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Cerebral Autoregulation Monitoring in Traumatic Brain Injury: An Overview of Recent Advances in Personalized Medicine

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Abstract:

Impaired cerebral autoregulation (CA) in moderate/severe traumatic brain injury (TBI) has been identified as a strong associate with poor long-term outcomes, with recent data highlighting its dominance over cerebral physiologic dysfunction seen in the acute phase post injury. With advances in bedside continuous cerebral physiologic signal processing, continuously derived metrics of CA capacity have been described over the past two decades, leading to improvements in cerebral physiologic insult detection and development of novel personalized approaches to TBI care in the intensive care unit (ICU). This narrative review focuses on highlighting the concept of continuous CA monitoring and consequences of impairment in moderate/severe TBI. Further, we provide a comprehensive description and overview of the main personalized cerebral physiologic targets, based on CA monitoring, that are emerging as strong associates with patient outcomes. CA-based personalized targets, such as optimal cerebral perfusion pressure (CPPopt), lower/upper limit of regulation (LLR/ULR), and individualized intra-cranial pressure (iICP) are positioned to change the way we care for TBI patients in the ICU, moving away from the "one treatment fits all" paradigm of current guideline-based therapeutic approaches, towards a true personalized medicine approach tailored to the individual patient. Future perspectives regarding research needs in this field are also discussed.

Keywords: Autoregulation, Digital Medicine, Individualized Care, Personalized Medicine, TBI

Introduction to Cerebral Autoregulation in TBI:

Cerebral autoregulation (CA) impairment in moderate/severe traumatic brain injury (TBI) has emerged in the past two decades as a critical aspect of secondary injury to consider during care provision.[1–6] First characterized in detail in felines in the 1930's by Fog,[7] and then in humans by Lassen in the 1950's,[8] static CA refers to the innate ability of the cerebral pre-capillary arterioles to maintain a relatively constant cerebral blood flow (CBF) over a range of mean arterial pressures (MAP) or cerebral perfusion pressures (CPP). Figure 1 provides an overview of the general shape of the static cerebral autoregulatory curve, highlighting a lower and upper inflection point, referred to as the lower limit of autoregulation (LLA) and upper limit of autoregulation (ULA), respectively. Between the LLA and ULA, there is a relative plateau of the relationship between MAP/CPP and CBF, where slow CBF variations caused by changes in MAP/CPP are actively supressed.[7,8] Values of MAP/CPP beyond the LLA/ULA expose the brain to pressure-passive CBF, where MAP/CPP values below the LLA lead to hypoperfusion and ischemia, and pressures above the ULA cause hyperperfusion states with hyperemia, cerebral edema and blood-brain-barrier disruption as potential consequences.[7–9] Though one must acknowledge, the plateau between the LLA and ULA described may not be a true plateau, and may in fact have a slight slope,[10] depending on individual biological and genetic differences and presence/absence of medical co-morbidities. Figure 1 highlights some of the changes in the shape of the static CA curve, based on different physiologic states.

*Figure 1 here

Since the original seminal works of the 1930's and 1950's on static CA[7,8], various studies in moderate/severe TBI have described the presence of CA impairment and failure in this population, using intermittent measurement techniques.[11] Such intermittent methods evaluated CBF pre- and post-perturbation and included enhanced neuro-imaging methods, such as xenon computed tomography of the brain, or intermittent transcranial Doppler (TCD) insonations of the middle cerebral artery (MCA).[11–14] Perturbations classically included alterations in MAP through both non-invasive methods, such as thigh-cuff deflation or orthostatic challenge techniques, and invasive methods, through direct manipulation of MAP with intra-venous vasoactive pharmaceuticals. Such early works

formed the foundation of our understanding of CA impairment in TBI,[11] though given their intermittent nature, had limited bedside utility in clinical care. The intermittent methods have been replaced by continuously derived dynamic CA indices, using modern biomedical signal processing.[1–3]

Continuous Bedside Measurement of CA in TBI – Pressure Reactivity Index (PRx):

With the acknowledgment of the role that CA impairment may play in secondary insult burden after moderate/severe TBI, the neurocritical care community has pursued the development of continuously derived measures.[1–4] The development of these dynamic metrics has focused on utilizing available continuous physiologic data streams in moderate/severe TBI care, those being MAP and ICP.[4,15–17] Through evaluating the phase-shift between a driving pressure for flow, such as MAP or CPP, and a surrogate measure of pulsatile CBF or cerebral blood volume (CBV) (such as ICP), one can make comment on CA capacity if focused on the frequency range associated with active cerebral vasomotion. Slow changes in driving pressure, ~between 0.05 to 0.005 Hertz (Hz) are actively counteracted by cerebral vasoconstriction and vasodilatation while faster chances are passively led through (high pass filter principle of dynamic CA).[18,19] However, due to relative complexities of frequency-domain signal transfer function analysis (TFA), use of metrics such as angular phase-shift, coherence and gain, was recognized by many as a limitation to clinical end-user uptake at the bedside.

As such, time-domain analysis was adopted in the late 1990's for the creation of the current form of continuous CA metrics for bedside monitoring and care.[2] Using the moving Pearson correlation between a driving pressure for flow, such as MAP/CPP, and a surrogate measure of pulsatile CBF/CBV, such as ICP, the pressure reactivity index (PRx) was created.[2] Now commonly derived using 30 consecutive 10-second mean values of MAP and ICP, updated every minute, PRx has emerged as a relatively simple yet efficient and understandable method for CA trend assessment in a continuous fashion at the bedside.[1,3,5] This index ranges from +1, indicating impaired CA, to close to -1, indicating intact CA, with numerous studies on PRx documenting the strong association between impaired CA and poor long-term outcome in moderate/severe TBI patients.[2,20–23] Figure 2

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provides an example of continuous cerebral physiology in TBI at the bedside, including the derivation of PRx in real-time.

*Figure 2 here

However, it must be acknowledged, despite the many advances made with the development of the PRx metric, there are some known limitations. PRx is an inherently noisy parameter, influenced by artifact in both the parent ICP and MAP waveforms, which must be considered during real-time bedside interpretation. In addition, the presence of decompressive craniectomy has a known impact on the ICP waveform and it's representation of changes in CBV, leaving unclear implications for the accuracy of PRx data in this setting.[20,21,24] Though, recent time-series analytics using data from the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) highlights that previous concerns with craniectomy patients and the MAP/ICP relationship, may not necessarily be warranted.[25] Furthermore, the method of ICP measurement carries major implications for the derivation of PRx. Use of external ventricular drains for ICP measurement in TBI may limit the ability to derive PRx continuously, particularly when the drain is utilized in the therapeutic management of ICP.[26–28] In addition, regardless of the ICP measurement technique, we assume that the ICP measure represents a global measure of pressure, and thus PRx represents a global measure of CA, ignoring potential regional variation in CA capacity.[1,3,5] These concerns mean that despite a large volume of statistical, retrospective, evidence for the benefits of adding of PRx to the battery of neuromonitoring tools, its incorporation into routine clinical practice requires further work.[5]

Pre-Clinical Validation of Continuous CA Metrics:

The development of any new physiologic metric necessitates some degree of validation. With continuous CA measures, like PRx, validation of its ability to measure aspects of the static CA curve is critical, particularly the LLA and ULA. Given such validation is not possible in human studies, pre-clinical validation is required. Over the past decade, pre-clinical validation of PRx, and other continuous multi-modal monitoring (MMM) based CA measures, has occurred.[29–33] In healthy neonatal piglets, using both elevated ICP and

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arterial hypotension as drivers of MAP/CPP change, PRx has been demonstrated to respect and detect the LLA in multiple studies.[29–31,33] Similarly, in a rabbit model of intracranial hypertension, PRx has also been confirmed to detect and measure the LLA.[32,34] These findings provide a degree of confidence in the ability of PRx to measure important aspects of CA. Unfortunately, to date, the same cannot be said regarding the ULA. Attempts to drive MAP above the ULA in piglet models have been unsuccessful due to early cardiovascular failure. It has been hypothesized that CA might be better adapted to compensate for increasing, rather than for decreasing, MAP/CPP.[35–37] Though some preliminary data from these works suggests the potential for PRx to detect the ULA,[38] further pre-clinical validation of this aspect is required, ideally utilizing techniques that can directly assess changes in cerebral blood flow and blood volume.[36]

Cerebral Autoregulation and Outcomes in TBI:

As mentioned previously, impaired CA in moderate/severe TBI exposes an already damaged brain to potential ongoing secondary insult. The relationship between impaired CA and poor patient outcomes in TBI has been highlighted since the original PRx study was published in the late 1990's.[2] Those with more positive mean PRx values have been noted to have higher rates of unfavourable functional outcomes and increased mortality at 6 and 12 months post-TBI.[2,20–23,39,40] Critical thresholds for outcome associations for PRx have been documented in moderate/severe TBI cohorts.[20,21] The PRx threshold of +0.05 and +0.25 are associated with favourable/unfavourable outcome and mortality respectively, in mixed TBI cohorts[5,20]. Evaluating those TBI patients without decompressive hemicraniectomy, the PRx threshold of +0.35 for both unfavourable outcome and death has been documented.[21] Similarly, evaluating the insult burden or dose exposure of PRx above these defined critical thresholds has also recently been demonstrated to correlate with 6-month Glasgow Outcome Score, in various single and multi-center analyses.[41–45] Recent data from the CENTER-TBI High-Resolution Intensive Care Unit (HR ICU) sub-study has confirmed these outcome associations,[22,46] relevance of the defined thresholds,[22,46–48] and independence of PRx to predict outcome in moderate/severe TBI (multi-variable model AUC's of up to 0.825, $p<0.0001$).[23] Further, the addition of PRx to current prognostic models in moderate/severe TBI, appears to improve upon the accounted variance in

patient outcomes of between 7.5 to 19.3% (delta Nagelkerke's pseudo-R^2, p<0.0001), depending on the core model used.[23] Finally, it appears that using current MMM techniques in TBI, that impaired CA dominates the majority of patients' acute-phase ICU stay, with over 50% of any given day spent with impaired CA (Figure 3).[46–49] Further, it appears that this impairment in CA overshadows ICP, CPP and $PbtO_2$ derangements in terms of physiologic insult burden during current guideline-based care provision,[49] highlighting the importance of CA impairment in moderate/severe TBI. Yet, our knowledge of what drives impaired CA is currently limited.[1,9] Some preliminary data supports the association between diffuse intracranial injury patterns[50–53] and poorly controlled ICP,[2,39,41,48] with worse CA. Thus, much further research into drivers of CA dysfunction are required.

*Figure 3 here

Management of Cerebral Autoregulation Impairment in TBI:

Despite impairment of CA appearing to dominate the ICU-phase of care of moderate/severe TBI patients,[39,41,43,46–49] we unfortunately have limited therapeutic options currently.[54] Evaluation of the impact of current TBI guideline-based therapeutic interventions on CA has demonstrated little-to-no influence on PRx, despite changes in these approaches over a 25-year period.[41,54] CENTER-TBI data has confirmed that there appears to be no impact of current treatments on the % of time with impaired PRx, with treatments and therapeutic intensity quantified using the Therapeutic Intensity Level (TIL)[55] composite and sub-scores collected daily (Figure 4).[47] Single center time-domain analytics of the influence of various sedative agents (propofol and fentanyl) and vasopressors (norepinephrine, phenylephrine and vasopressin) have confirmed limited impact of dose manipulations (off-on drug state, increase dose, decrease dose, or on-off drug state) on measured PRx in high temporal frequency.[56,57] Though, it must be acknowledged, such previous works have not been able to account for individual pharmacodynamics profiles of patients. The only positive impact seen by current TBI therapeutic strategies, has been with the administration of hyperosmotic/hypertonic agents for ICP reduction.[58,59] However, the reduction in PRx seen with hyperosmotic/hypertonic agent administration is short-lived, and likely a function of ICP

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reduction, as ICP elevation is a known driver of impaired PRx values in TBI patients.[2,48] Thus, moving forward with CA management in TBI requires the development of novel therapeutics aimed at the molecular pathways driving its dysfunction. As such, given limited therapeutic options, the current paradigm of CA management in TBI is the targeting of CPP values where PRx is the "least bad" (ie. the lowest value). This concept, utilizing the continuous relationship between CPP and PRx at the bedside has developed in the derivation of personalized 'optimal' CPP (CPPopt).[60–64] We will touch in this in more detail within the sections to follow.

*Figure 4 here

Personalized Physiologic Targets using Cerebral Autoregulation:

Aside from monitoring CA using PRx at the bedside, such data streams have been utilized to derive new personalized physiologic targets in moderate/severe TBI patients, with CPPopt as the most well-known exemplar. Below, we provide a brief overview of: CPPopt, lower limit of autoregulation (LLA)/upper limit of autoregulation (ULA), and individualized ICP (iICP) thresholds.

A. *'Optimal' CPP (CPPopt)*

Optimal CPP is an attractive proposition for a CA oriented approach to management of TBI patients. As outlined above, being able to measure CA continuously does not by itself translate easily to clinical actions. However, knowledge of the value of CPP that has been in the recent hours associated with the best state of CA provides an indication for management of CPP, the individualised CPP target to aim for.[61] This concept was originally proposed nearly two decades ago, along with an example protocol taking advantage of this new metric.[60] When mean PRx was plotted against corresponding CPP (binned into 5 mmHg intervals), across the whole cohort of TBI patients, it revealed a U-shape curve indicating that both high and low CPP values should probably be avoided (Figure 5).

*Figure 5 here

The location of the nadir of this curve was interpreted as pointing to the CPP values optimizing CA and termed CPPopt. It also turned out that these CPPopt values when

examined within patients varied considerably, thus pointing to the individual nature of this metric and the necessity for its estimation for each patient.

*Figure 6 here

However, not until an algorithm for continuous automated derivation of CPPopt became available[61] and further improved to ensure better coverage[65] and robustness,[63] it became possible to apply this technique in clinical settings to inform management of CPP in TBI patients (Figure 6). Several retrospective studies demonstrated that when CPP remained close to the dynamically adjusted CPPopt value throughout the observation period (over several days post injury) the 6 months outcome was significantly better.[61,65–68] Furthermore, it was also demonstrated that patients treated at CPP values below CPPopt had lower rate of survival while those with high CPP, well above CPPopt, tended to end up with more disabilities.[61] These statistical findings eventually prompted a randomized, phase II, trial of CPPopt in 60 TBI patients, the COGITATE study.[69] This has recently been completed, showing feasibly and safety of this paradigm, paving the way for the next step, the outcome benefit trial.

However many questions and concerns still remain, as articulated by the Delphi consensus meeting in 2019.[5] The reality of TBI is that its presentation is highly heterogenous, in time as well as in space, across the whole brain. PRx provides an inherent spatial averaging, as it relates global (in the first approximation) changes in CBV to changes in systemic MAP. The PRx-CPP relationship summary on which CPPopt is calculated on the other hand injects time averaging. In order to estimate the nadir of this relationship there needs to be enough of CPP variability captured to 'probe' a wide range of possible CPP values. And this often necessitates a long observation window of many hours, during which the ability of the cerebral vasculature to autoregulate might be modulated by the pathological biochemical storm occurring within the acute phase of TBI, independent of CPP. These problems are further exacerbated by the properties of PRx metric, which relies on clear transmission of spontaneous, pronounced, slow waves in MAP for accurate reflection of the vascular reactivity of the brain arterioles. The result of all of those effects together is that often the character of the PRx-CPP relationship within individual calculation windows can be far from conclusive. The COGiTATE study attempted to overcome those difficulties,

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with some success, by including certain algorithmic adjustments. However, a robust clinical protocol for implementing this otherwise highly appealing and physiological plausible concept into the standard clinical practice is yet to be proposed.

It will likely not be until the phase III trial is conducted that a definitive confirmation of clinical benefits of this methodology may be obtained. Until then use of the CPPopt methodology for TBI management will likely continue to be limited to specialized centers.[67,68,70,71]

B. Lower Limit of Regulation (LLR)/Upper Limit of Regulation (ULR)

CPPopt, despite the appeal of its relatively simplistic, conceptual nature, has one fundamental limitation. It provides one value, at which the vascular reactivity is best preserved, or least impaired. It does not differentiate between different potential scenarios giving the same CPPopt value. That is one could imagine a case where the reactivity is lost almost completely across the entire range of observed CPP values except for a small focal spot at the CPPopt where it shows signs of recovery. Attempting to adjust the CPP to values close to that spot may be therefore justified. On the other hand if, for the same CPPopt value, the underlying PRx-CPP relationship shows a very wide range of fully functional reactivity there is clearly no need to 'optimise' the reactivity any further by manipulating the MAP, as long as PRx is already in the 'working (i.e. intact) zone. This concept was well presented using a CPPopt landscape visualisation,[72,73] with CPP plotted against the colour coded CPP-time map of vascular reactivity (Figure 7) showing a zone of CPP values associated with intact CA over time.

*Figure 7 here

The practical essence of this landscape visualisation can be well represented by the notion of upper and lower limit of autoregulation, LLA and ULA respectively. That is if these limits were monitored and plotted alongside with the current CPP values the clinician would be presented with a lot more information than if only a single CPPopt value is provided, allowing the two scenarios described above to be easily separated. Such concepts of the LLA and ULA have been recently objectively validated in large pre-clinical models.[74]

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Fortunately the algorithm that allows to produce CPPopt values can also be extended to estimate the LLA and ULA values (Figure 8).

*Figure 8 here

The theoretical benefits of taking into account the limits of CA is that it can potentially allow to bridge two different schools of thoughts when it comes to managing CPP in TBI patients: A. keeping the CPP up to ensure proper brain perfusion, and B. keeping the CPP down to minimize the risks of disruption to the brain-blood barrier in a fragile environment of severely injured brain.[75] With dynamically estimated LLA one could aim to keep CPP just above that value turning to other priorities of TBI management. As with CPPopt, there is statistical evidence from retrospective studies that doing so might insure better outcome,[76] although a lot more work in this area needs to be done. The two additional points of difficulty is that estimation of LLA often requires extrapolation of the PRx-CPP curve, which increases uncertainty of estimation, and the fact that the 'average' LLA returned by the algorithm might just not be enough for some more vulnerable parts of the brain. In this situation the CPPopt value – located in the safer middle of the CA curve - might be preferred. All in all, the LLA-ULA and CPPopt concepts should be considered together, going forward toward the large outcome trial, to maximize on the benefits of and facilitate better integration of CA oriented management with the current treatment protocol in TBI.

C. Individualized ICP (iICP) Thresholds

Current guidelines for TBI management reference a population-wide ICP threshold target of 22 mmHg.[15–17] Such an approach ignores patient-specific heterogeneity in physiologic response post-injury. A relatively recent concept has emerged, utilizing the relationship between ICP and PRx, referred to as the individualized ICP (iICP) threshold.[77,78] This concept defines the iICP threshold as the ICP value above which PRx remains above the threshold of +0.20, as defined in the previous literature.[77,78] Figure 9 demonstrates an example of iICP derivation (data from representative patients from CENTER-TBI publication on iICP – figures not included in original publication).[78] The initial single center work highlighted the stronger association with poor outcome for patients with ICP above their

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individual iICP threshold, compared to the guideline-based threshold of 20 mmHg at that time.[77] Recent multi-center validation using CENTER-TBI data has confirmed that the time spent with ICP above iICP (AUC = 0.678, p = 0.029), compared to above current guideline target of 22 mmHg (AUC = 0.492, p = 0.035), displayed a stronger association with mortality at 6 months post-injury and was maintained while controlling for admission demographics.[78]

*Figure 9 here

However, despite the promising nature of iICP thresholds in TBI care, the findings should be considered entirely exploratory in nature at this time. To date, only two studies have been published on the personalized physiologic target in TBI,[77,78] necessitating further validation. Further, both studies have utilized the entire recording period for derivation, with no work to date on continuously updating derivation of iICP. The recent CENTER-TBI work had some improvements,[78] creating a semi-automated algorithmic derivation of iICP in place of the original work's manual inspection/derivation from plots. However, both previous works demonstrated that only ~60-70% of patients have an identifiable iICP threshold, with some iICP thresholds documented well below 20 mmHg. Thus, much future work in this area of iICP thresholds is required for validation of outcome association, improvement of algorithmic derivation, development of continuous derivation pipelines, and assessment of potential patient factors which may influence yield of iICP calculations. This is particularly made difficult by the complexity of interaction between the thresholds of ICP, the state of CA, modulated by the duration, and number of ICP hypertension events, as demonstrated by the ICP insults intensity maps, stratified by PRx (Figure 10).[44–46]

*Figure 10 here

<u>Cerebral Autoregulation Monitoring and "Other" Multi-Modal Monitoring:</u>

While not the focus of this narrative review, it is necessary to understand continuous CA monitoring in the context of "other" MMM data streams commonly encountered in bedside TBI care. For interested readers, we direct them to the referenced literature sources in the subsection, where various systematic reviews on MMM in TBI have recently been conducted[3,79–82]. Continuous CA monitoring and its associations with other MMM

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continuous data streams has, to date, only been discussed in a limited number of small, typically retrospective studies. We refer the readers to the following systematic reviews, highlighting the current knowledge gaps.[79–81]

With respect to cerebral oxygen delivery, there is some preliminary data to suggest that impaired CA is associated with increased episodes of low PbO_2.[48,49,83–85] However, both impaired CA and low $PbtO_2$ are not mutually inclusive, with recent data suggesting that the landscape of physiologic insult burden seen by patients with moderate/severe TBI is dominated by impaired CA, often in the absence of low recorded $PbtO_2$ values.[48,49] Similarly, CA indices derived from $PbtO_2$ monitoring (ie. oxygen reactivity index; ORx) have been shown to not behave in a similar fashion to standard ICP-based CA metrics (like PRx).[3,86,87] This likely stems from the inherent differences in the input signal, with $PbtO_2$ being based on a slow response extra-cellular O_2 diffusion measure using a Clark electrode.[88] Further analysis in the time-domain is required to fully understand the temporal relationship between $PbtO_2$ changes and CA capacity, derived CPPopt and LLR/ULR.

Similarly, literature assessing the association between continuous CA metrics and NIRS-based rSO_2 delivery is underdeveloped.[79,89–94] In general, studies assessing the utility of NIRS in moderate/severe TBI are limited, as highlighted in a recent systematic review on the topic.[79] NIRS-based CA metrics do closely co-vary with standard ICP-derived versions.[86,94] However, direct high-frequency time-series assessments of the temporal relationships between rSO_2 and CA measures has not been conducted to the author's knowledge. Preliminary data from small cohort studies suggests a positive relationship between rSO_2 and both CPP and CBF measures.[79] Yet, much further analysis is required, including the development of high-resolution commercial NIRS platforms for bedside monitoring in moderate/severe TBI care (given current monitors are limited to 20 Hz max (typically 1Hz for most) data sampling frequency – limiting the extent of waveform analysis that can be performed).[89]

Data on invasive CBF assessments, using Hemedex thermal diffusion or Laser Doppler methodologies, and their associations with continuous CA monitoring remain scarce. This is a function of the cost and expertise needed for such concurrent monitoring and data

collection. A recent systematic review on the topic highlighted the rarity of such monitoring in general within the moderate/severe TBI populations.[3,80] Such limited data suggests a temporal relationship between CBF measures and CA, with worse CA metrics values associated with poor CBF. However, it must be acknowledged, that such studies have been small heterogeneous cohorts, with limited long-term outcome data collection and no high-frequency time-series analysis.

Finally, cerebral micordialysis analytes have been explored in relation to continuous CA measurements, though in only a few studies to date.[95–100] A recent large systematic review on microdialysis in moderate/severe TBI highlights the overall knowledge gap.[81] However, exploratory analysis does currently suggest a temporal link between impaired CA and elevated lactate:pyruvate ratio (LPR), glycerol and glutamate,[96,97] with potential sex-based disparities in CA and metabolic dysfunction after moderate/severe TBI.[99] However, the true temporal-causal relationship between the two entities remains unclear. Meaning, does impaired CA drive elevated LRR? Or is the build-up of metabolic by-products of anaerobic metabolism/secondary brain injury (as denoted by elevated LPR) which drive subsequent impairment of CA? Such data sets with serial microdialysis analytes remain scarce, given expertise and costs associated with deployment of such monitoring in bedside care. Similarly, the sampling rate of current bedside microdialysis has been classically limited to hourly assessments. As microdialysis technology improves with lab-on-chip developments, we expect sampling frequency to improve, which will facilitate better assessments of the temporal relationships between CA monitoring and microdialysate measures.

Future Directions:

Widespread adoption of continuous CA monitoring in moderate/severe TBI will require additional research. At the moment, PRx and other continuously derived CA metrics, have mainly be studied/employed by specialized academic centers, where biomedical engineering and signal processing expertise is present and bedside interpretation is frequently practised.[5] Thus, the true clinical end-user uptake of continuous CA monitoring for the derivation of personalized medicine targets in TBI has mainly be relegated to research purposes to date, with recent progress into randomized trials (as mentioned

above).[63,69] Some progress has been made with increased clinician knowledge surrounding the importance of CA assessments in moderate/severe TBI, with both recent MMM consensus statements[4,5] and updated treatment guidelines.[17] These are the closest to "best practice" guidelines on the topic we have to date. As such, generalizability of the method still suffers from various outstanding issues such as: method of CA metric derivation (ie. which MMM device is best for CA index calculation), sampling frequency of data required, outcome vs. physiologically relevant thresholds, and algorithm optimization for improved calculation yield for personalize targets based on CA monitoring. Similarly, cost-effectiveness of continuous CA monitoring has yet to be quantified. Such work would need to evaluate method of derivation and have a better understanding of MMM implications of impaired CA (ie. if we have CA monitoring, do we need other devices present? Or does CA monitoring (and aiming for personalized targets based on CA monitoring) help us avoid other MMM assessed brain injury?).

Future adoption to the wider clinical end-user in the ICU will necessitate improvement in signal acquisition software/interfaces, such that minimal involvement of the clinical team would be required to set-up and utilize. Part of this improved accessibility will involve investigation of lower-resolution physiologic data streams for CA metric derivation. Many commercially available ICU monitors have limited data export frequency (i.e. one-minute-based resolution or worse).[101–103] As such, derivation of CA metrics with such data leads to the creation of low-resolution metrics which contain information below the lower frequency range classically associated with CA and difficulty with automated recognition of artefacts. Some preliminary works on these low-resolution metrics have occurred, documenting associations with long-term outcomes in moderate/severe TBI.[102–105] In a large single centre TBI study, as well as in the CENTER-TBI dataset it was recently argued that in the absence of the high resolution based PRx its low resolution (minute-by-minute) version, LPRx, show similar, even if inferior, patterns of association with outcome and could potentially be used to track the CA status.[66,106] However, such work remains preliminary at this time. With increased accessibility, future larger phase III trials of individualised CPPopt vs. guideline CPP therapeutic targeting would be feasible. To date, the only prospective phase II study comparing these two CPP strategies was relegated to a

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few specialized centers.[63,69] Thus, despite this study demonstrating safety and feasibility of targeting CPPopt in severe TBI, future widespread adoption/trials need proper preparation and education for the participating centers. Such trials would also benefit from a widespread consensus on what is "high resolution" monitoring in the ICU for moderate/severe TBI. The academic literature surrounding CA and MMM has classically referred to this as full-waveform sampled data streams (ie. typically 50 Hz or much higher). Moving forward with further validation and clinical investigation in CA and other MMM techniques, it would be prudent for a general consensus to be obtained regarding what would be considered the minimum sampling frequency for high resolution studies, and a clear rationale for its need (ie. Fourier and wavelet analytics, etc.). Though, such future consensus must understand limitations of current commercially available bedside patient monitors with regards to data export frequency, where many vendors only allow low-frequency export that limits high resolution data analytics and metric derivation. With future consensus, we may be able to set the future expected industry standard for such monitors, facilitating an "even playing field" for all ICU's globally and access to true high resolution MMM in TBI care.

Aside from PRx, as the exemplar continuously derived CA metric for TBI, many other MMM-based CA measures have been described to varying degrees in the literature.[1,3,5,86,104] Utilizing the same concept in PRx derivation, Pearson correlation coefficient based metrics have been derived between MAP/CPP and other surrogate measures of CBF (ie. TCD-based cerebral blood flow velocity (CBFV),[107] parenchymal thermal diffusion based CBF (TD-CBF) or near infrared spectroscopy (NIRS) based regional oxygen saturation (rSO_2)[108]) or surrogate measures of cerebral blood volume (i.e. NIRS derived changes in total haemoglobin concentration).[109] Such novel metrics have varying associations with PRx, with recent literature highlighting that they do not all behave similarly when evaluating using multi-variate co-variance techniques.[86] However, those derived from TCD and NIRS appear to be promising, as they seem to show significant association with PRx,[86,109–114] with both having varying degrees of pre-clinical validation in their ability to measure aspects of the CA curve.[29,31,38] Further, the ICP waveform can be processed for additional ICP-based CA metrics, using the fundamental amplitude of ICP

(AMP) to derive the pulse amplitude index (PAx; correlation between AMP and MAP)[21,22,115] or RAC (correlation (R) between AMP (A) and CPP (C)).[116] The utility of PAx and RAC remains unclear, though preliminary data suggests superiority in detecting impaired CA in patients where ICP remains low.[115] All of these MMM-based continuous CA metrics require focused research to determine their clinical utility.

To date, continuous characterization of CA impairment in moderate/severe TBI patients has been relegated to the acute-phase of ICU care, given the requirement of MMM of cerebral physiology in concert with invasive arterial line MAP monitoring. Reliance on such data streams has prevented such continuous data collection in the subacute or outpatient follow-up phases of care. If NIRS/TCD metrics are proven as close surrogates for PRx, generating these metrics with full waveform arterial blood pressure (ABP) data from finger-cuff based methods has been demonstrated to be feasible for the derivation of entirely non-invasive CA metrics. With this advent, we now have the ability to evaluate the association between acute-phase CA behavior and long-term CA, using similar measures. Further, such non-invasive metrics produce the capacity to perform CA follow-up assessments at the bedside or in the clinic setting, negating the need for expensive and poorly tolerated intermittent CA assessments using magnetic resonance imaging techniques.[117] Future investments in this emerging area is required to demonstrate ongoing feasibility and utility of such non-invasive continuous techniques.

Finally, as highlighted above, we currently do not have specific therapeutics for impaired CA.[54] Development of such precision interventions aimed at prevention and treatment of impaired CA will required extensive research into the molecular pathways driving dysfunction. Our current understanding around CA control mechanisms is predominantly focused on long-existing theories, where we refer the interested reader to the referenced literature for more details.[9,13,118–127] However, in short, current theorized mechanisms of CA control hinge on four main areas: myogenic, endothelial, neurogenic and metabolic. The myogenic theory focuses on tunica media calcium-mediated stretch response to changes in CBF, and is the most simplistic of current theories. The endothelial theory is predicated on CBF mediated shear-stress on cerebrovascular endothelial cells sparking vasoactive pathways, mediated through nitric oxide and endothelin driven vaso-motion.

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While the neurogenic theory rests on direct mono-amine based neural input on cerebral vessels, facilitating rapid changes in tone and diameter. Finally, the metabolic theory focuses on metabolic by-product build-up leading to alterations in vessel tone. However, the metabolic theory doesn't explain the rapidity of response seen in the cerebral vessels, given the time is takes for by-product build-up. Aside from these four existing core theories on CBF regulation, other aspects have emerged in TBI as potential modifiers of the above, including: host cerebral inflammatory response,[128–130] cortical spreading depression[131] and autonomic mediation.[132–135] In short, it is unlikely that a single theory explains all aspects of CBF/CA control, and the truth likely involved a combination of the above mechanisms.

As such, future work in this area will require integrating the MMM cerebral physiome, with genome/epigenome, protoeome and metabolome data with comprehensive patient demographics, injury, treatment and outcome data sources to uncover such molecular pathways and develop personalized therapeutic strategies.[9] As such, multi-disciplinary expertise in genomics/epigenomics, proteomics, metabolomics, cerebral physiomics and clinical epidemiology will be required in order to make progress. Further, integrative neuroinformatic approaches will be critical to make sense of such complex data streams, assuredly requiring application of artificial intelligence approaches.[136] Information gleamed from this approach may then be utilized in a "top-down" fashion to inform both cellular/small-animal and large animal pre-clinical platforms for precision pharmaceutical development directed at various pathways of CA dysfunction/failure. Work is currently underway to develop such comprehensive clinical data collection schemes and pipelines, as well as the pre-clinical infrastructure, for such future precision medication approaches in moderate/severe TBI care.[136–139]

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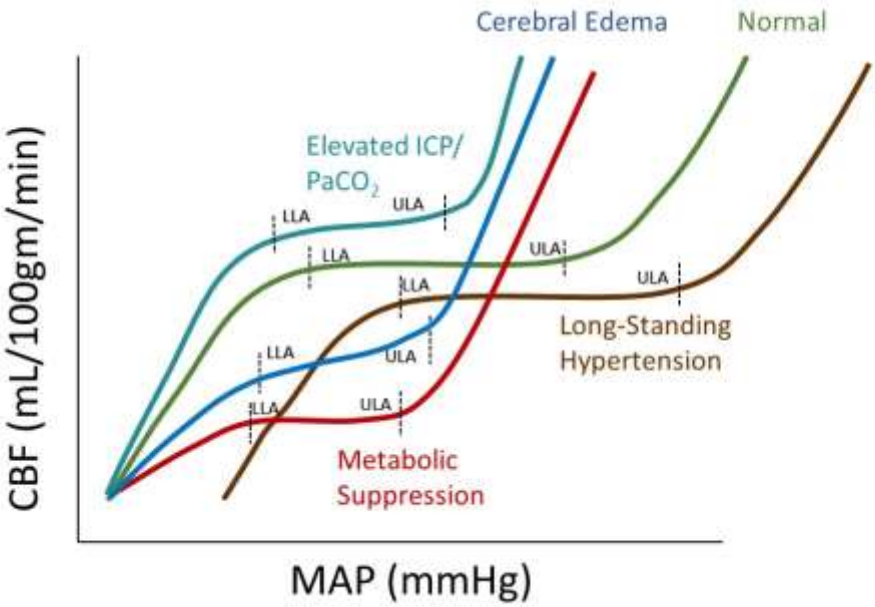

Figure 1: Theoretical Depiction of the Cerebral Autoregulatory Curve in Humans

CBF = cerebral blood flow, gm = gram, LLA = lower limit of autoregulation, MAP = mean arterial pressure, min = minute, mL = milliliters, mmHg = millimeters of Mercury, ULA = upper limit of autoregulation. Figure depicts the theoretical representation of the CBF vs. MAP relationship during normal and various physiology/pathophysiologic states. Note the change in shape of the curve based on different situations, with alterations in the position of the LLA, ULA, plateau and shape of plateau.

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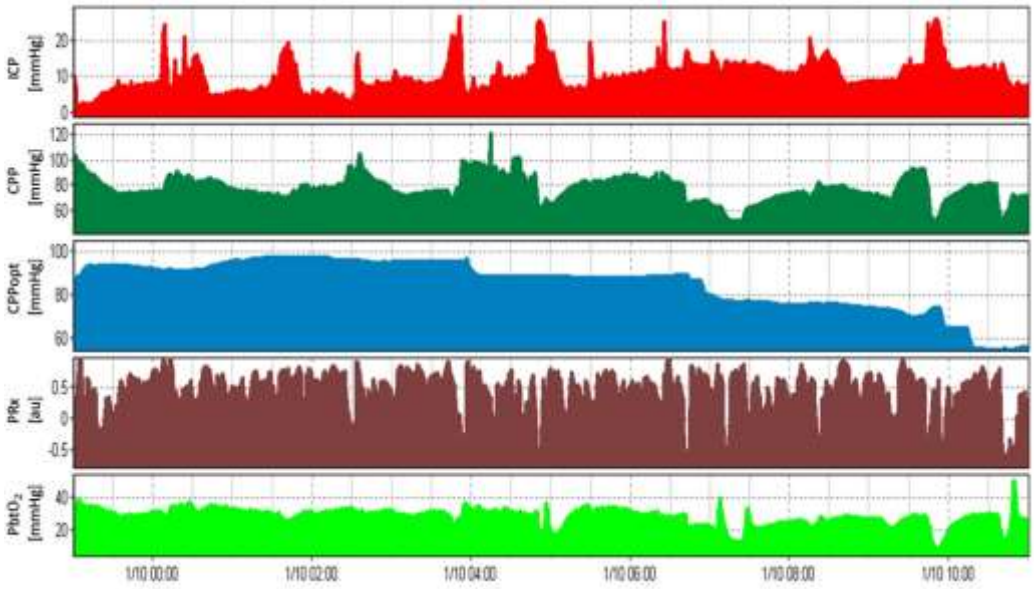

Figure 2: Example of High-Frequency Cerebral Physiology in TBI Patient

au = arbitrary units, CPP = cerebral perfusion pressure, CPPopt = optimal CPP (personalized CPP target based on real-time relationship between PRx and CPP), ICP = intracranial pressure, mmHg = millimeters of Mercury, PbtO2 = brain tissue oxygen, PRx = pressure reactivity index (correlation between ICP and mean arterial pressure (MAP)). Figure displays an example of real-time multi-modal cerebral physiology in TBI seen at the bedside, including continuous cerebral autoregulation measurement by deriving PRx. Patient data for this figure generation was utilized under existing research ethics approval at the University of Manitoba (REB #'s: H2017:181 and B2020:118).

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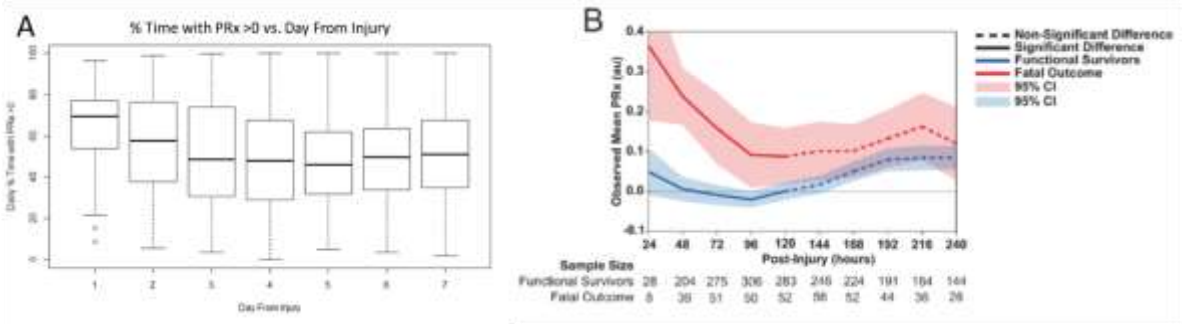

Figure 3: Daily Rates of Impaired PRx in Moderate/Severe TBI Patients

a.u. = arbitrary units, CI = confidence interval, PRx = pressure reactivity index (correlation between intracranial pressure (ICP) and mean arterial pressure (MAP)). Panel A - highlights that over the first 7 days of ICU stay over 50% of a patient's day is spent with PRx >0, based on a population of 249 patients (total of 1230 days of ICU stay). Figure is adapted (with permission of corresponding author) from open access CENTER-TBI publication of Zeiler et al. Acta Neurochir (Wein). 2019.[47] Panel B – represents the variation in daily mean PRx values based on time from injury in both those with fatal outcome (red) and those with functional outcomes (blue) at 6-months (based on cohort 601 moderate/severe TBI patients). Figure adapted with permission of authors from open access publication Adams et al.[39]

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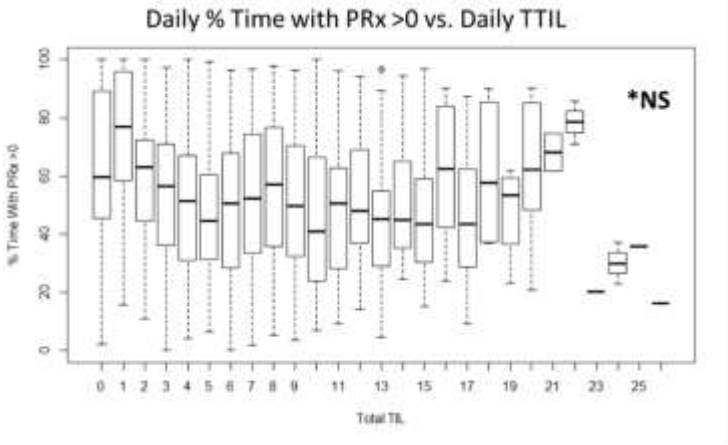

Figure 4: Daily Therapeutic Intensity and Impact of % Times with PRx Above 0

NS = not significant (Kruskal-Wallis testing), PRx = pressure reactivity index (correlation between intracranial pressure (ICP) and mean arterial pressure (MAP)), TTIL = total cumulative therapeutic intensity level score. Figure highlights that there is no association between daily therapeutic intensity and daily % time with PRx above zero, indicating treatment independence of PRx to current guideline-based therapeutic approaches in moderate/severe TBI (based on a population of 249 patients (total of 1230 days of ICU stay). Figure is adapted (with permission of corresponding author) from open access CENTER-TBI publication of Zeiler et al. Acta Neurochir (Wein). 2019.[47]

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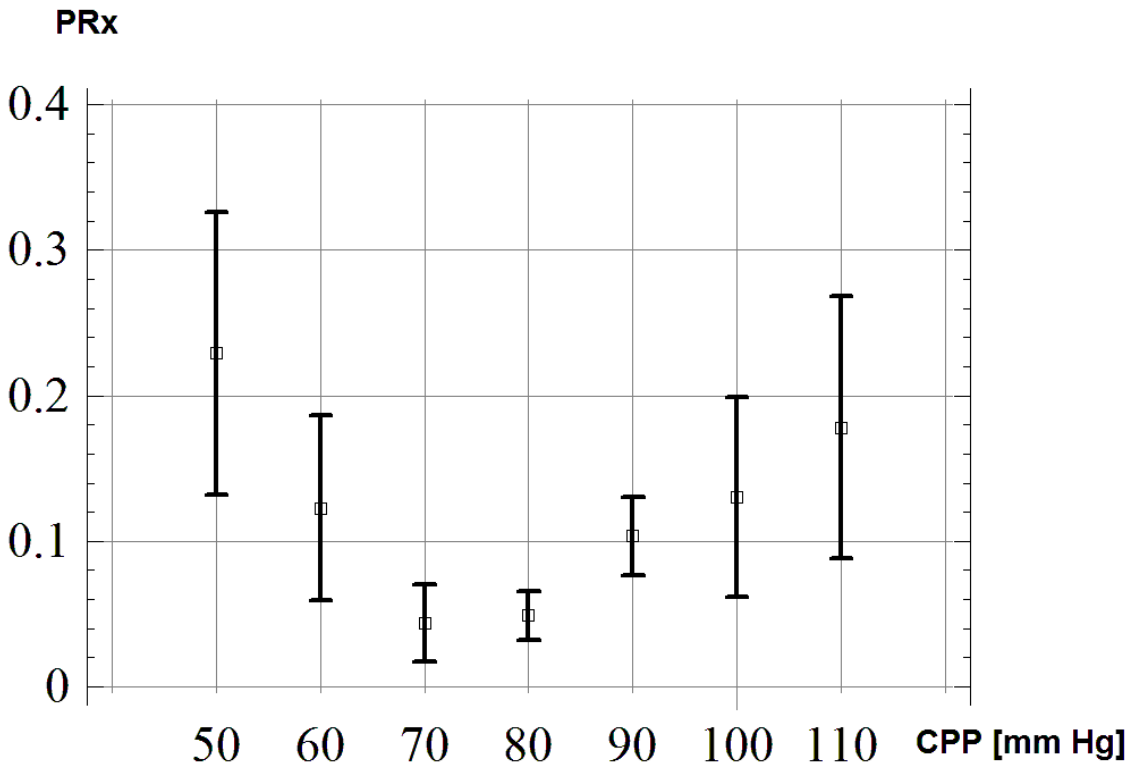

Figure 5: Population-Wide CPP vs PRx Relationship - 500 TBI patients

CPP = cerebral perfusion pressure, mmHg = millimeters of Mercury, PRx = pressure reactivity index (correlation between intracranial pressure (ICP) and mean arterial pressure (MAP)). Plot of over 500 patients reveals a U-shaped relationship between the vascular reactivity index (PRx) and CPP. Data used to generate this figure was obtained from the prospectively maintained cerebral physiology database at the University of Cambridge, where data is collected and entered in an entirely de-identified format for research purposes. Within this institution, patient data may be collected with waiver of formal consent, as long as it remains fully anonymized, with no method of tracing this back to an individual patient. Such data curation remains within compliance for research integrity as outlined in the Governance Arrangements for Research Ethics Committees (GAfREC) in the United Kingdom, September 2011 guidelines, section 6.0.

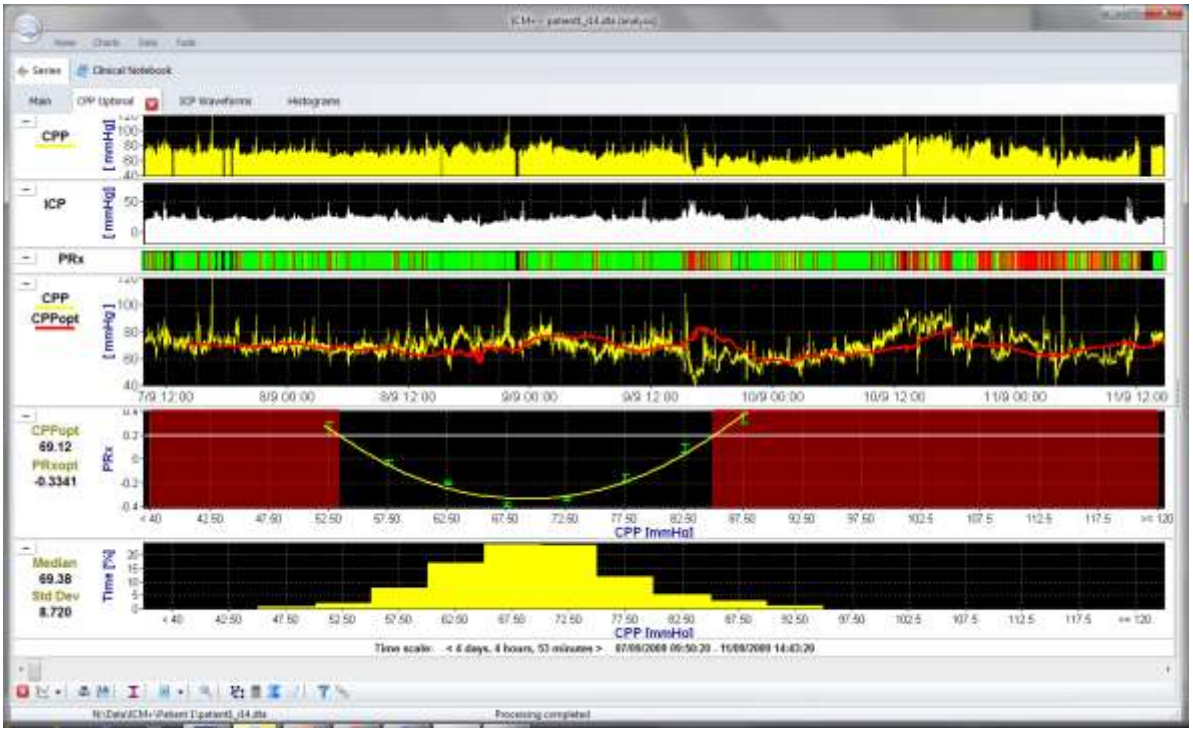

Figure 6: ICM+ Screen Shot – Patient Example of ICP, PRx, CPP and CPPopt Time Trends

CPP = cerebral perfusion pressure, CPPopt = optimal CPP, ICP = intracranial pressure, mmHg = millimeters of Mercury, PRx = pressure reactivity index (correlation between ICP and mean arterial pressure (MAP)). ICM+ screen shot showing trends of CPP, ICP, colour coded PRx (green and red), and the calculated CPPopt, in red in the bottom panel. Informed consent was obtained for observational data collection (study approval by medical ethical committee Maastricht number 16-4-243)

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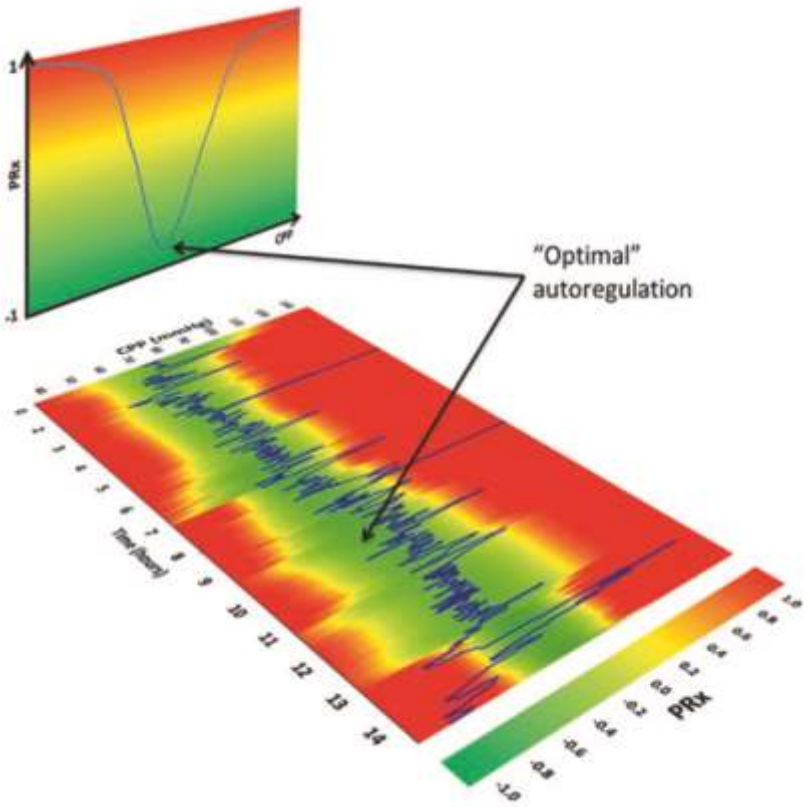

Figure 7: Concept of CPPopt Landscape Visualization

CPP = cerebral perfusion pressure, CPPopt = optimal CPP, mmHg = millimeters of Mercury, PRx = pressure reactivity index (correlation between intracranial pressure (ICP) and mean arterial pressure (MAP)). The vertical PRx-CPP colour gradient represents the colour-mapping scheme for PRx values. The blue line drawn on that colour map denotes the trajectory of the CPPopt curve fitted at that time point, and is coded in the PRx-CPP landscape map (horizontal), according to the colours it covers in the colour gradient (vertical). Figure adapted with permission from authors of Ercole et al. 2018.[74]

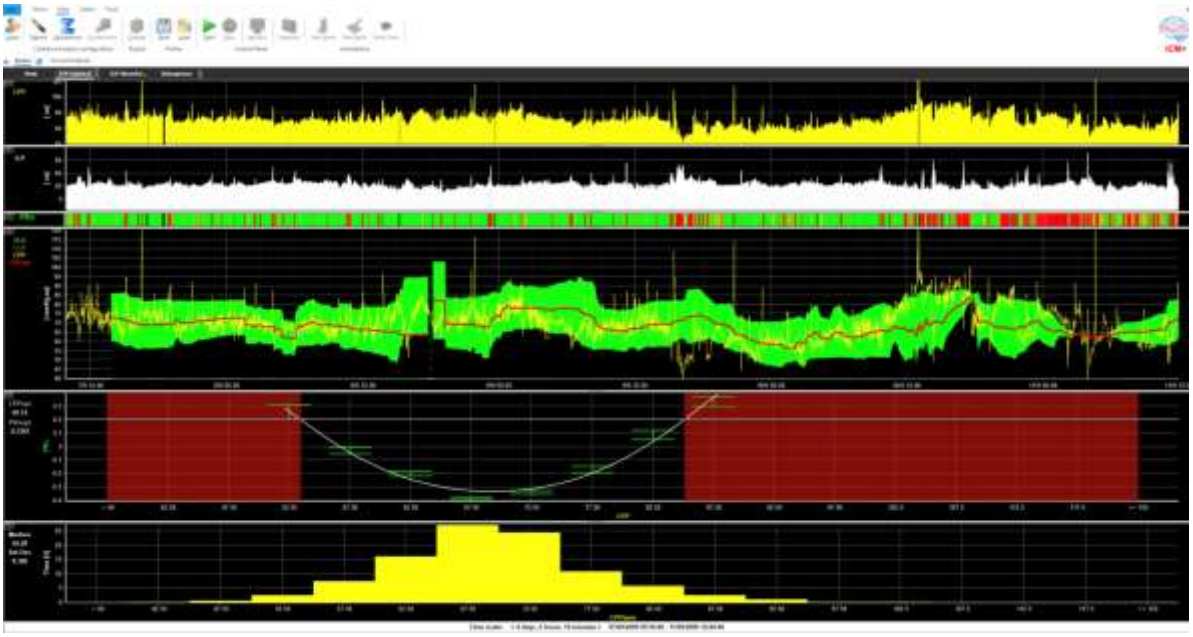

Figure 8: Patient Example of Time Trend of CPPopt, LLA and ULA Concepts

CA = cerebral autoregulation, CPP = cerebral perfusion pressure, CPPopt = optimal CPP, ICM+ = intensive care monitoring plus software, LLA = lower limit of autoregulation, mmHg = millimeters of Mercury, PRx = pressure reactivity index (correlation between intracranial pressure (ICP) and mean arterial pressure (MAP)), ULA = upper limit of autoregulation. Figure depicts a screenshot of ICM+ showing the trends of the upper and lower limits of autoregulation (the green band) and the CPPopt in the middle (red line) with the actual patients' CPP superimposed (yellow line). The second panel from the bottom shows an overall CPPopt chart (PRx vs CPP) over the total monitoring period, displaying a clear U-shaped character. The vertical, red bands, on both side of the curve denote CPP zones (ULA/LLA) with impaired reactivity using a threshold of +0.20 to define impaired CA (horizontal white line). Informed consent was obtained for observational data collection (study approval by medical ethical committee Maastricht number 16-4-243)

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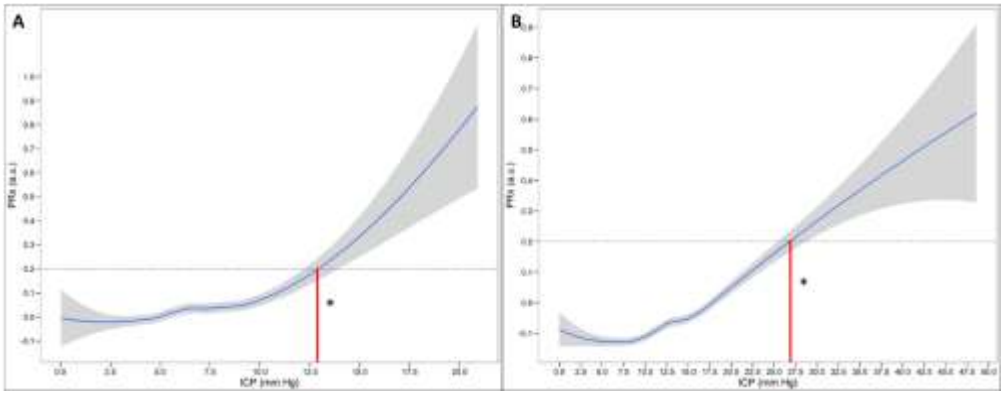

Figure 9: Examples of iICP Derivation in TBI

ICP = intracranial pressure, iICP = individualized ICP threshold, PRx = pressure reactivity index (correlation between ICP and mean arterial pressure (MAP)). Figure highlights two examples of iICP derivation in TBI patients, with Panel A demonstrating iICP threshold below 20 mmHg (*red line), and Panel B demonstrating iICP threshold of above 22 mm Hg (* red line). iICP is derived using the intersection between the locally weighted scatterplot smoothing ((LOWESS) function of PRx vs. ICP and the line PRx = +0.20. LOWESS function is depicted with 95% confidence intervals in grey. Data example from CENTER-TBI HR ICU cohort and adapted with permission of authors (figures not previously published).[79] Data used in these analyses were collected as part of the CENTER-TBI study which had individual national or local regulatory approval; the UK Ethics approval is provided as an exemplar: IRAS No: 150943; REC 14/SC/1370). The CENTER-TBI study (EC grant 602150) has been conducted in accordance with all relevant laws of the EU if directly applicable or of direct effect and all relevant laws of the country where the Recruiting sites were located, including but not limited to, the relevant privacy and data protection laws and regulations (the “Privacy Law”), the relevant laws and regulations on the use of human materials, and all relevant guidance relating to clinical studies from time to time in force including, but not limited to, the ICH Harmonised Tripartite Guideline for Good Clinical Practice (CPMP/ICH/135/95) (“ICH GCP”) and the World Medical Association Declaration of Helsinki entitled “Ethical Principles for Medical Research Involving Human Subjects”. Informed Consent by the patients and/or the legal representative/next of kin was obtained, accordingly to the local legislations, for all patients recruited in the Core Dataset of CENTER-TBI and documented in the e-CRF.

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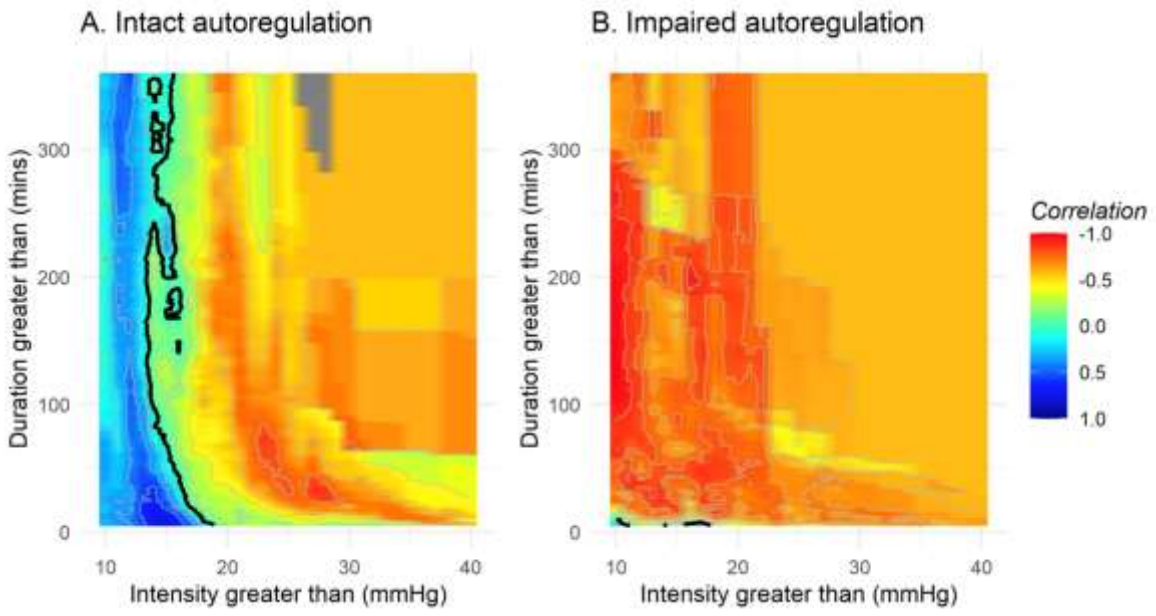

Figure 10: Example of Population Based ICP Insult Intensity Maps – Stratified by PRx Status

ICP = intracranial pressure, mins = minutes, mmHg = millimeters of Mercury, PRx = pressure reactivity index (correlation between ICP and mean arterial pressure (MAP)). Panel A – ICP insult intensity and duration in those with intact PRx (PRx <= +0.30), Panel B – ICP insult intensity and duration in those with impaired PRx (PRx > +0.3). Heat maps demonstrate the correlation (ranging from -1 (red) to +1 (blue) with Glasgow Outcome Score. Red areas indicate poor outcome, while blue areas indicate good outcomes. Figures demonstrate that with intact autoregulation, patients can tolerate longer duration and intensity of ICP elevations compared to those with impaired autoregulation. Reprinted with permission from open access publication corresponding author, Akerlund et al.[46]

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This paper has been peer-reviewed and accepted for publication, but has yet to undergo copyediting and proof correction. The final published version may differ from this proof.