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VIEWPOINT

Are We Ready for Clinical Therapy based on Cerebral Autoregulation? A Pro-con Debate

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Abstract

Cerebral autoregulation (CA) is a physiological mechanism that maintains constant cerebral blood flow regardless of changes in cerebral perfusion pressure and prevents brain damage caused by hypoperfusion or hyperperfusion. In recent decades, researchers have investigated the range of systemic blood pressures and clinical management strategies over which cerebral vasculature modifies intracranial hemodynamics to maintain cerebral perfusion. However, proposed clinical interventions to optimize autoregulation status have not demonstrated clear clinical benefit. As future trials are designed, it is crucial to comprehend the underlying cause of our inability to produce robust clinical evidence supporting the concept of CA-targeted management. This article examines the technological advances in monitoring techniques and the accuracy of continuous assessment of autoregulation techniques used in intraoperative and intensive care settings today. It also examines how increasing knowledge of CA from recent clinical trials contributes to a greater understanding of secondary brain injury in many disease processes, despite the fact that the lack of robust evidence influencing outcomes has prevented the translation of CA-guided algorithms into clinical practice.

Keywords: Cerebral autoregulation, Multimodality monitoring, Vasomotor reactivity, Carbon dioxide, Cerebral perfusion pressure, Pharmacology, Outcome

Introduction

Cerebral autoregulation (CA) is a physiological mechanism that accommodates and counterbalances changes in cerebrovascular dynamics, mean arterial pressure, and cerebral perfusion to maintain stable cerebral blood flow (CBF) and tissue perfusion. However, CA's stabilizing functions can only be maintained within certain physiologic bounds, and cerebral perfusion pressure (CPP) levels outside of this range can cause cerebral injury due to hypoperfusion, hyperperfusion, or other mechanisms. The first consolidated review on CA, a phenomenon described since the 1940s, was published in 1959 [1, 2]. Since then, a plethora of studies have investigated the range of systemic blood pressures at which cerebral vasculature alters intracranial hemodynamics to maintain cerebral perfusion [3–6].

CA was previously thought to be an "all or nothing" pressure–flow relationship measured by the change in CPP over different levels of a physiological stimulus, such as arterial blood pressure (ABP), but we now know it to be a complex dynamic phenomenon involving interplays and changes in cerebrovascular resistance via myogenic, neurogenic, endothelial, and metabolic responses [7]. Static measures of CPP changes measured by neuroimaging have paved the way for dynamic measures of autoregulation. The increasing knowledge of CA is fueling greater understanding of these complexities, enhancing our ability to translate the physiological complexity into clinical trials. CA-based targets in clinical

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paradigms may be the missing link in translational cerebrovascular physiology, which can help tailor hemodynamic management in acute brain injury. However, despite decades of research on the role of autoregulation, proposed clinical interventions to improve autoregulatory status have failed to show clear clinical benefit. As future trials are designed, it is critical to understand the underlying cause(s) of our inability to produce robust clinical evidence supporting the concept of CA-targeted management.

This review provides pro and con perspectives on various aspects of our understanding of CA, ranging from the technological aspects of assessing autoregulation to the current state of clinical trials using autoregulation-based targets. We describe technological advances in monitoring techniques that are rapidly improving our ability to translate the physiological complexity of CA into clinical trials, as well as provide critical insight into the accuracy of continuous assessment of autoregulation methods used in intraoperative and critical care settings today [8]. We discuss how recent clinical trials are increasing our understanding of CA, which is fueling greater understanding of secondary brain injury in many disease processes, but a lack of robust evidence impacting outcomes, particularly in traumatic brain injury, a disease in which most work has been done in CA, has prevented translation of CA-guided algorithms into clinical practice. Finally, even if CA-targeted management strategies improve outcomes, we need CA optimization interventions. We discuss the limitations of CA-targeted therapies in clinical trials, as well as why techniques such as hypocapnia and drugs such as statins or L-arginine have not demonstrated strong clinical efficacy.

Technological Aspects of Assessing CA

Pro: Technological Advances Enable Bedside Capture of Physiological Complexities of CA

Static Versus Dynamic Assessment of CA

Bedside evaluation of CA was initially focused on static measurements, assessed by evaluating CBF at two different mean arterial pressures (MAPs), which are manipulated using vasoactive drugs, or by physiological challenges expected to induce dynamic changes in CPP. Interestingly, the CA terminology has been used synonymously to represent carbon dioxide (CO_2) or vasomotor reactivity and neurovascular coupling between flow and metabolism, although experts emphasize CA to be restricted to cerebrovascular response to CPP changes. CA was once considered an "all or nothing" pressure–flow relationship evaluated by the change in CPP over different physiological stimulus levels, such ABP. We now comprehend the complexity and physiological applications of autoregulation thanks to dynamic neuroimaging assessments of CPP variations [7]. Interventions have been introduced to assess dynamic autoregulation using carotid compression tests [9] and Aaslid's thigh cuff deflation test to yield Tiecke's model for autoregulation index [10, 11]. Carotid compression test involves assessing middle cerebral artery (MCA) mean flow velocity(MF) measured by transcranial Doppler (TCD) in response to a short compression of a common carotid artery [9]. When autoregulation is intact, there is transient hyperemia, whereas when autoregulation is impaired, MFV returns to baseline without any active "overshoot." The MFV observed immediately after compression release to the precompression value is a good indicator of autoregulation [9]. Aaslid's thigh cuff deflation test is a dynamic approach that compares MAP and MFV assessed with TCD by using the rapid drops in ABP caused by the release of thigh blood pressure cuffs as an autoregulatory stimulus. Tiecke's model calculates an autoregulatory index based on CBF velocity (CBFV) and ABP values after cuff release. This index reflects the change in cerebrovascular reactivity per second in relation to the change in ABP. Higher autoregulatory values indicate increasingly better dynamic CA [11].

The availability of continuous measurement of slow wave oscillations of CBFV using TCD, continuous invasive intracranial pressure (ICP) monitoring using fiberoptic probes, local brain tissue oxygen concentrations, or various near-infrared spectroscopy (NIRS) modalities further allowed dynamic measurements over hours of physiological changes to be observed in critically ill patients. On the downside, it expanded the simplistic notion that CA is either present or absent, which is not true, as most clinically applied methods provide an index of autoregulation, which is a graded metric. On the upside, this elaborated that CA is a physiological phenomenon that engages at certain ranges of blood pressures and CO_2 values and has its own latency and efficiency in preserving CBF. The premise that acute brain injury causes progressive impairment in CA that first affects autoregulatory response led to an emphasis on assessing static as well as dynamic autoregulation. As early investigations brought forth the association of dynamic autoregulatory indices as predictive markers of neurological outcomes, further investment was fueled in this realm [8, 12].

Technological advances have allowed continuous acquisition of systemic hemodynamics using arterial line or end-tidal CO_2 monitors with time locked calibrated data displays. Multimodality monitoring (MMM) integrates these systemic parameters with intracranial metrics, such as ICP using fiberoptic probes, CBF surrogates using TCD-derived CBFV, or NIRS cerebral oximetry. Although the expertise in invasive cerebral monitoring

continues to be restricted to centers with neurosurgical expertise, noninvasive alternatives, such as point-of-care TCD, cerebral oximetry, and robotics-based TCD, have opened a potential for wider scalability of MMM by assessment of CA with low-risk portable devices. Initial attempts at discerning CA used visual display of parameters for autoregulation patterns as qualitative waveforms correlation (Fig. 1). These have now evolved into sophisticated data acquisition and display systems that can provide millions of high-frequency time-synchronized data points generated by continuous physiological variables in critically ill patients. Computational analytics and data management have also evolved to allow analysis of curated and harmonized data to generate usable metrics, such as the pressure reactivity index (PRx), the mean flow index (Mx), and the tissue oxygenation index (explained in subsequent sections).

Data Analysis for CA Assessment

Analytic concepts that have allowed the aforementioned metrics to be measured by the bedside have been validated in clinical algorithms. These include transfer function analysis or wavelet analysis [13], which rests on spectral analysis of gain and phase shifts and coherence between ABP and mean flow velocity. Time domain analysis, which measures a moving Pearson correlation coefficient over 30 time-averaged values of ABP and CBF velocity, proved to be particularly useful in continuous CA monitoring. PRx measures the response of small cerebral vessels to spontaneous changes of ABP as a moving correlation coefficient between changes in ICP and ABP [14]. Mxa is a moving correlation coefficient between spontaneous slow changes in ABP and slow changes in mean CBFV measured by TCD [15]. The cerebral oximetry index or tissue oxygenation index(COx) is derived from NIRS changes in response to ABP and is the correlation coefficient between blood pressure and cerebral oxygen saturation measured using NIRS [16]. Recently, there has been exploration into nonparametric methods, such as project pursuit progression, that characterize nonlinear relationships between ABP and CBF to define thresholds for these measures, in which changes in these

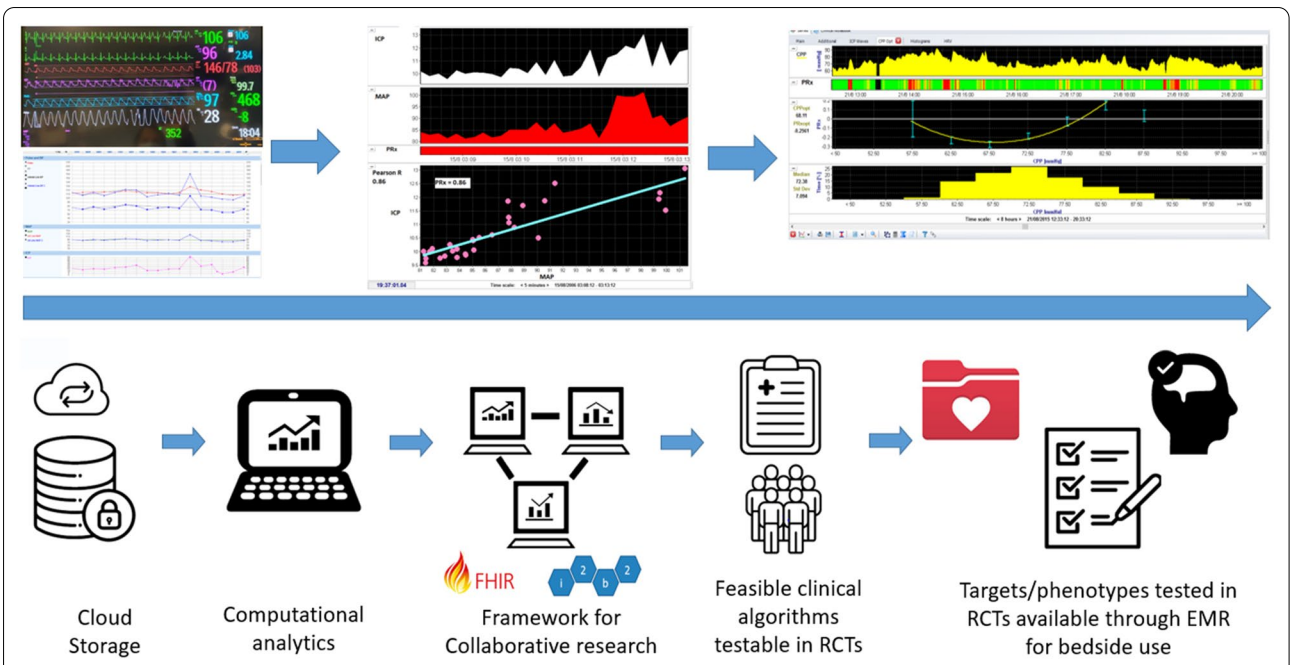

Fig. 1 The evolution of data acquisition and analytics has advanced to provide patient centric targets based on autoregulatory indices. Concomitantly, the informational technological framework is ready for prime time to allow testing of such patient centric targets in large, randomized control trials. Upper panel describes the early attempts at bedside visualization of mean arterial pressure (MAP) along with intracranial pressure (ICP) waveforms (left). Multimodality platforms (ICM+, Cambridge, UK) now allow visualization of moving correlation coefficient (PRx) between MAP and ICP to provide bedside visualization (middle). Dynamicity of PRx over systemic blood pressures showed a relationship plotting a U-shaped curve relationship between PRx and cerebral perfusion pressure (CPP). The most optimal CPP typically is the bottom of the U shape curve (right) hence called optimal cerebral perfusion pressure (CPPopt). Lower panel highlights the individual components of informatics support that had to evolve to support the evolution of bedside visualization shown in upper panel. Data storage on cloud that allowed big data analysis led to need for standardized data formats that allowed collaborative information exchange and creation of clinical algorithms that would be tested across multiple centers. Such framework can now be tested to create rigorous trials (e.g., BOOST-3, CogiTate) that test clinical algorithms that target patient specific autoregulation targets

relationship can be used to predict clinically meaningful autoregulatory indices [17]. Each of the aforementioned indices has a unique threshold for discerning impaired autoregulation, but overall, a positive correlation between systemic and cerebral hemodynamic parameters suggests impaired autoregulation. The advent of continuous MMM and the ability to synthesize hours of continuous data covering a wide range of physiological changes have allowed a clearer understanding of the complex, dynamic nature of autoregulatory phenomena. This has provided us guidance into ascertaining optimal CPPs and ABPs based on detection of point of best autoregulation potential, giving us the concept of the optimal CPP [18]. The optimal CPP is calculated by plotting a given autoregulation index (PRx, MXa, or COx) over a range of recorded CPP (or ABP, when ICP is not monitored) data over a 4-h period and identifying the CPP or ABP range where autoregulation is most preserved. The availability of such analytic capabilities has allowed us to formulate more detailed investigations, such as optimal CPP, that match the complexity of data obtained on cerebral hemodynamics.

Data Storage and Archiving

Advances in informatics have made it feasible to store high-resolution data generated from the aforementioned efforts. There has been significant work toward standardization of data software library and file formats that support large, complex, heterogeneous data (Hierarchical Data Formats). Efforts have been made to make open-source clinical data warehousing and analytics research platforms available to researchers more widely, a classic example being the Informatics for Integrating Biology at the Bedside data model. Further development of such framework for physiological metrics, such as CA, will allow collaborative exchange of information necessary for broader clinical translation. There are already ongoing efforts in standardizing data processing using deep learning that will allow scalability of CA data-based thresholds between sites. To expand availability of these measures to bedside use, a large data analysis framework has been created that allows individual patients' real-time autoregulation data to become available at the bedside. Currently, such technologies are expensive and require software such as ICM+ (University of Cambridge, Cambridge, United Kingdom, https://www.enterprise.cam.ac.uk/opportunities/icm-software-for-brain-monitoring-in-neurological-intensive-care-research/). However, bedside clinical monitoring integrating ICM+ or Moberg now allows clinician access to these data in real time to inform decisions. As most technologies progress, further advancements in creating application programming interfaces will facilitate bedside use of metrics such as optimal CPP, calculated through such software, and appear to be around the corner [19]. The excitement created by widespread availability of such technologies has fueled investigations into different disease processes concerning autoregulation and into revisiting established clinical algorithms and hypotheses to mitigate secondary brain injury.

Con: Accurate Assessment of CA and Autoregulation Indices is Still a Mystery

Availability

In parallel with evolving technology that allows widespread application of specific autoregulation-oriented therapies, we need to address the issue of limited availability and accuracy of metrics used in monitoring autoregulation.

Interventions added to assess dynamic autoregulation using carotid compression tests [9] and Aaslid's thigh cuff deflation test to yield Tiecke's model for autoregulation index [10, 11] have limited widespread scalability. The safety and validity of these tests in critically ill brain-injured patients has not been systematically investigated. Although technological advances have enabled more practical bedside continuous monitoring paradigms based on easy-to-monitor correlations between systemic and cerebral hemodynamic measures, MMM frameworks, data infrastructure for the large amounts of data generated, and computational support to provide physiological signals require large resource commitments that are not feasible for many medical centers unless the infrastructure becomes more affordable.

Accuracy

Feasibility of bedside availability of moving correlation coefficients such as PRx, Mx, or COx has encouraged a simplistic notion of CA as being either present or absent. Data have shown that these metrics are graded over a range, and singular thresholds for discerning impaired autoregulation is an oversimplification and may not be accurate in all clinical scenarios. For moving correlation indices assessed using continuous monitoring devices validated in critical care, such as the TCD-based Mxa, the 95% confidence limit for agreement between the left and right side of Mxa has been assessed as 0.18 (arbitrary units) [20]. This value can be taken to define the accuracy for Mxa. Specifically, if patient A has greater Mxa than patient B by more than 0.18, then we can state that patient A has worse autoregulation than patient B. Similar accuracy may be seen for PRx. In those rare cases when two intraparenchymal transducers are placed in both hemispheres, limit of agreement between left and right may be observed around 0.15–0.2 (unpublished data). This can be seen only in patients without substantial midline

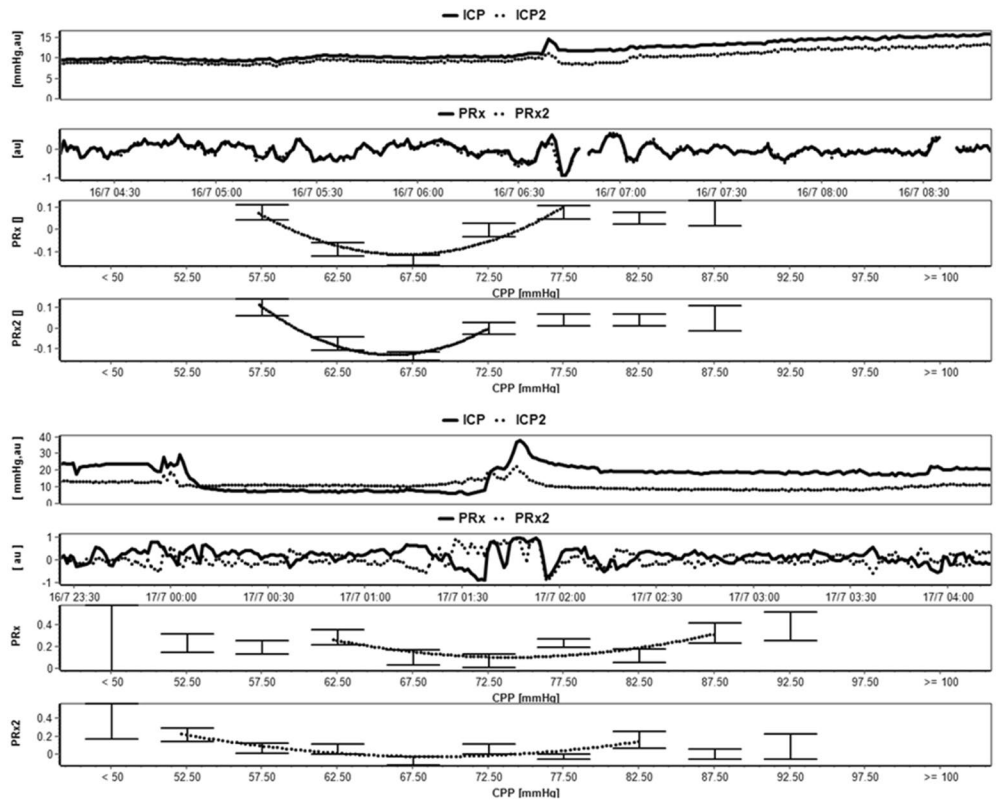

Fig. 2 Because cerebrovascular reactivity may be different in various compartments of the brain, discrepancy between left (PRx) and right (PRx2) may occur. On average optimal cerebral perfusion pressure (CPPopt) in two hemispheres is identical (**a**) but it may occasionally increase like in case (**b**), around 5-mmHg difference. We do not have robust guidance on which CPPopt is a valid target. ICP: Intracranial Pressure. **a** Good agreement between two hemispheres intracranial pressure (ICP) sensors (ICP, ICP2), PRx calculated from two ICPs (PRx and PRx2 line overlap) and CPPopt: 67 mmHg and CPPopt2: 65.5 mmHg. **b** Example of differences between two sensors in the same patient a day later. CPPopt differences: CPPopt 73 mmHg and CPPopt2: 67 mmHg

shift. When the brain structures are asymmetrical, this limit may increase (Fig. 2). Inaccuracy in the assessment of PRx and NIRS-derived indices produces errors of assessment of optimal CPP or optimal MAP. Generally, there is a lack of studies investigating the accuracy of estimating optimal CPP and optimal MAP with defined errors of estimation of used autoregulatory indices. Various methods have been studied to improve the accuracy of autoregulation monitoring. Wavelet-based indices [21] or use of positive end-expiratory pressure 1-min oscillations [22] was promising, but none of these techniques has been tested yet in clinical practice (Table 1).

Autoregulation as a Target for Therapy

Pro: Clinical Trials are Underway

The concept of autoregulation, first described more than half a century ago [1], has been a target for management of CPP in brain-injured patients (Table 2). The concept of individualized CPP has drawn growing interest, coinciding with the availability of tools that can potentially assess the intrinsic and specific autoregulatory capacity of each patient. The calculation of optimal CPP and MAP appears to be a useful application of CA assessment, as the individualization of CPP/MAP targets may minimize the risk of secondary brain damage and improve outcomes in traumatic brain injury (TBI) and non-TBI, allowing phenotyping of patients for prospective interventions [23]. Interestingly, underlying disease states such as traumatic injury, neurosurgical interventions, heart failure, diabetes, or hypocapnia may affect such correlations, emphasizing the need for more physiological data to be integrated into investigating predictive correlations of autoregulatory indices with outcomes [23]. Prospective studies are focusing on showing safety and feasibility of autoregulation-targeted clinical algorithms, which will lead to further investigations into the possibility of individualized hemodynamic targets and their relationships to outcomes. A recent systematic review focused on CA in cerebrovascular disease found 48 total studies: 23 studies on ischemic stroke, 18 studies

Table 1 Emerging clinical evidence of feasibility of cerebral autoregulation-targeted clinical algorithms and the use of autoregulation indices as a biomarker for prognostication

	Current evidence on autoregulation targeted clinical algorithms or Biomarker for prognostication	Feasibility data on testing autoregulation targeted therapy
TBI	CPP close to the optimal CPP (CPPopt) in patients with severe TBI associated with optimal brain tissue oxygenation [23, 28],better cerebral energy metabolism profile, and favorable outcomes [24, 25, 29, 30]	COGiTATE demonstrated the feasibility and safety of targeting an individual and dynamic CA-guided CPP in TBI patients without a concomitant increase the therapeutic intensity level [27, 32]
SAH	Impaired CA in SAH associated with delayed cerebral ischemia, vasospasm, and unfavorable outcome [28–30, 33-35]	Feasibility of CPPopt assessment in patients with severe SAH demonstrated [31, 36]
Hemorrhagic stroke	Serial decline in autoregulatory parameters correlate to outcomes in hemorrhagic stroke [34, 39]	Feasibility of hypercapnia-induced improvement in CA in small volume ICH patients without intraventricular hemorrhage [37, 42]
Acute ischemic stroke	Impaired CA in the very early phase of AIS predicts poor response to intravenous thrombolysis [39, 44]. BP exceeding individual CA threshold following reperfusion in LVO associated with hemorrhagic transformation and worse functional outcome in a time-dependent manner irrespective of final infarct volume [40, 41, 45, 46]	Patients with LVO causing AIS undergoing thrombectomy, the feasibility of continuous estimation of optimal BP with CA assessment using an NIRS-derived tissue oxygenation index [45]
Sepsis-associated encephalopathy	Impaired CA independently predicted adverse neurological outcomes and sepsis-associated encephalopathy [48–50]	TCD-derived MXa or NIRS-derived COx can identify optimal MAP in patients with sepsis-associated encephalopathy [42, 43, 47, 48]
Perioperative hemodynamic management	Reduction in the frequency of postoperative delirium after surgery in patients with CA-guided management [52, 53]	Patients older than 55 years undergoing nonemergency cardiac surgery randomized to maintaining MAP during CABG based on the patient's lower limit of CA or standard practice [53]

AIS, acute ischemic stroke, BP, blood pressure, CA, cerebral autoregulation, CABG, xxx, COGiTATE, xxx, COx, xxx, CPP, cerebral perfusion pressure, ICH, xxx, LVO, large vessel occlusion, MAP, mean arterial pressure, MXa, xxx, NIRS, near-infrared spectroscopy, SAH, subarachnoid hemorrhage, TBI, traumatic brain injury, TCD, transcranial Doppler

Table 2 Main parameters studied and failure in the clinical applications

Parameter	Potential effect on autoregulation	Failure
Carbon dioxide	Hypocapnia has been suggested to reduce intracranial pressure and improve cerebral autoregulation. It is still not clear how hypocapnia affects upper autoregulation limit	Decrease in PaCO2 may cause ischemia, particularly after TBI, in which control of CBF distribution may be affected locally (mainly by CBF steal phenomenon). The optimal target of PaCO2 is not clear, and its effect on cerebrovascular reactivity has not shown consistent results
Cerebral perfusion pressure/arterial blood pressure	Individualized management of cerebral perfusion pressure and definition of optimal range of autoregulation can improve patients' cerebrovascular dynamics and minimize secondary brain damage. A phase II trial (COGITATE) showed that active control of cerebral perfusion pressure to follow dynamically monitored optimal cerebral perfusion pressure is safe and feasible	No randomized studies are available to confirm that a cerebral perfusion pressure-targeted therapeutic approach can improve patients' outcome. We need to be humble and wait for results of such trials
Statins administration after SAH	Single center randomized study indicated that statins may improve cerebral autoregulation, reduce DIND, and improve neurological outcome after SAH	A phase III multicenter trial (STASH) did not confirm any advantage of statin therapy after SAH on functional outcomes
Continuous monitoring of PRx, Mx, and COx	Autoregulation indices, such as PRx, may be monitored continuously. Noninvasive monitors of pressure reactivity (MX with TCD, and COx with NIRS) are of use in clinical practice	Accuracy of indices of autoregulation is limited. Methods of improving accuracy (use of wavelet PRx and PEEP waves) are not used in clinical practice; they are just nice publications
L-arginine	L-arginine is a potential mediator of cerebrovascular autoregulation. Phase I/II clinical trials and preclinical studies suggest that agents impacting L-arginine metabolism may prevent intracranial pressure elevation and improve neurologic outcomes in TBI and ICH	Other agents have shown varying results, and there is currently no phase III clinical trial that has confirmed functional outcome improvement with any of these agents in any condition

CBF, cerebral blood flow, COGITATE, xxx, COx, xxx, DIND, xxx, ICH, xxx, Mx, mean flow index, NIRS, near-infrared spectroscopy, PaCO2, partial pressure of carbon dioxide, PEEP, positive end- expiratory pressure, PRx, pressure reactivity index, SAH, subarachnoid hemorrhage, STASH, Simvastatin in aneurysmal subarachnoid haemorrhage, TBI, traumatic brain injury, TCD, transcranial Doppler

on aneurysmal subarachnoid hemorrhage , five studies on ICH, and two studies on systemic hypertension [3]. Another review focused on non-brain-injured patients found an additional 22 studies on septic shock, intraoperative monitoring, and the pediatric population [4].

Traumatic Brain Injury

The Brain Trauma Foundation guidelines recognize that the minimum optimal CPP threshold is unclear and may depend on the autoregulatory status. Current guidelines suggest a CPP target of 60–70 mmHg in patients with TBI [24] and a MAP challenge to assess autoregulatory status to recommend optimal CPP targets for the management of intracranial hypertension [24]. In 2002, Steiner et al. [18] proposed an algorithm to evaluate individualized optimal CPP based on distribution of PRx. The Seattle International Severe Traumatic Brain Injury Consensus Conference recommended a consensus management algorithm that incorporated the assessment of CA to define individual CPP goals in patients with TBI [25]. However, CA may evolve with the temporal evolution of TBI, and hence continuous assessment of CA to identify optimal CPP for blood pressure titration may be a more useful and appropriate target for interventions [18, 26]. A retrospective analysis showed that CA varies according to CPP and that greater deviations of CPP from optimal CPP were associated with worse clinical outcomes. Since then, the calculation of optimal CPP using automated software has been progressively refined. Current approaches consist of the application of an advanced computerized algorithm that continuously estimates the indexes representing the relationship between CPP/MAP and the surrogate of strength of CA (such as PRx, COx, etc.), with continuous updating of the optimal CPP curve as a target [27].

Maintaining CPP close to the optimal CPP in patients with severe TBI has been shown to be associated with optimal brain tissue oxygenation [28], a better cerebral energy metabolism profile [29], and favorable outcomes [30]. Additionally, previous studies have demonstrated that patients with impaired CA (high PRx) have better outcomes if treated with ICP-guided therapy with relatively lower CPP targets, whereas patients with intact CA (low PRx) benefit from CPP-guided therapy with relatively higher CPP targets [31].

A recently published CPPopt Guided Therapy: Assessment of Target Effectiveness((COGiTATE) study (a phase 2 trial) randomized 28 patients with TBI to current guidelines management and 32 patients to autoregulation-guided CPP management [27]. The primary end point was feasibility, evaluated as the percentage of time of patients spent with CPP concordant (within 5 mmHg) with the defined CPP targets, with secondary outcomes being safety and an increase in the therapeutic intensity level. The trial demonstrated the feasibility and safety of targeting an individual and dynamic CA-guided CPP in TBI patients without a concomitant increase in the therapeutic intensity level [32]. It also found that when the dynamic optimal CPP was targeted, patients spent a significantly higher percentage of time with CPP concordant with the set CPP target given by optimal CPP [32]. The clinical outcomes of patients with and without dynamic CA-guided CPP management were comparable, but the trial was not designed to assess outcomes [32]. The current evidence indicates that CA-guided management leads to optimization of cerebral physiology after TBI and is safe and feasible but needs a phase III study to prospectively demonstrate the potential outcome advantage of real-time CA-guided management.

Subarachnoid Hemorrhage

Impaired CA in subarachnoid hemorrhage (SAH) is well known to be associated with delayed cerebral ischemia, vasospasm, and unfavorable outcome [33–35]. The feasibility of optimal CPP assessment in patients with severe SAH has also been demonstrated [36]. As expected, a CPP below optimal CPP is associated with low CBF [37]. In fact, the autoregulatory status may evolve with the development of cerebral vasospasm, indicating the need for more individualized blood pressure goals and hence optimization of cerebral physiological milieu. Nevertheless, concrete evidence showing improvement in clinical outcomes with CA-guided therapy is lacking.

Intracranial Hemorrhage

Dynamic CA has been showed to be impaired bilaterally in patients with supratentorial hemorrhage for up to 12 days since onset, especially in the presence of small vessel disease, and slowly recovers over a month [38–40]. Autoregulatory indices derived from ICP and ABP (PRx), as well as CBFV, ABP (Mx), and serial decline in these parameters, have shown to correlate with poor clinical status in ventricular hemorrhage and poor clinical outcomes in hemorrhagic stroke [39]. Larger hematoma volumes tend to have poor CA ipsilateral to the hematoma [39, 41]. A recent experimental study, BREATHE-ICH, explored the feasibility of hypercapnia-induced improvement in CA in small-volume ICH patients without intraventricular hemorrhage [42].

Acute Ischemic Stroke

CA impairment has been shown to occur in different subtypes of ischemic stroke but generally improves after successful recanalization [43]. Impaired CA in the very early phase of acute ischemic stroke (AIS) increases the likelihood of poor response to intravenous thrombolytic

therapy, as assessed by an National Institute of Health Stroke Scale (score at 24–48 h [44]. Autoregulation assessment early after AIS may be a potential strategy to predict response to thrombolytic therapy, which may have implications for planning neuroprotective strategies and additional interventions. Further, in patients with large vessel occlusion undergoing thrombectomy, the feasibility of continuous estimation of optimal ABP with CA assessment using the NIRS-derived tissue oxygenation index has been demonstrated [45]. Using this approach, blood pressure exceeding the individual CA threshold following reperfusion is associated with hemorrhagic transformation and worse functional outcome in a time-dependent manner irrespective of the final infarct volume [45, 46]. However, the feasibility of personalized blood pressure management targeting a dynamic optimal blood pressure and its impact on outcomes in patients with AIS needs further investigation.

Sepsis-Associated Encephalopathy

CA monitoring with TCD-derived Mxa is moving correlation coefficient or NIRS-derived COx has been used to identify optimal blood pressure in patients with sepsis-associated encephalopathy and reveals that optimal blood pressure varies between patients and within patients over time during sepsis [47, 48]. Studies have shown that CA is impaired more often in patients with sepsis-associated encephalopathy than in patients with sepsis without encephalopathy and that impaired CA independently predicts adverse outcomes [48–50]. This makes CA-guided hemodynamic management an attractive approach to optimize and individualize cerebral physiology in this population [47, 51].

Perioperative Management in Coronary Bypass

Another interesting avenue for CA-based therapy is during the intraoperative period. Patients undergoing cardiac surgery (especially those who require cardiopulmonary bypass) are known to be at an increased risk of perioperative neurological complications and exposure to blood pressure below the autoregulatory limits. Hence, rather than empiric blood pressure targets, there has been an interest in a personalized approach to hemodynamic management using bedside CA monitoring. A recent randomized control trial investigating perioperative management during cardiopulmonary bypass surgery with CA-guided management [52] did not find a reduction in the frequency of the composite end point of neurological complications (clinical stroke, restricted diffusion weighted imaging lesions, or change from baseline cognitive score) on those with target MAP based on CA monitoring and those without. Interestingly, it noted a reduction in the frequency of delirium and better performance on tests of memory 4–6 weeks after surgery in patients with CA-guided management [52]. More recently, in a trial involving patients older than 55 years undergoing nonemergency cardiac surgery, patients were randomized to maintaining MAP during cardiopulmonary bypass based on the patients' lower limit of CA or to standard practice [53]. The odds of the primary outcome of the incidence of postoperative delirium were reduced by 45% in patients randomized to the autoregulation group [53]. Given the significant burden and impact of postoperative delirium in surgical patients and the lack of agreement on the appropriate blood pressure target during cardiopulmonary bypass, monitoring CA during surgery provides an alternative, practical method to individualize the blood pressure goals. Similar work has shown utility of determining the ABP-dependent limits of autoregulation in the pediatric population and Extracorporeal Membrane Oxygenation population [54, 55].

There is ongoing work examining similar CA-based approaches in other surgical populations, for example, older patients undergoing spine surgery. Whether this approach is effective in those populations remains to be seen.

Con: Lack of Level I Evidence for Optimal CPP/ABP-Oriented Management in TBI

Despite all aforementioned efforts, strategies aimed at preserving or restoring CA based on optimal blood pressure in neurocritical care have not as yet produced class I evidence for improving outcomes [18]. Several observational studies suggest potential benefit from determining optimal CPP to improve outcomes in critical care [26]. A recent systematic review [56] found a large number of observational studies that had tried to determine the feasibility of finding patient-specific optimal CPP to obtain optimal MAP or CPP at the patients' bedside in different clinical scenarios, such as TBI, SAH, intracerebral hemorrhage, and hypoxic encephalopathy. These studies suggested that both the duration and the magnitude of deviations in the difference between CPP and optimal CPP were associated with unfavorable outcomes. More conclusive evidence exists for intraoperative optimization of MAP during cardiac surgery in that a recent multicenter trial produced at least partially positive results [52]. However, the application of the optimal CPP to guide management of critically ill patients still needs data from randomized controlled trials.

The recently published CPPopt Guided Therapy: Assessment of Target Effectiveness((COGiTATE) study randomized patients with TBI to current guidelines management in a control arm and autoregulation-guided CPP management in a control arm [32]. The primary

end point of feasibility was achieved, and CPP in the intervention group was in the target range for 46.5% of monitored time, without an increase in the therapeutic intensity level. However, the study was underpowered for clinical outcomes and does not justify the application of protocols based on optimal CPP/MAP.

Despite numerous experimental and clinical studies investigating CA and its application [57], there is still no definite proof that using autoregulation as a clinical marker improves functional outcome in most acute neurological diseases (Fig. 3). Therefore, at present, autoregulation-directed clinical management cannot currently be part of routine clinical practice, and it should be evaluated by large prospective randomized controlled trials to assess effects on patient outcomes.

Interventions for Modulating Autoregulation

Con: Failures of Autoregulation-Targeted Interventions

We acknowledge that the existence of autoregulation as a physiological mechanism has been demonstrated and described in almost countless experimental and clinical studies. Even if we find definitive proof that using autoregulation as a clinical marker improves outcomes in any acute neurological disease, we need interventions that will help us modulate autoregulation to desired parameters. We do not have these interventions. A classic example is a failure of hypocapnia as a strategy to lower cerebral blood volume to reduce elevated ICP and, at the same time, improve CA by shifting the lower limit of autoregulation to lower values. Theoretically an ideal strategy, this intervention has been shunned by neurocritical caregivers because of the risk of regional ischemia. Pharmaceutical therapies targeted at autoregulation, such as statins or L-arginine, have not shown clinical efficacy in acute neurological diseases.

A significant number of investigations have been conducted to investigate CA-targeted therapies that have not yielded positive results. A good example is the failure of hypocapnia as a strategy to lower cerebral blood volume, thereby reducing elevated ICP and, at the same time, improving CA by shifting the lower limit of autoregulation to lower values of CPP [58]. Theoretically, it looks almost ideal, but because of the risk of regional ischemia in the presence of a vascular bed with heterogeneous reactions to changes in CO_2 levels, it is prohibited in neurocritical care, especially in severe TBI [59]. Autoregulation-targeted medications, such as statins (in SAH) or L-arginine, have not shown definitive clinical efficacy in acute neurological diseases. A critical insight is needed into the failure of such interventions as we address improving the poor accuracy of

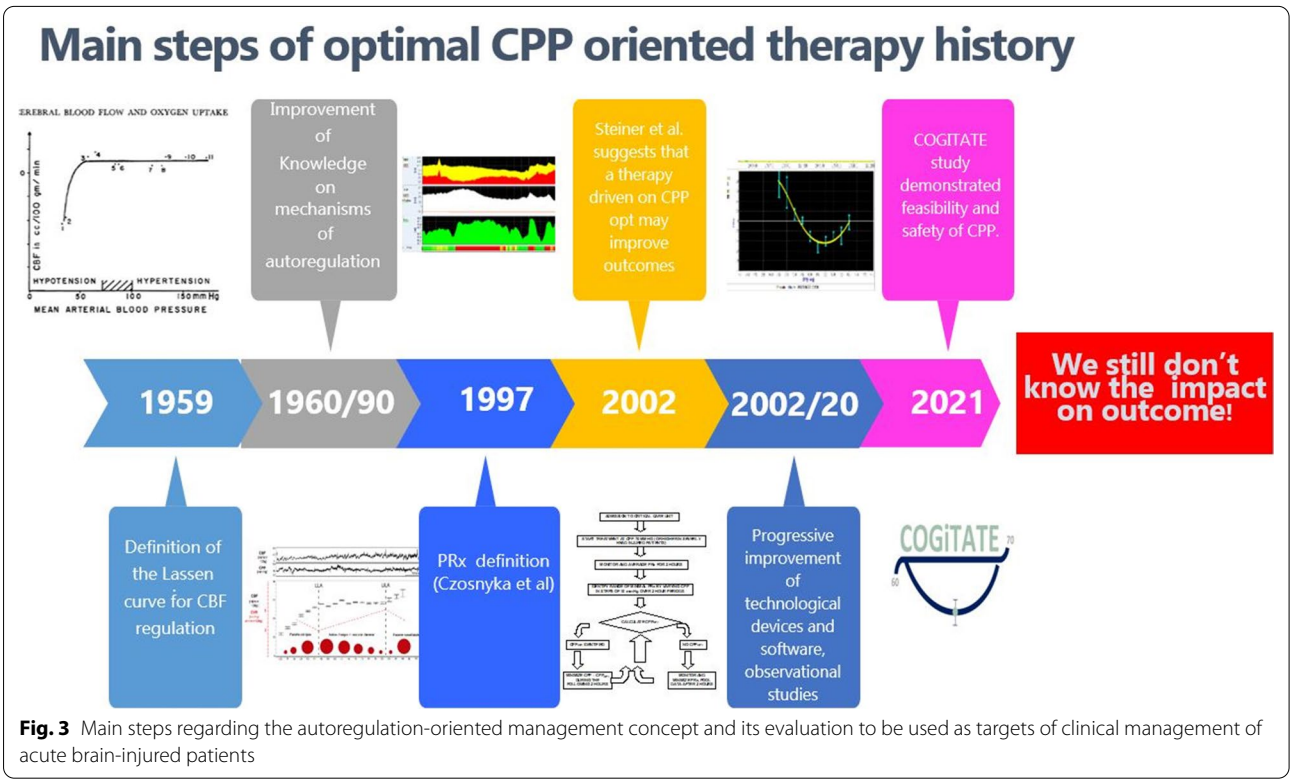

Fig. 3 Main steps regarding the autoregulation-oriented management concept and its evaluation to be used as targets of clinical management of acute brain-injured patients

continuous assessment of autoregulation methods used currently in neurocritical care units and intraoperatively (Fig. 3).

Mild Hypocapnia

The exact mechanisms modulating CA are complex and not completely understood. The literature generally considers the following pathophysiological mechanisms:

1. Endothelial and myogenic function is one of the most studied mechanisms and is related to the mechanical receptors of endothelial cells that change consequent to stress and transmural pressure and regulate the production of nitric oxide (NO) and endothelin to control the tone of smooth muscle cells and modify the vascular tone/diameter in response to MAP changes to maintain constant CBF.
2. The cerebral vessels receive afferent and efferent nerve terminations that modulate the cerebrovascular tone through neurogenic mechanisms [60].

Cerebrovascular reactivity is importantly regulated by other variables, in particular, partial pressure of oxygen and partial pressure of carbon dioxide (PaCO2). Both arterial hypoxia and hypercapnia can precipitate cerebral hypoxemia and can cause a compensatory cerebral vasodilation, whereas hyperoxia and hypocapnia can lead to cerebral vasoconstriction and thus affect the shape, length, and position of the plateau in the Lassen curve [61–63]. Because PaCO2 is one of the most important modulators of vascular tone and CA, its role in the management and optimization of autoregulation has been widely studied, with the aim to assess the values of PaCO2 (the upper and lower limits) beyond which cerebrovascular reactivity is altered [64–66]. Some authors have explored this issue with physiological studies, suggesting a potential role of hypocapnia in reducing ICP and optimizing cerebrovascular reactivity. In an experimental study from Harper et al. evaluating cerebral reactivity and cerebrovascular diameter at different levels of PaCO2, CBF did not decrease further below a PaCO2 of 20 mmHg after induction of hyperventilation, and maximum dilatation was reached beyond a PaCO2 of 80 mmHg [67]. However, when MAP was reduced, the increase in blood flow on raising PaCO2 from 40 to 80 mmHg was only 50% of the capacity compared to normotensive experiments and did not change at all for MAP below 50 mmHg. This suggests that in conditions of hemodynamic instability, modulating PaCO2 values to manipulate CBF may not be able to optimize CBF but instead could have deleterious effects. Hypocapnia may shift the lower limit of autoregulation to lower values of MAP, in this way extending the range of autoregulation.

Some studies suggest that hyperventilation can lead to reduced CBF, increased ischemic burden, and worse outcome [64, 66]. This has led physicians to recommend hyperventilation only in extreme life-threatening situations with high risk of cerebral herniation and only for limited periods [24]. However, other evidence suggests that brief hyperventilation, despite causing reductions in CBF, does not affect energy failure [65]. In fact, a recent substudy of the CENTER-TBI project demonstrated that the use of hyperventilation does not affect patient outcomes [68], and the recent Seattle algorithm recommends the use of PaCO2 values of 32–35 mmHg in case of refractory intracranial hypertension, possibly together with the use of additional advanced multimodal neuromonitoring for the evaluation of cerebral oxygenation and metabolism [69]. Thus, at present, the clinical use of modulating PaCO2 to reduce intracranial hypertension and optimize CA remains under debate.

Statins

Statins have been investigated for their impact on autoregulation independent from their effect on lowering cholesterol level. Early experimental studies indicate that individuals treated with statins have a stronger autoregulatory response probably through upregulation of endothelial NO synthase [70]. It is well documented that effective cerebrovascular protection from a short treatment course of statins after aneurysmal SAH may function through cholesterol-dependent mechanisms, in addition to the cholesterol-independent pathway. This was a subject of a single-center randomized trial showing better neurological outcome in patients treated with statins [71]. Secondary analysis of the results has shown that the neuroprotective effects of acute treatment with pravastatin following aneurysmal SAH are associated with the enhancement of autoregulation [71]. A routine and daily assessment of CA using the transient hyperemic response ratio may help identify patients at high risk of delayed ischemic neurological deficit . However, the phase III multicenter Simvastatin in aneurysmal subarachnoid haemorrhage(STASH) trial did not detect any benefit in the use of simvastatin for long-term or short-term outcome in patients with aneurysmal SAH [72]. Despite demonstrating no safety concerns, it has been concluded that patients with SAH should not be treated routinely with simvastatin during the acute phase. Therefore, another attempt to use autoregulation-oriented medication in acute neurological disease failed.

L-arginine

L-arginine is a potential mediator of vascular autoregulation based on its role as a substrate for several enzymatic pathways involved in the production of NO and L-citrulline, which are catalyzed by NO synthases (NOS) [73]. NO is a potent vasodilator and contributes to maintenance of resting CBF and cerebrovascular reactivity to metabolic activity [74]. Depletion of L-arginine can lead to disturbances in the NO pathway through oxidative stress due to uncoupling of NOS resulting in oxygen radical formation [75]. NO depletion can enhance neuroinflammation, and arginase, a direct competitor with NOS, may promote inflammation by decreasing cellular NO, which enhances the Nuclear Factor NF-kβ pathway and contributes to endothelial dysfunction [76]. Deficiency of NO may also result in vasoconstriction of cerebral vessels, causing decreased CBF or even ischemia.

Impairment of the NO pathway leads to reduction in vasoactive responses in experimental TBI, which can be rescued by either L-arginine supplementation or arginase inhibition [77]. Cationic arginine-rich peptides, such as polyarginine-18, were found to reduce axonal injury in experimental TBI but without improvement in hippocampal neuronal loss or functional outcome [78]. Clinically, reductions in L-arginine concentrations have been associated with unfavorable clinical outcome in intracranial hemorrhage, SAH, and TBI, although increases in systemic L-arginine are described after the acute phase [73]. NO accumulates in the brain, both immediately after injury due to endothelial NOS and neuronal NOS and again several hours to days later [75]. Excess production of NO could result in cytotoxicity because NO is metabolized to peroxynitrite. The immediate increase in NO by neuronal NOS can be inhibited by preinjury 7-nitroindazole, which has been shown to improve neurologic outcome in TBI models [79]. However, treatment with NOS inhibitors, such as L-NG-Nitro arginine methyl ester (L-NAME) or 7-nitroindazole (7-NI), during the early postinjury time has been disappointing and inconsistent [79]. The initial NO peak is followed by a period of low NO levels associated with low CBF, during which L-arginine administration can improve both CBF and outcomes in experimental models by restoring NO levels [79]. Finally, a late peak in NO after TBI is thought to be due to inducible NOS, which can be inhibited with neuroprotective effects.

Recent clinical trials investigating therapeutic strategies with L-arginine metabolism have yielded varying results. Inhibition of NOS by the endogenous metabolite, asymmetric dimethylarginine, a product of L-arginine methylation, had detrimental effects on vasospasm after aneurysmal SAH [79]. Several exogenous agents have been investigated in phase I/II clinical trials. VAS203 (Ronopterin), an inhibitor of NOS at the tetrahydrobiopterin cofactor binding site (as opposed to the L-arginine binding site), is currently under evaluation in the phase III trial called Efficacy of VAS203 (Ronopterin) in Patients With Moderate and Severe Traumatic Brain Injury(NOSTRA-III) (ClinicalTrials.gov Identifier: NCT02794168) for moderate to severe TBI. Preclinical evaluation in a mouse TBI model showed that intravenous administration prevented ICP elevation and a decrease in CBF without impacting MAP and with significant neurologic improvement after 6 days [80]. Mechanistically, VAS203 appears to contribute to prevention of posttraumatic arteriolar vasodilation and therefore inhibition of endothelial NO production. A phase II clinical trial called NOSTRA (NCT02012582) conducted in 32 patients showed a reasonable safety profile but no significant impact on ICP, CPP, or partial brain oxygen pressure compared to placebo-treated patients [81]. Nevertheless, functional outcome at 6 months showed improvement in favor of the VAS203 group. The NOSTRA-III study is currently underway (NCT02794168) [82]. A cationic arginine-rich peptide, CN-105, is also currently under investigation in a phase 2 clinical trial for ICH patients, the Evaluation of CN-105 in Subject With Acute Supratentorial Intracerebral Hemorrhage(SCATCH) study (NCT03711903), following the proof-of-concept A Proof of Concept Study to Evaluate CN-105 in ICH Patients (CATCH) study (NCT03168581), which showed no increase in adverse events and no increase in hematoma expansion or neurological deterioration compared to a contemporaneous cohort [83]. The mechanism of action of CN-105 is via apolipoprotein E signaling, which mediates anti-inflammatory and neuroprotective effects rather than directly via L-arginine metabolism. Following promising results in a preclinical brain injury murine model that showed decreased neuroinflammation, a phase I trial indicated safety in humans [84]. Thus, several candidate drugs related to L-arginine metabolism have shown supportive preclinical data in acute brain injury and may represent promising therapies for translation to more definitive efficacy trials. However, at this time, variable results and lack of randomized placebo-controlled studies limit enthusiasm for this approach at least based on autoregulatory mechanisms.

Conclusions and Future Perspectives

The concept of CA is fascinating, and there is increasing interest especially for the concept of optimal CPP or optimal MAP to individualize brain perfusion targets in critical care patients. Although many retrospective studies show that better outcomes from acute neurological disorders are associated with stronger autoregulation, there is a lack of definitive proof that targeted restoration

of CA improves outcome. It is possible that a lack of a reliable means for rapid, graded, and repetitive autoregulation improvement underlies the apparent lack of evidence for this seemingly attractive concept. Previous studies have failed in the application and modulation of physiological factors, such as PaCO2, and pharmacological treatments to optimize CA. We have technologically "complex and cool" monitoring paradigms to assess our patients' autoregulation, but targeting such a strategy is difficult to apply in acute neurological diseases that require high-resource framework. The goal of showing positive effects of autoregulation-guided management on outcomes will require prospective randomized controlled trials powered for clinical outcome. In addition, future studies should focus on the evaluation of a combination of both clinical and pathophysiological end points, such as biomarkers, cerebral ischemia, and altered cerebral metabolism.

We also recognize that larger randomized clinical studies will have to address the current limitations in autoregulatory research, namely heterogeneity in bedside assessment of autoregulation, lack of standardized definitions and costs associated with maintaining an infrastructure of monitoring devices, and lack of data analysis/display platforms to support integration of monitoring data and bedside display using MMM. Strategies to optimize CBF according to CA will benefit from evidence using different technological tools, including noninvasive methods, especially in patients with no indications for invasive monitoring (such as cardiac arrest patients) and in different groups of brain-injured patients, including those with SAH and nontraumatic intracranial bleeding. With evolving clinical expertise ignited by early trials, it is only a natural evolution that further technological advances in this field will yield cheaper and more accessible industry models that allow individualized autoregulatory ranges to be tested with high rigor and translated to bedside use, facilitating tangible precision medicine in cerebral hemodynamic monitoring [85, 86]. But it has not happened yet.

Early signals from clinical trials have shown the feasibility of autoregulation being a target for goal-directed therapy as well as a potential biomarker for prognostication in both cerebrovascular diseases and patients at risk of brain injury in systemic diseases. Integration of validated autoregulatory indices as part of MMM may provide us phenotypes for designing future trials that could use autoregulation-based targets for testing therapeutic interventions. Retrospective studies have shown associations with outcomes, and prospective studies are showing safety and feasibility; we need rigorous prospective data in a well-designed clinical trial using one of the known methodologies before we can say it is game time.

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Declarations

Conflict of interest
Aarti Sarwal's institution has received compensation for research support for her role as site investigator for conducting multicenter clinical trial from Bard, Biogen, Novartis, and CVR Global, Inc. In addition, they have received compensation from LungPacer, Inc, and National Institutes of Health National Institute on Aging grant R01 AG066910-01 (Brinkley/Shaltout) for her role as a consultant for ultrasound image analysis in clinical research trials. She has received honoraria, free meeting registration, and/or reimbursement of travel expenses for her role as a speaker at continuing medical education activities conducted by the Society of Critical Care Medicine, the Neurocritical Society, the Indian Society of Critical Care Medicine, the Indian Academy of Neurology, the American Institute of Ultrasound in Medicine, the Intensive Care Society, the American College of Chest Physicians, the American Thoracic Society, and the American Association of Physical Therapists. Chiara Robba has received payment or honoraria for lectures and presentations at educational events sponsored by GE and Masimo. Carla Venegas has nothing to disclose. Wendy Ziai is supported by the National Institutes of Health and receives consulting fees from C.R. Bard, Inc., outside of the area of work commented on here. Marek Czosnyka gets royalties/licensing fees for ICM+ software; consulting fees from Delica, Shenzan, China; and honoraria for speaking engagements from Integra Lifesciences. Ltd. His institution is paid through research grants funded by the National Institute of Health Research, Cambridge center. Deepak Sharma is the immediate Past President for the Society for Neuroscience in Anesthesiology and Critical Care.

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