Individualized cerebral perfusion pressure in acute neurological injury: are we ready for clinical use?

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None.

Abstract

Purpose of Review

Individualizing cerebral perfusion pressure based on cerebrovascular autoregulation assessment is a promising concept for neurological injuries where autoregulation is typically impaired. The purpose of this review is to describe the status quo of autoregulation-guided protocols and discuss steps towards clinical use.

Recent findings

Retrospective studies have indicated an association of impaired autoregulation and poor clinical outcome in traumatic brain injury (TBI), hypoxic-ischemic brain injury (HIBI) and aneurysmal subarachnoid hemorrhage (aSAH). The feasibility and safety to target a cerebral perfusion pressure optimal for cerebral autoregulation (CPPopt) after TBI was recently assessed by the COGITATE trial. Similarly, the feasibility to calculate a MAP target (MAPopt) based on near-infrared spectroscopy was demonstrated for HIBI. Failure to meet CPPopt is associated with the occurrence of delayed cerebral ischemia in aSAH, but interventional trials in this population are lacking. No level-I evidence is available on potential effects of autoregulation-guided protocols on clinical outcomes.

Summary

The effect of autoregulation-guided management on patient outcomes must still be demonstrated in prospective, randomized, controlled trials. Selection of disease-specific protocols and endpoints may serve to evaluate the overall benefit from such approaches.

Key words (3-5):

cerebral autoregulation, optimal cerebral perfusion pressure; cerebral perfusion; targeted medicine; COGITATE trial

Introduction

Acute neurological injury comprises primarily cerebral crises such as traumatic brain injury (TBI), subarachnoid hemorrhage (SAH) or hypoxic-ischemic brain injury (HIBI) due to out-of-hospital cardiac arrest (OHCA). Many patients require intensive care unit admittance due to comatose state. Neuromonitoring for secondary cerebral injury caused by for example increased intracranial pressure (ICP), decreased cerebral perfusion pressure (CPP) or delayed cerebral ischemia (DCI) should be started as soon as possible. Several non-invasive and invasive techniques have been recommended by a consensus statement (1). Transcranial Doppler ultrasonography (TCD), near-infrared spectroscopy (NIRS) or electroencephalography can be used complementarily to monitor blood flow velocities, bifrontal oxygen saturation (rSO_2) or epileptic activity, respectively, but are limited through interferences of in-between skull and scalp tissues. Invasive probes may deliver robust measurements directly from parenchyma with relatively low complication rate (2). Measuring ICP/CPP is at the forefront of invasive neuromonitoring both in TBI and SAH. Partial brain tissue oxygen ($p_{ti}O_2$) or jugular bulb oximetry ($SjvO_2$) probes, cerebral microdialysis or electrocorticography can detect critical oxygenation, disturbed metabolism or cortical spreading depolarizations (CSD), respectively. Some detected pathologies can be treated with specific measures, such as increasing blood oxygenation for local hypoxia, treating seizures with anti-epileptic drugs or lowering ICP by adjusting ventilation, sedation or cerebrospinal fluid drainage. Furthermore, many treatment options aim to optimize CBF to underserved areas, such as in edematous brain, DCI areas or ischemic penumbra. Population-based fixed CPP targets between (TBI) or over (SAH) 60-70mmHg can be superseded by temporary elevations such as induced hypertension in SAH or a mean arterial pressure (MAP) challenge for ICP control in TBI patients (3). However, defining “optimal” perfusion targets specific for an individual patient and their momentary requirements has been notoriously difficult. The cerebral homeostasis is suggested to be ensured by cerebral autoregulation (CA) in healthy humans where cerebral vessels actively adjust perfusion according to mean arterial pressure and local demand. As CA can be severely disturbed in acute neurological injury, “optimal” management at the bedside becomes paramount to prevent secondary injury, although means to improve CA have long been unknown. Twenty years ago, an observation was made that the functionality of CA fluctuates according to CPP and that deviation from a hereby derived “optimal” CPP where CA functions best – called CPPopt – was associated with worse clinical outcome (4). Since then, the automated calculation of CPPopt has been continuously refined, consisting now of an advanced computerized algorithm with continuous updating of the “optimal” target (Figure 1) (5). The purpose of this review is to highlight the latest evidence on individualizing CPP targets to optimize CA in adults and whether the concept is ready to be transitioned into clinical practice. Based on availability of evidence and promise of clinical use, the review will focus on aneurysmal SAH, TBI and HIBI requiring intensive care.

Recent developments in HIBI after cardiac arrest

In initial survivors of OHCA, HIBI is the major cause of additional mortality and poor neurological outcome, underlining the importance of preventing secondary injury (6). After return of spontaneous circulation (ROSC), CBF is not equally restored. A short phase of hyperemia can be followed by a prolonged reduction of CBF and together with impaired CA and instable hemodynamics can cause ischemic injury (7). This complex relationship has been primarily established from animal models, TCD and NIRS measurements and the NIRS-based Cerebral/Tissue Oximetry autoregulation index (COx or TOx) as the correlation between slow waves of MAP and rSO_2 (7, 8). The agreement of CA indices based on non-invasive NIRS or invasive ICP (COx vs. pressure reactivity index, PRx) was recently found to be limited, suggesting that we are maybe looking to different homeostatic mechanisms (9). As invasive monitoring is not typically applied after OHCA and TCD gives only snapshot information, NIRS remains the preferred, continuous neuromonitor after cardiac arrest. Lower NIRS values have been associated with worse neurological outcomes (10). Preliminary data appear to indicate that impaired CA assessed by NIRS is associated with worse outcomes in OHCA (11). Most recently, researchers from the COMACARE trial found TOx based disturbed CA in 70% of patients with ROSC (12).

An "optimal" MAP (MAPopt) can be calculated from COx/TOx and MAP, analogously to CPPopt. The feasibility of calculating MAPopt was investigated by Sekhon et al., wherein the patients' MAP deviated more than 5mmHg from individual MAPopt during half of the monitoring period (13). The CONCEPT-HIBI study group (Cerebral Oximetry to assess Cerebral autoregulation in Hypoxic-Ischemic Brain Injury) recently demonstrated high rates of COx-based MAPopt values despite individual variability (14). The authors found time to ROSC but not percentage of time with cerebral 'hypoperfusion' (MAP–MAPopt < -5mmHg) or disturbed CA (COx >0.3) as independent predictors of unfavorable outcome. However, the study was not primarily designed for outcome prediction. A trial on Cerebral Autoregulation Monitoring using COx and PRx in Hypoxic Ischemic Brain Injury (CAMP-HIBI) by the same study group found a relationship of MAPopt and brain oxygenation ($PbtO_2$, $SjvO_2$, rSO_2), as oxygenation improved with MAP values closer to MAPopt (15). Invasively measured MAPopt (MAP and PRx) was 89mmHg on average, once more higher than the MAP guideline-recommendation >65mmHg (16). Follow-up studies will continue to explore the meaningfulness of optimizing autoregulation by targeting MAPopt after HIBI.

Recent developments in aneurysmal SAH

The devastating event of aneurysmal SAH can be followed by DCI, becoming symptomatic in a delayed fashion, associated with progression of cerebral vasospasm, CSD, but also disturbed CA (17). Besides the known predictors, stratification of patients at risk for DCI is still relatively inaccurate as the exact triggers are often unknown (18). Blood pressure augmentation is frequently applied in these patients, but CA monitoring and optimization of CPP is not part of clinical routine. In a small cohort study, we recently found that spontaneous CPPopt (assessed with invasive ICP-based PRx) is high in these patients, around 90mmHg at time of DCI (Figure 2) (19). Before the occurrence of DCI, the CPP fluctuated within a 5mmHg range around this CPPopt. However, in the hours preceding the diagnosis a progressive increase in the deviation of CPP from CPPopt (-8mmHg on average) was observed, explained by a combination of slowly increasing CPPopt and a slight but recognizable MAP decrease. The CPP at time of DCI was around 80mmHg, and although this is a perfectly acceptable CPP target after aSAH, it was significantly lower than CPPopt. In view of the small sample size, these findings should be interpreted with caution, but it appears that relative cerebral 'hypoperfusion' in combination with CA worsening precedes DCI. We hypothesized that the brain vessels do not dilate in response to the MAP decrease, resulting in an immediate effect on local CBF which becomes apparent as clinical deterioration and/or hypoperfusion on brain imaging (DCI). As such, knowledge of CPPopt (trends) could help to individualize CPP targets and recognize individual cerebral 'hypoperfusion' before symptom development. Fan et al. reported a similar finding, wherein patients with DCI had longer episodes of cerebral 'hypoperfusion' than patients without DCI (20). There are currently few studies in aneurysmal SAH suggesting an association of deviation from CPPopt with poor clinical outcome (20, 21). The largest retrospective study up to date could not confirm this relationship (22). It should be noted that MAP augmentation after aneurysmal SAH might affect these retrospective CPPopt calculations, as PRx calculation methods use spontaneous MAP fluctuations and can only recommend a CPP target in the observed blood pressure range. Hence a clear separation of phases with spontaneous and augmented blood pressures may be required to meaningfully investigate the observed high CPPopt values in patients with aneurysmal SAH.

It is uncertain whether interventions to optimize blood pressure targets based on autoregulation assessment are potentially useful in the SAH population. Availability of an individual parameter such as an up-to-date objective perfusion target could finally help to select (both awake and comatose) patients eligible for hypertensive treatment, avoid futile trials of hypertension, and timely selection of other treatments like endovascular procedures for vasospasm. At the moment it is not clear whether PRx-derived CPPopt can be such a target and whether it is sensitive enough for single perfusion territory abnormalities like DCI.

Despite certain differences, integrating findings from research on TBI and SAH might benefit the understanding and treatment of the other. SAH may feature some patterns of TBI, owing to a "trauma from the inside" with

sudden ICP increase after aneurysm rupture. Conversely, important complications such as vasospasm/DCI are also frequently reported after TBI (23, 24). Vasospasm/DCI, edema or CSD could temporarily require different and sometimes comparatively high CPP targets (19, 22). Targeting of extreme CPP values (>90mmHg) in TBI is not common practice due to worries about intracranial complications (edema) and systemic (respiratory) problems. Learning from similarities between diseases could streamline the research progress while keeping in mind inherent differences.

Recent developments in TBI

CA dysfunction after TBI is one of the pathological cascades that may lead to secondary neurological injury (24). Observational studies suggest that patients with functional CA are able to tolerate periods of intracranial hypertension and lower CPP values better than those without (25-28). The concept of improving CA originates from observational studies in TBI patients, which indicated that CPP values both above and below the patients' calculated CPPopt were associated with poor clinical outcome (4, 29-31). This culminated in the design of the COGITATE trial (CPPopt Guided Therapy: Assessment of Target Effectiveness) (Figure 3) (32). The main objective was to evaluate the feasibility and safety of an intervention protocol that guided patients' CPP targets 4-hourly by a CPPopt calculation algorithm at the bedside. In four European centers, 32 patients were randomized to a dynamic CPP target versus 28 control patients with a fixed CPP target (CPP 60-70mmHg). Patients in the intervention group were 46.5% (IQR 41.2-58) of the monitoring time concordant with the dynamic CPP target, significantly higher than the powered 36% to demonstrate feasibility (5). The CPPopt target was around 75% of the time available for the clinical team. The intracranial hypertension Therapeutic Intensity Level (TIL) score as the major safety endpoint was not different between the groups. Only a third of the CPPopt recommendations were within the range of 60-70mmHg, indicating the potential of individual and dynamic treatment. The trial was not powered to detect differences in clinical outcome but, as a safety endpoint, a statistical trend (p=0.08) for improved outcome in the intervention group was found.

The authors have speculated on several other limitations that require attention before transition into clinical use and which may be considered in the next trial design (32). Improved methods to gain attention when exceeding the recommended CPP target could improve the amount of time on target. Timely initiation of the protocol after ICP bolt insertion could be expedited by using deferred consent in a phase III trial. Integrating the CPPopt calculation into existing patient monitors is gaining more attention from medical companies which may ease the barriers for widespread clinical introduction. As the COGITATE trial was conducted in centers with longstanding experience in autoregulation monitoring and the research software, the extension to less experienced centers will

require preparation and training of the clinical teams involved. The intervention was limited to 5 days in the COGITATE trial to increase comparability between patients in the study. The impact of targeting CPPopt on outcome could become clearer with an earlier and longer intervention period. While clinical outcome scales such as the extended Glasgow Outcome Scale (GOSE) should capture improvements on all kinds of levels as a natural and historical endpoint, the addition of physiological study endpoints may unravel more specific treatment effects e.g., on tissue oxygenation or metabolism, markers of cellular damage like neuron specific enolase, imaging markers such as new cerebral infarction or contusion progression. To summarize, targeting CPPopt after TBI still needs to be proven as efficacious and finetuning of applicability.

Conclusion

There is increasing interest in CPPopt or MAPopt to individualize brain perfusion targets in critical care patients. However, their clinical benefit still needs to be proven. In a heterogeneous population of severely brain injured patients, establishing appropriate endpoints for clinical trials is typically challenging, as small effect sizes would require large patient sample sizes, and clinical outcome scales (such as the GOSE) might not be sensitive enough to detect subtle benefits. Future trials might select a combination of both clinical and pathophysiological endpoints (e.g. DCI occurrence, cerebral infarction, contusion progression, damage biomarkers). Protocols to optimize perfusion are complex, and the proposed interventions might be designed as a treatment bundle (33), where CA and other monitoring modalities are used to steer therapy to target, but also to detect eventual complications. Strategies to optimize perfusion according to CA after OHCA (MAPopt) are based mainly on non-invasive techniques (NIRS), since invasive measurements are not routinely done in this population, and the appropriateness of the proposed targets requires further validation. Strategies to optimize perfusion after aSAH have not yet been implemented in clinical practice, and future trials might focus on the impact on complications such as DCI as their primary endpoints. The research track on CA-based CPP management is probably most advanced for TBI, in particularly after the COGITATE trial. The next and necessary step should be a well-designed clinical trial to investigate the impact on clinical outcome. Insights from research on autoregulation guided therapy in a particular condition and setting might also deliver insights in the design of protocols for other conditions. Ultimately, the concept might extend to other patient populations such as pediatric patients, extracranial conditions such as spinal cord injury, or even non-neurological disease such as sepsis, where a disturbed central nervous system perfusion because of deficient autoregulation is assumed to play a role (34, 35).

Key points:

3-5 key bullet points that summarize the article after the main text (one sentence each)

- Optimizing cerebral perfusion by optimizing cerebral autoregulation (CPPopt or MAPopt) may have positive effects in neurological injuries associated with unstable hemodynamics.
- The COGITATE trial has demonstrated feasibility and safety of targeting CPPopt in TBI patients
- Prospective, randomized, controlled trials to investigate the effect of targeting CPPopt on neurological outcome or complications can be a next step towards clinical use
- Alternative non-invasive target parameters (e.g., MAPopt based on NIRS) are under investigation

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*** for special interest, ** for outstanding interest**

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Figure 1. Calculation of CPPopt using the Pressure Reactivity Index.

Reproduced from Tas et al. (32). The classical basis for CPPopt is the Pressure Reactivity index (PRx) as the statistical correlation between slow waves of ABP and ICP (first panel). Disturbed CA is assumed when vessel diameter and ICP fluctuate passively both with low and high ABP, leading to a positive PRx. MAPopt can be calculated similarly from MAP and rSO_2 (COx/TOx). Presenting CPP at the x-axis and PRx at the y-axis, the automated curve-fitting software generates a U-shaped graph as PRx values tend to increase (=worsen) both with descending and increasing CPP values, while the nadir of the curve where PRx becomes lowest is the resulting CPPopt (second panel). In the most recent algorithm update, multiple and weighted windows of corresponding PRx and CPP data – covering the patients' latest 8 hours – are applied (5). A CPPopt trendline results from moving the window of this calculation forward (third panel).

Figure 2. CPPopt in a patient with aneurysmal SAH.

Illustrative case of a 72-year-old female patient with aneurysmal SAH (anterior communicating artery aneurysm, Hunt and Hess 3, modified Fisher 3, analgosedated). **A**: 3-hourly means of CPP, CPPopt, deviation of CPPopt (=CPPopt-CPP; all left x-axis) and PRx (right x-axis) 6 days prior to DCI (diagnosed by severe perfusion deficit on CT perfusion), 0 is time of DCI diagnosis. Mean CPPopt was 82.9±9.7mmHg. **B**: Detail view of the last 24 hours before DCI diagnosis with 1-hourly mean values. CPP and CPPopt increase slowly (mean CPPopt 88.9±10.7mmHg), while deviation of CPP from CPPopt revolves around 0mmHg. Cerebral 'hypoperfusion' (CPPopt–CPP < -25 mmHg) occurs few hours before DCI diagnosis, accompanied by a worsening of PRx. This patient was part of a cohort study on DCI patients where a similar dynamic profile before DCI was observed (19).

Figure 3. Review screens of the COGITATE trial.

Reproduced from Tas et al. (32). In 4-hourly intervals, ICM+ software generates a pop-up screen (1) with the new CPP target (2) until the next review, followed by questions and instructions for the treating clinical team (3-6) and a review summary (7).