created with BioRender.com

10.3.2 Other physiological fluctuations

Despite the different ranges, the frequency range recommended by CARNet includes more frequencies compared to the PRx range. Therefore, these additional frequencies might be more susceptible to physiological oscillations unrelated to the CA and might affect the signals for CA assessment. Well-known oscillations are Mayer waves. Mayer waves are about 0.1 Hz sympathetic oscillations affecting the vasomotor tone and hence present in the blood pressure signal [29]. In addition, for our 'NIRS-only' model, the frequencies 0.2 - 0.5 Hz are used for the BF/BV-TT correction to account for microvascular hemodynamics (serial measurements) (**Chapters 7-8**). Since the ventilator frequency is about 0.25 - 0.35 Hz (breathing frequency between 15 – 21 cycles per minute), we observed that the correction was in a selection of the patients affected by sudden high increased coherence values for this ventilator frequency. In addition, we observed a corresponding 'sudden' increased phase shift outside the CA range (**Figure 4**). Further investigation needs to elucidate

why this resulted in an increased phase shift. In line with the interpretation of blood flow/ blood volume oscillations, it is suggestive that breathing causes relatively large changes in cerebral blood flow compared to changes in blood volume.

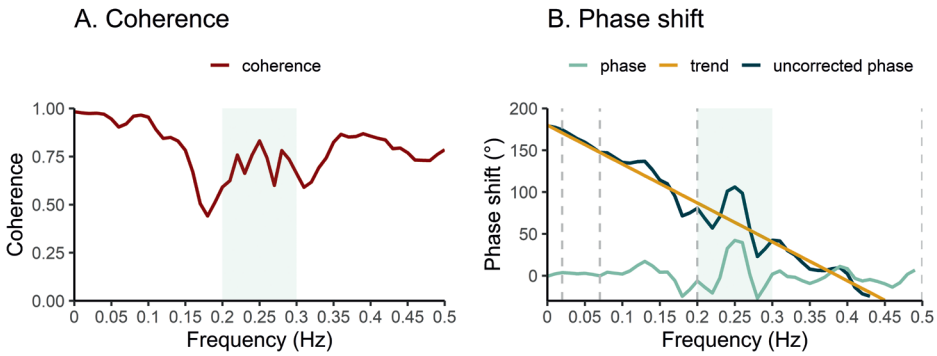

Figure 4 | Near infrared spectroscopy analyzed data segment patient example. Illustrative example (**Chapter 8**) of a coherence and phase shift difference result from a 10-min data segment. Figure **4A** show a 'sudden' increase in coherence around 0.25 Hz (shaded green area). Figure 4B show the corresponding TFA phase shift result with a clear increased phase shift around 0.25 Hz (shaded green area). The increased coherence and phase shift are expected to be the result of the breathing frequency as for this patient the ventilator rate was 15 /min (0.25 Hz).

10.3.3 Clinical applicability of time- and frequency analysis

According to Zeiler et al., time domain analysis was introduced because frequency domain analysis was too complex for the clinician to be informed about the CA [30]. PRx is a simple statistical Pearson correlation coefficient between slow changes in ABP and ICP. To be clinically useful, the PRx is integrated into a complex algorithm to compute an automated and continuously updated CPPopt value. These complexities include improving the stability and yield of CPPopt, as shown in **Chapter 3.1**. In short, over a retrospective period of 2-8 hours, 36 CPP-PRx curves (i.e. CPPopt values) fitted with different calculation window periods. The curves and CPPopt values are either included or excluded based on curve characteristics. For the final CPPopt number displayed, a weighting is applied to the last 2 hours of the included CPPopt moving average values with a higher weighting for more recent CPPopt values. For the COGiTATE study there were two additional features added for safety reasons; no CPPopt was presented in case 50 mmHg < CPPopt > 100 mmHg, and the maximum change in CPPopt was set at 10 mmHg compared to the previous CPP recommendation by the software.

Although limited people can replicate the exact algorithm components at the bedside, the final CPPopt number seems rather trusted by clinicians as in

the COGITATE study 93% of the CPPopt recommendations were accepted (**Chapter 4**). In addition, the RAUMEDIC company recently introduced a CE-marked monitoring device that includes new features such as the automated CPPopt value (but states that it should not be used clinically) [31]. This illustrates the acceptance and interest in the CPPopt value but also the need to prove clinical benefit. What could contribute is that CPPopt is an easy treatment target (i.e., blood pressure management). In contrast, the main output measure of the 'NIRS-only' model that includes CA information is a phase shift [32]. The phase shift includes oxyHb and deoxyHb signals only. Therefore, implementing the model as an 'optimization' target might complicates neurocritical care as it is less clear which intervention is needed to optimize the CA.

10.4 FUTURE PERSPECTIVES ON CEREBRAL AUTO-REGULATION MONITORING FOR THERAPY, PROG-NOSIS AND CLINICAL OUTCOME ASSESSMENT

The future perspectives of the current clinical studies involve three near-future directions for CA-guided perfusion therapy, CA-monitoring using the 'NIRS-only' model, and clinical outcome assessment using the MDS-ABI.

10.4.1 Cerebral autoregulation guided perfusion therapy

Since there is no direct therapy for restoring the myogenic function available yet, CA monitoring and optimizing CPP (i.e., optimizing brain physiology) is currently the best option. The Seattle Severe Traumatic Brain Injury Consensus Conference algorithm (SIBICC) consensus for TBI patients recognizes the clinical relevance for optimizing CPP and recommends a static CA challenge, by in- and decreasing the MAP by 10 mmHg up to 20 minutes and observing the interaction between MAP, ICP, CPP and brain tissue oxygenation signals ($PbtO_2$) [33]. In contrast, we studied continuous CA monitoring computed from spontaneous fluctuations in the COGiTATE study (**Chapter 3-4**).

Although targeting a single and six-times daily updated target is feasible and safe in patients with TBI, some challenges require attention before an outcome study can be performed.

First challenge, exploration of increasing the percentage of patients' CPP concordant with the recommended CPP target. A promising method might be a Closed loop monitoring (CLM) vasopressor system [36,37,38]. A CLM vasopressor regulation regulates the blood pressure using a controller for norepinephrine. Joosten et al. published the results of the first RCT comparing manual norepinephrine titration with CLM during middle and high-risk surgery. They showed a percentage of time of MAP concordant (± 5 mmHg) with the MAP

target of 94.2% (SD, 4.8) in the CLM group and 69.7% (SD, 12.6) in the control group. However, this technique is still not at the stage of clinical application, as regulatory, technical, and ethical challenges are present [38]. The current research results can also not be extrapolated to the ICU, and blood pressure regulation in TBI patients might be more complex compared to surgical patients as hemodynamic instability is common in TBI patients [39,40]. Nevertheless, the potential advantages of a center-independent increased adherence of CPP concordant with CPPopt, directly triggering the blood pressure and the reduced workload for the nursing staff as manual titration is labor intensive, is worthwhile exploring this approach for CPP management.

Second challenge, increasing the availability of a reliable CPP target. This can be achieved by induced ABP waves. Either via a direct MAP challenge (e.g., the CLM vasopressor system) or via PEEP-induced ABP waves **(Chapter 5)**, which is an easy-to-apply and innovative application, but in the end a direct MAP challenge might be simpler. This because in our research we did not include continuous information about the complex interplay between the heart, lungs, and brain. For example, Mascia et al. showed that hyperinflation causes an increased ICP, whereas recruitment of the lungs results in a stable ICP [34]. Continuing with the PEEP oscillations requires therefore an investigation towards the relationship between lung mechanics and ICP when the ventilator sigh is applied [34,35]. In addition, the PEEP oscillations are ideally applied to improve the yield and stability of the CPPopt calculation. We showed in that the PEEP oscillations caused a maximum MAP in- and decrease of 6.9 (1st – 3rd quartile, 4.5 - 8.8) mmHg during each oscillation without showing changes in ICP. In the COGiTATE study (**Chapter 4**), we defined a CPP concordant with the target as ± 5 mmHg. From a practical point of view, although the CPPopt yield and stability might increase, the PEEP oscillations might complicate targeting a single value manually.

Third, the CPPopt methodology needs further evaluation after the improvement of the CA assessment methodology, as induced oscillations might shorten the calculation window of the first available CPPopt, and it might increase the stability of CPPopt. As we have shown, the variance of PRx is reduced by induced ABP waves that may be extrapolated to the CPPopt calculation.

10.4.2 Cerebral autoregulation monitoring using the 'NIRS-only' model

CA-monitoring using the 'NIRS-only' model in critically ill patients might be difficult to succeed as new treatment target for critically ill adult ICU patients. **First,** because frequency domain analyzes using high-frequency (50 Hz) NIRS data was investigated by a complex model with several limitations at this stage (**Chapter 8**). **Second,** the lack of ABP data in the 'NIRS-only' model, limits the

clinical relevance to explore further. NIRS monitoring for CA-estimations for ICU research was introduced in 2007 [26]. They computed the Pearson correlation coefficient between time-domain ABP and the cerebral oxygen saturation index to compute the COx for frequencies between 0 and 0.04 Hz and validated these results with TCD recordings [26,41]. Recently, Melvin et al. compared the hemoglobin volume reactivity index (HVx) and derived the ABPopt values using a similar algorithm as for CPPopt. They showed an increased ability to compute the ABPopt compared to the COx [42]. HVx is computed as the Pearson correlation between ABP and optical density. Optical density (OD) is a measure of total hemoglobin changes. In more detail, oxyHb and deoxyHb absorb light equally at 810 nm. Therefore, the changes in concentration at 810 nm are primarily due to changes in volumes of hemoglobin below the sensor (personal communication INVOS, about INVOS 5100c, Medtronic, Minneapolis, MN, USA). The OD signals are stored in the INVOS 5100c device, which has a low sampling rate of 0.2 Hz (1/5 sec). The advantage is that signals collected with a lower sampling rate are less contaminated by 'sudden' artifacts i.e., a step increase in the signal. These step changes include several high and low-frequency oscillations that might affect the CA-estimation. In addition, the measurements are easy to perform, so it is worth continuing research with the ABPopt - HVx in critically ill patients as a potential new treatment target for adult critically ill ICU patients.

However, the 'NIRS-only' model might be helpful for the ward, as those patients do not have invasive ABP monitoring available. On the ward, non-invasive assessment of the CA-status could contribute to an early warning system for the detecting of deterioration of brain functioning [44]. Near-future research for the 'NIRS-only' model could focus on abilities to simplify the data analysis and validation of the model by e.g.: (1) investigate the effect on the phase shift results using the data segment methodology with and without raw data artifact cleaning, as it may be that the TFA data segment selection makes raw data artifact cleaning redundant; (2) perform a large validation study using the updated model that compares NIRS and TCD monitoring results in combination with different conditions (e.g. healthy population using deep breathing instructions).

10.4.3 Clinical outcome assessment

The MDS-ABI is a promising tool for a refined outcome assessment. However, the long time required to take the interviews (about 75 minutes) and the inability to answer all questions by phone are significant limitations hampering its general use. However, for specific research purposes, a refined outcome measure might be preferred. Different research purposes and outcome measures are illustrated in **Figure 5**. First, for individualized therapies, the

effectiveness of therapies might be unnoticed by rough measures such as the GOSE [45], whereas individualized therapies might reduce the severity of 'milder' symptoms. Therefore, for evaluating the effectiveness of a therapy, a refined measure might be preferred, whereas a rough measure could be used e.g. to evaluate the safety of a study. Second, for outcome prediction (e.g., during the initial assessment in the emergency department), a rough measure might be preferred as subtle differences in outcome are irrelevant in the emergency department. Overall, a near-future recommendation would be to include the multi-domain MDS-ABI for the evaluation of long-term outcome in combination with a clinical outcome (phase III) study.

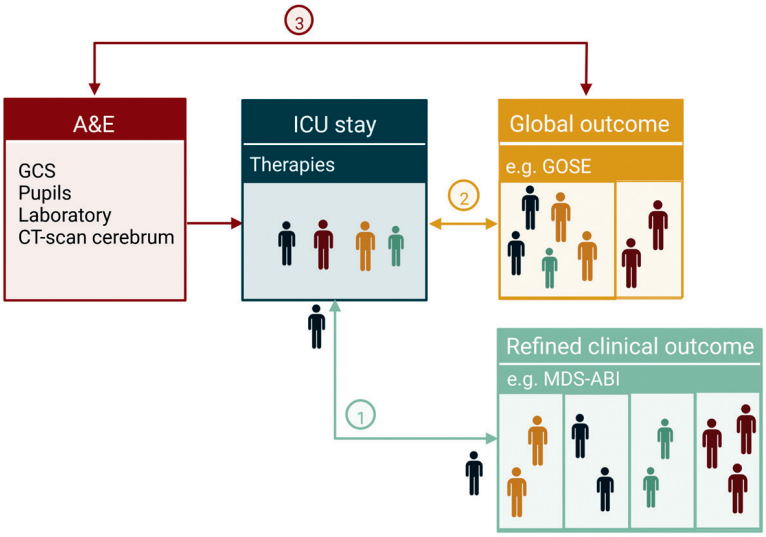

Figure 5 | Clinical outcome measures for different purposes. Clinical outcome measures for different purposes. (1) For the evaluation of individualized therapies, a refined clinical outcome measure might be preferred to evaluate therapy effectiveness but (2) a global outcome measure can initially assess the safety of a new therapy; (3) for the prediction of clinical outcomes using emergency department variables, a global measure seems sufficient (e.g., favorable versus unfavorable outcome); A&E, accident and emergency department; GOSE, Glasgow outcome scale extended; ICU, intensive care unit; MDS-ABI, Minimal Dataset for Acquired Brain Injury. Created with BioRender.com

10.4.4 Is doing 'more' doing 'better'?

On the one side we try to improve patient care through more research towards individualizing care by using more monitoring to obtain more information and a better insight in to the clinical outcome of the patients. On the other side, one might argue that doing more results in e.g. (I) more data, which need to be interpreted and integrated (see **paragraph 10.2.2**. of the discussion) and (II) also an even higher workload for the clinical team and (III) increased medical cost. The question is how we can achieve 'doing more' in this context. The

answer could lie in working ‘smarter’. Examples of working ‘smarter’ are given, such as centralizing (neurocritical)care, closed-loop monitoring, but also being better informed about (unfavorable) prognosis. In addition, validated advanced algorithms (e.g., machine learning or artificial intelligence) could facilitate with precise information, advices and decisions.

10.5 CONCLUSIONS

In this thesis, we described aspects contributing towards precision medicine for predominantly adult TBI patients. We showed that MMM is applied across different acute brain injuries with a large heterogeneity in study design, setting and type of interventions hampering conclusions about the benefits. Using unimodal monitoring to individualize treatment targets showed that targeting a dynamic ‘optimal’ CPP using CA perfusion guidance is feasible and safe in patients with TBI and ICP monitoring. However, the availability and reliability of a CA-guided CPP target could be enhanced by increasing the amount of slow ABP waves. One way to achieve this is by using the ventilator PEEP based sigh function. We showed that this PEEP based sigh function induced slow ABP waves and reduced the standard deviation of the PRx. Further increasing the reliability of CA estimations might result from reducing the amount of external ‘noise’ in the signal. We reported on the alternating anti-decubitus bed mattress that affected both the ABP and ICP signals and may seemingly adversely affect the PRx calculation. Besides to invasive CA-assessment, we showed that the ‘NIRS-only’ model could provide estimates of the CA and differentiate clinical outcome groups. Finally, we showed that a multi-domain outcome assessment tool (MDS-ABI) might contribute to a refined outcome assessment used to evaluate individualized therapies in ICU patients with TBI. Accordingly, our research contributed to the dual meaning of precision medicine: either aiming for a ‘specific treatment to a subset of patients’ or the ‘quality of being careful and accurate’. A combination of increased multidisciplinary collaborations, improved data quality, and innovations, could further improve neuromonitoring for neurocritical care patients and hence the implementation of precision medicine.

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APPENDICES

SCIENTIFIC AND SOCIETAL IMPLICATIONS

The main incentive of this thesis is the unmet need for an improved assessment, therapy, and clinical outcome in a critically ill patient with a focus on traumatic brain injury patients. From the clinical side, this need is exemplified by the limited availability of information and therapies to treat or protect the injured brain. In addition, families and the clinical team have uncertainties about the clinical outcome. This goes along with (prolonged) intensive care unit (ICU) stay as well as remaining post-ICU disabilities and consequently high social and financial costs.

Professionals working in the ICU care for patients who require continuous monitoring and treatments to maximize the chance of surviving critical illness. An organ like the heart can be supported by machines and/or medication. The brain function is usually assessed by bedside questions and tests for the 'awake' patient. In other words, their behavior is assessed. However, in the ICU, most patients with acute brain injuries are comatose or sedated, so a continuous behavioral assessment of the brain functioning is not possible. Alternatively, the brain can be monitored using signal monitoring devices inserted into the brain (invasive) or devices that do not require insertion through the skull (non-invasive monitoring). This monitoring information could contribute to the development of new therapies or outcome prediction of brain-injured patients.

Unique for the brain as an organ is that an incompressible skull encloses it. After a trauma, such as a fall on the head, the brain of the patient can swell after which the volume increases and the pressure in the skull increases. Too high-pressure results in tissue compression and eventually loss of brain tissue. The pressure is invasively measured via a meter inserted through a hole in the skull. Not only is the pressure in the skull relevant, but also the pressure to supply the tissue with sufficient blood, called cerebral perfusion pressure. Up to now, patients are treated according to the critical thresholds based on group values i.e., 'one size fits all' principle. However, there is an increasing interest in changing the treatment from this concept towards a therapy based on the individual patient. This is called precision medicine.

In our research, we study examples of precision medicine by performing neuromonitoring measurements in more than 100 patients with mainly a brain injury after trauma, also called traumatic brain injury (TBI). The patients received either invasive intracranial pressure monitoring or non-invasive monitoring by applying a simple sensor on the forehead. Both devices can measure a complex mechanism in the brain that regulates cerebral perfusion

pressure. This mechanism, called cerebral autoregulation, is often impaired in patients with TBI but also in some other critically ill patients.

With our research, we focus on the feasibility and safety of an individualized treatment that aims to optimize the perfusion pressure by using information from this complex mechanism. Our research results show that it is possible to start an individual treatment driven by neuromonitoring data. Although the current patients do not profit from these results, one of the next steps is to study if the therapy results in an improvement in outcome in patients with TBI. When these results are promising, the therapy will be integrated in treatment guidelines for TBI patients.

For the general ICU population is only non-invasive monitoring available, whereas we are for these patients interested in information from this complex mechanism too. Therefore, we used the non-invasive sensor to evaluate the degree of impairment of this mechanism in a typical critically ill ICU population. Our results show that the mechanism is more often impaired in patients who passed away within six months after their acute illness. By using a non-invasive assessment method for the general ICU population, more information from the brain becomes available. For future patients, this might contribute to individualizing care and/or decision making and finally outcome improvements.

Patients who discharged from the ICU alive are often not yet fully recovered but instead require a long recovery phase. That is why an important question is what the outcome is after an ICU stay. In our last research, we focused on such clinical outcome. However, outcome measures are often only rough measures. For example, patients with a favorable outcome (able to work and take care of themselves) versus patients with an unfavorable outcome (unable to work and unable to take care of themselves). Of course, there are also patients with a range of milder symptoms and impairments such as fatigue, concentration problems etc. which may be very disabling to people in their daily lives. These outcome measures generally receive only minor attention in an acute intensive care perspective. We obtained a detailed insight into the long-term outcome of ICU patients that included a range of symptoms and impairments such as fatigue and concentration problems. Therefore, these surviving TBI patients were interviewed by a neuropsychologist at home. More than half of the 52 patients suffered from cognitive impairments such as memory problems, fatigue and/or restrictions in participating domains (mostly work or education and going out). Also, about a third of the caregivers experienced a high workload by taking care of the former patients with TBI. Although the current patients do not profit from our results, the societal implications of our results

are that a detailed outcome assessment of the patients could contribute to the evaluation of new individualized therapies that are developed for ICU patients.

We started this paragraph with the need for therapies and the need to obtain insight into brain functioning. Our research questions contributed to solutions for this need. However, we also showed in our studies that measuring signals in an ICU environment can be challenging as the signals can be disturbed by several external or internal factors. For example, we observed in some data an unwanted frequent in- and decrease in the pressure signals. This simple observation resulted from the bed mattress that in- and deflated to overcome bedsores. Indeed, we actually often do not fully understand the exact meaning of the signals due to e.g., heterogeneity in injury location and injury severity. This is even further complicated when invasive, non-invasive, local, and global signals are combined.

On the other hand, when we want to obtain information from the brain's mechanism that regulates the cerebral perfusion pressure, we need to challenge the mechanism. A translation to a more daily example is when we want to evaluate somebodies hearing. We need a sound (is challenge) to test the system (hearing) However, in the ICU challenging the cerebral autoregulation mechanism is difficult as patients are sedated and comatose. Therefore, often no challenge is performed. In this thesis, we applied an innovative methodology – adapted from an animal study - by turning on the 'sigh' function on the ventilator. A 'sigh' results in a change in the blood pressure and hence a challenge for the brain's mechanism to respond to.

Throughout our research we show a dual meaning of precision medicine. On the one hand, we aim for individual therapies and a refined clinical outcome. However, on the other hand, we show the complexity of monitoring as external factors can adversely affect the signals and we show a way to improve measurements, so precision defined by the Cambridge dictionary as: 'the qualities of being careful and accurate'. Simply said, it is a matter of time and quality. Improving measurements might delay the introduction of new therapies for clinical use but continuing research towards the effectiveness of new therapies limits the ability to first improve the quality of the measurements. In other words, do we aim for the best or for the fastest way to improve outcome (prediction) for neurocritical care patients?

SAMENVATTING IN HET NEDERLANDS

Kritisch zieke patiënten worden op de intensivecare afdeling (IC) opgenomen voor de ondersteuning van één of meerdere organen. Voor deze ondersteuning wordt gebruik gemaakt van diverse therapieën en continue monitoring van o.a. het hart en de longen. Een deel van deze patiënten is opgenomen vanwege een acuut ernstig hersenletsel waaronder ernstig traumatisch schedelhersenletsel (ETSHL), hersenbloeding/herseninfarct en acuut hypoxische hersenschade (zuurstoftekort) na een hartstilstand. Voor deze patiënten is additionele neuromonitoring van de hersenen beschikbaar. Recentelijk is er door de opkomst van geavanceerde therapieën en technologische innovaties een toename in interesse voor gepersonaliseerde geneeskunde. Dit wordt ook wel 'precisie' geneeskunde genoemd. In dit proefschrift onderzoeken we drie voorbeelden van precisie geneeskunde binnen de groep van acuut hersenletsel patiënten waarbij de focus ligt bij ETSHL. Allereerst bespreken we multimodale monitoring ofwel het toepassen van meerdere monitoring modaliteiten bij een patiënt. Ten tweede onderzoeken we methodes om geïndividualiseerde behandelstreefwaarden na te streven gebruikmakend van cerebrale autoregulatie (CA) informatie. Ten derde bestuderen we de lange termijn klinische uitkomst van ETSHL-patiënten binnen diverse uitkomstdomeinen.

In 2014 verscheen een consensus review van Le Roux et al. (*Neurocrit Care, 2014*) waarin de vijf-jaar verwachtingen ten aanzien van de cerebrale multimodale monitoring (MMM) toepassing werd geschetst. Dit betreft monitoring van meerdere modaliteiten van de hersenfunctie. In **hoofdstuk 2** bestuderen we MMM studies, gepubliceerd in de periode 2014 – juli 2022 waarin onderzoek werd gedaan naar volwassen IC-patiënten met een acuut hersenletsel. De 112 geselecteerde studies laten zien dat MMM voornamelijk wordt toegepast bij ETSHL-patiënten en in veel gevallen (52%) bestond MMM slechts uit twee monitoring modaliteiten. Verder wordt MMM veelal onderzocht in kleine studiepopulaties en beschrijft men voornamelijk observaties in plaats van het bestuderen van interventies. De geïncludeerde interventiestudies laten zien dat er veel verschillende type interventies worden onderzocht. Zo worden in de 44 interventiestudies 20 verschillende interventies onderzocht. Een specifieke groep gecombineerde interventies zijn MMM-gestuurde therapieën zoals het geven van bloeddrukmedicatie en het aanpassen van de beademing. In tegenstelling tot het toepassen van een interventie en onderzoeken van de response hierop, wordt in de MMM-gestuurde studies een interventie afgestemd op de afwijkende gemonitorde waarden. In deze onderzoeken zien we weliswaar dat MMM-gestuurde therapie in zeven van de negen studies een verbetering in klinische uitkomst oplevert, maar uit onze observaties blijkt ook dat MMM studies heterogeen zijn qua studie setting en design (o.a.

variatie in de omstandigheden waaronder de onderzoeken werden uitgevoerd, inclusieperiodes, analysemethode), waardoor we voorlopig beperkt conclusies kunnen trekken over de voordelen van MMM voor de individuele patiënt.

In hoofdstuk 3-4, bestuderen we een geïndividualiseerde therapie voor ETSHL-patiënten met invasieve intracraniële druk monitoring. Retrospectieve studies hebben een betere klinische uitkomst aangetoond voor ETSHL-patiënten wanneer tijdens de behandeling de hersendoorbloedingsdruk (Engelse term, *cerebral perfusion pressure*, CPP) in de buurt lag van de 'optimale' CPP. De 'optimale' CPP is de CPP-waarde waarvoor de CA het beste functioneert (CPPopt). Deze waarde is voor iedere patiënt en conditie uniek. In dit proefschrift onderzoeken we de haalbaarheid en veiligheid van CA-gestuurde CPP-therapie. Met andere woorden, is het mogelijk om een geïndividualiseerde CPP-streefwaarde te behalen in vergelijking met de standaardbehandeling (een in de geldende richtlijn vastgelegde CPP-waarde tussen de 60-70 mmHg). Zestig patiënten werden geïncludeerd en gerandomiseerd; 28 patiënten in de controlegroep (CPP 60-70 mmHg, standaardbehandeling) en 32 patiënten in de interventiegroep (nastreven van een CPP-streefwaarde ofwel CPPopt). Op basis van retrospectieve data was de verwachting dat ten minste in 36% van de monitoringtijd de CPP-waarde in de buurt van (±5 mmHg) de CPP-streefwaarde (CPPopt) zou liggen. De resultaten laten zien dat dit percentage in de interventiegroep met een percentage van 46.5% significant is toegenomen ten opzichte van de veronderstelde 36%. Verder was de intensiteit van de gegeven behandeling tussen beide groepen gelijk en waren er geen verschillen in additionele events, en/of andere orgaandysfunctie parameters. De conclusie is dan ook dat het nastreven van CA-gestuurde CPP-streefwaarde haalbaar en veilig is, wat verder onderzoek naar de klinische uitkomst aanmoedigt.

In hoofdstuk 5-6 onderzoeken we de invasieve signalen en het monitoren van de CA. Om de functionaliteit van de CA betrouwbaar in kaart te brengen zijn voldoende trage arteriële bloeddruk (Engelse term, *arterial blood pressure*, ABP) schommelingen noodzakelijk, omdat deze ABP-schommelingen ervoor zorgen dat de CA respondeert en daardoor betrouwbaar meetbaar is. In **hoofdstuk 5** onderzoeken we in 10 ETSHL-patiënten een methode om trage ABP-schommelingen op te wekken. Hierbij maken we gebruik van de zuchtfunctie op het beademingsapparaat. Het opwekken van cyclische veranderingen in de uitademingsbeademingsdruk (Engelse term: *positive end-expiratory pressure,* PEEP) resulteerde in ABP-schommelingen met eenzelfde trage frequentie. Gedurende de periode van het zuchten zagen we dat de standaarddeviatie van de CA-maat ofwel de Pressure Reactivity index (PRx, Pearson correlatie tussen trage ABP en ICP-schommelingen) significant afnam van gemiddeld 0.25 in de uitgangsperiode (PRx-periode) naar 0.14 in de periode waar ABP-schommelingen

werden opgewekt, zonder dat er klinisch relevante fysiologische veranderingen optraden. Deze afname in PRx variabiliteit kan bijdragen aan een verbetering van de in **hoofdstuk 3-4** beschrijven we CA-gestuurde CPP-therapie. Dit doordat de benodigde tijd om de eerste CPPopt waarde te berekenen mogelijk verkort kan worden (Appendix, *graphical abstract chapter 5*).

Een tweede voorbeeld waarin de neuromonitoring signalen worden beïnvloed beschrijven we in **hoofdstuk 6**. In dit hoofdstuk rapporteren we over een onbedoeld neveneffect waarbij we in een selectie van de ETH-patiënten een herhaalde toe- en afname zien in de intracraniële druk en ABP-signalen. Deze observatie was het resultaat van het alternerend opblazen en leeglopen van het antidecubitusmatras. De precieze fysiologische interpretatie is onbekend, maar doordat het de PRx beïnvloedt, draagt deze interferentie mogelijk negatief bij aan het monitoren van de CA.

In **hoofdstuk 7-8** bestuderen we niet-invasieve neuromonitoring om de CA te onderzoeken. Het niet-invasief monitoren van de CA wordt veelal bestudeerd met transcraniële Doppler (TCD) in combinatie met het ABP-signaal. Men bepaalt vervolgens de relatie tussen het ABP en het TCD afgeleide cerebrale bloeddoorstromingssnelheid (Engelse term: *cerebral blood flow velocity*, CBFV) signaal door gebruik te maken van een wiskundige overdrachtsfunctie (Engelse term: *transfer function analysis*, TFA). In **hoofdstuk 7** beschrijven we een nieuwe methode om de CA te monitoren. De gebruikte techniek heeft overeenkomsten met een zuurstofmeter (pulse-oximeter) waarmee het zuurstofgehalte continu in het bloed wordt gemeten. Near-infrared spectroscopie (NIRS) meet de continue oxyhemoglobine (oxyHb) en deoxyhemoglobine (deoxyHb) concentratieveranderingen in het hersenweefsel. Op de relatie oxyHb en deoxyHb kan ook de TFA toegepast worden. Eveneens liet eerder onderzoek zien dat het bestuderen van deze relatie informatie oplevert over de CA. Echter, omdat de locatie waar gemeten wordt anders is voor de ABP en CBFV in vergelijking met de NIRS-signalen was de hypothese dat er een additionele correctie moest worden uitgevoerd om de resultaten te kunnen vergelijken. Gebruikmakend van simulaties en wiskundige berekeningen zijn we tot een dergelijke correctie gekomen. Onze resultaten hebben we vervolgens vergeleken met TCD-metingen die simultaan met de NIRS-metingen zijn uitgevoerd in een groep van 15 gezonde vrijwilligers tijdens drie fysiologische condities: rust, milde hypocapnia (veroorzaakt door diepe in- en uitademhaling instructies) en milde hypercapnie (veroorzaakt door diepe in- en uitademhaling instructies en het tegelijkertijd inhaleren van een 8% CO_2 mengsel). De vergelijking tussen ABP-CBFV en oxyHb-deoxyHb berekeningen laat zien dat er een goede *interclass* correlatie tussen beide methoden is en daarmee laten we zien dat er een goede overeenstemming is tussen de CA-schattingen van beide technieken.

In **hoofdstuk 8** evalueren we het ontwikkelde 'NIRS-only' model in een kritisch zieke comateuze IC-populatie. Voor deze evaluatie hebben we het originele model verbeterd en hebben we een methode toegepast om 'geautomatiseerd' tien minuten datasegmenten te selecteren om de robuustheid en de consistentie van de resultaten te verbeteren. Om de klinische relevantie vervolgens te bestuderen hebben we gebruik gemaakt van een multivariaat logistisch regressie model waarin de CA-maat (uitgedrukt in een faseverschil tussen de oxyHb-deoxyHb signalen) werd gebruikt om de zes maanden overleving te voorspellen (een faseverschil dichtbij nul impliceert een verstoorde CA-status, terwijl een faseverschil in de buurt van 180 graden, een intacte CA-status impliceert). De resultaten van het verbeterde model laten zien dat het mogelijk is om criteria op te stellen waarmee automatisch niet interpreteerbare segmenten geëxcludeerd worden. Na het toepassen van de segment selectiemethode kwamen we uit op de inclusie van 54 kritisch zieke patiënten en 490 data segmenten. De klinische uitkomst resultaten laten vervolgens zien dat de primair neurologische patiënten die zes maanden na hun IC opname waren overleden, een slechtere CA-status hadden tijdens de IC opname hadden. Deze relatie was onafhankelijk van andere factoren zoals leeftijd en ernst bij opname op de IC. Alhoewel het verbeterde model mogelijk relevant is om (continu) geïnformeerd te worden over de individuele CA-status is toekomstig onderzoek noodzakelijk om onze resultaten te valideren (Appendix, *graphical abstract chapter 8*).

In het laatste deel van dit proefschrift (**hoofdstuk 9**) hebben we een explorerend cross-sectioneel onderzoek uitgevoerd naar de lange termijn klinische uitkomst van IC-patiënten met ETSHL en de impact van ETH op hun verzorgers. Van ETH-patiënten verzamelen we patiënten data (o.a. demografische gegevens, ernst van de primaire neurologische schade en zijn tijdens huisbezoeken meerdere vragenlijsten afgenomen door een neuropsycholoog. In vergelijking met de gangbare - grovere - klinische uitkomstmaat, geeft de huidige methode ook een beeld over het functioneren van de patiënt met gedetailleerde informatie in de verschillende domeinen (o.a. cognitie zoals geheugenproblemen en vermoeidheid). De resultaten van dit onderzoek laten zien dat de meerderheid van de 52 ETSHL-patiënten beperkingen ondervindt waaronder cognitieve klachten (62%), vermoeidheid (62%) en beperkingen bij deelname aan dagelijkse activiteiten (69%) (bijvoorbeeld werk, opleiding en uitgaan). Verzorgers van patiënten voelen zich over het algemeen competent om de zorg te leveren (81%), maar 31% van hen ervaart een disproportionele last. In tegenstelling tot onze verwachting zien we geen significante lange termijn uitkomst verschillen in de lange termijn uitkomsten tussen patiëntengroepen waarbij we ernstig aangedane patiënten hebben vergeleken met minder ernstig aangedane patiënten. Gezien de restklachten in meerdere domeinen binnen een ETSHL IC-populatie lijkt een

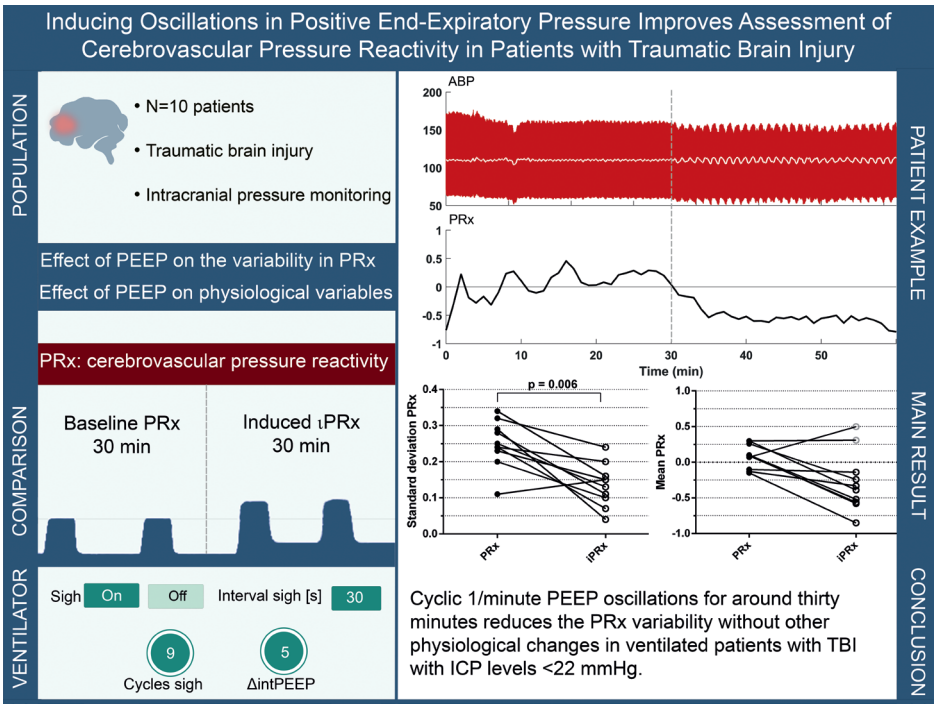
uitkomstmaat die meerdere domeinen omvat relevant om de effectiviteit van klinisch onderzoek naar gepersonaliseerde behandelingen te evalueren.

De onderzoeken in dit proefschrift laten een tweeledig aspect van ‘precisie’ geneeskunde gezien. Enerzijds presenteren we precisie in de zin van onderzoeksresultaten die betrekking hebben op het toewerken naar een gepersonaliseerde behandeling. Anderzijds laten we ‘precisie’ zien in de betekenis van het verbeteren van het monitoren van de hersenen, dus precisie als ‘nauwkeurige’ metingen. Door middel van een toename in multidisciplinaire samenwerkingen, verbetering van de datakwaliteit en door het toepassen van technologische innovaties, kunnen we beide aspecten van ‘precisie’ geneeskunde mogelijk op korte termijn verbeteren.

GRAPHICAL ABSTRACTS

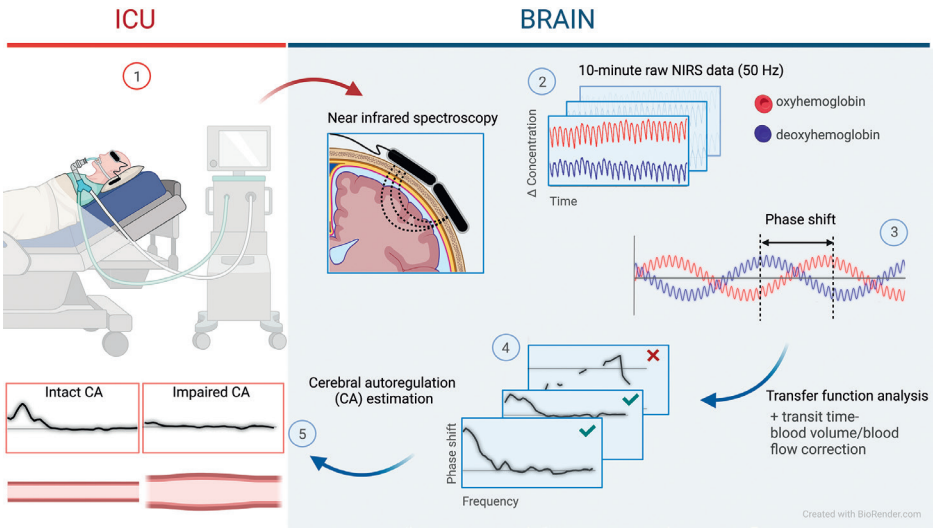
CHAPTER 5

Inducing Oscillations in Positive End-Expiratory Pressure Improves Assessment of Cerebrovascular Pressure Reactivity in Patients with Traumatic Brain Injury



CHAPTER 8

Cerebral Autoregulation Assessment Using the Near Infrared Spectroscopy 'NIRS-Only' High Frequency Methodology in Critically Ill Patients: A Prospective Cross-Sectional Study



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CURRICULUM VITAE

Jeanette Tas was born in 1990 on the 8th of October in Pijnacker, the Netherlands. After primary school she started the secondary school at Melanchthon de Kring (Bleiswijk, the Netherlands) and continued her education at Melanchthon Schiebroek (Rotterdam, the Netherlands). In 2011 she completed the secondary school (certificates: pre-vocational secondary education (VMBO-TL, 2007, senior general secondary education (HAVO, 2009) and pre-university education (VWO, 2011)). After that, she moved to Enschede and started the bachelor Technical Medicine at the University of Twente (2011 - 2014), followed by the master Technical Medicine - Medical Sensing and Stimulation.

Her first working experience as a technical medicine student started in her second year of her master (Feb 2016 - Jun 2017). She performed various traineeships combining clinical work and research projects in hospitals in the Netherlands and abroad: department of intensive care medicine (University Medical Center Groningen); department of vascular surgery (Rijnstate hospital, Arnhem), the brain physics lab in Cambridge (Addenbrooke's hospital Cambridge, United Kingdom) and the department of clinical neurophysiology (Medical Spectrum Twente, Enschede).

Jeanette's third and last master year began in the intensive care medicine department (Radboud UMC, Nijmegen) were she started a literature review and clinical study protocol to the effect of positive end- expiratory pressure on the intracranial pressure monitoring (Sep 2017 - Jan 2018). She continued her last year with a project in the department of clinical neurophysiology/stroke unit (Rijnstate hospital, Arnhem) under supervision of prof. dr. Jeanette Hofmeijer and prof. dr. ir. Michel JAM van Putten. The subject of her project was the detection of disrupted resting state networks using EEG monitoring in stroke patients. Jeanette graduated in December 2018 for her Master of Science.

After graduating, she moved to Maastricht for a PhD trajectory (0.6 FTE) in the intensive care medicine department (Maastricht University Medical Center+) under supervision of prof. dr. Iwan CC van der Horst, prof. Caroline M van Heugten and dr. Marcel JH Aries. An additional 0.4 FTE included a clinical position. Herr duties included clinical measurements, supervision of students and the coordination of the Maastricht Intensive Care COVID cohort during the first nine months of the COVID pandemic (Tas et al. BMJ Open. 2020).

PUBLICATIONS

*Shared authorship, † Publications part of the thesis

† Domensino F, **Tas J**, Donners B, Kooyman J, van der Horst ICC, Haeren R, Aries MJH, van Heugten CM. Long-term follow-up of critically ill traumatic brain injury patients: from intensive care parameters to patient and caregiver-reported outcome (submitted to J.Neurotrauma)

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