Inaugural State of the Union

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NEUROCRITICAL CARE SOCIETY

VIEWPOINT

Inaugural State of the Union: Continuous Cerebral Autoregulation Monitoring in the Clinical Practice of Neurocritical Care and Anesthesia

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Abstract

How continuous cerebral autoregulation (CCA) knowledge should be optimally gained and interpreted is still an active area of research and refinement. We now experience a unique situation of having indices clinically available before definitive evidence of benefit or practice guidelines, in a moment when high rates of institutional variability exist both in the application of monitoring as well as in monitoring-guided treatments. Responses from 47 international clinicians, experts in this field, were collected with polling and discussion of the results. The clinical use of CCA in critical illness was not universal among experts, with 34% not using it. Of those who use a CCA index in clinical practice, 64% use intracranial pressure–based Pressure Reactivity index (PRx). There seems to exist a considerable trust in the physiologic plausibility of CCA to guide individual arterial blood pressure and cerebral perfusion pressure therapy and provide benefit, regardless of the difficulty of proving this. A total of 59% feel the need for phase II and III prospective studies but would continue to use CCA information in their practice even if randomized controlled trials (RCTs) did not show clear clinical benefit. There was nearly universal interest to participate in an RCT, with agreement that the research community must together determine end points and interventions to reduce wasted effort and time, and that investigations should include the following: the most appropriate way of inclusion of CCA into the clinical workflow; whether CCA-guided interventions should be prophylactic, proactive; or reactive; and whether a CCA-centric (unimodal) or a multimodal monitoring-integrated tiered therapy approach should be adopted. Pediatric and neonatal populations were highlighted as having urgent need and even more plausibility than adults. On the whole, the initiative was enthusiastically embraced by the experts, with the general feeling that a strong push should be now made by the community to convert the plausible benefits of CCA monitoring, already implemented in some centers, into a more standardized and RCT-validated clinical reality.

Background

Continuous cerebral autoregulation (CCA) is associated with outcome in most acute severe brain injury, and it is accepted that continuous knowledge of a patient's state of CCA should influence perfusion goals [1, 2] or tolerance of intracranial hypertension in acute traumatic brain injury (TBI). How this knowledge should be optimally gained and interpreted is still an active area of

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research and refinement. Among the clinical community, there is a consensus that particular indices, such as intracranial pressure (ICP)-based Pressure Reactivity index PRx [3] or Near-Infrared Spectroscopy (NIRS)-based Cerebral Oxygenation reactivity index Cox [4], hold the most promise to support treatment decisions and should garner the prioritized focus of researchers [5, 6]. The propagation of technical knowledge to acquire, integrate, and analyze such indices has been supported by efforts within the academic community and through infrastructure of multicenter prospective clinical trials such as Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI) [7]. CPPOpt Guided Therapy: Assessment of Target Effectiveness (COGiTATE) [8] was the first successful randomized controlled trial (RCT) to test the feasibility of CCA-guided management by PRx at the bedside, in patients with TBI undergoing ICP monitoring. As a result, the technical ability to calculate such indices has increased widely and has made its way into practice in some centers on the basis of physiologic plausibility and absence of other quantitative tools to inform individual patient management. No universal or medical societal guidelines yet exist to inform standard of care, and yet there is a widely accepted call for individualized and precision medicine, with autoregulation-guided therapy as the first proposed example [1, 2, 9]. Anecdotally, it is known that the use of CCA indices information tends to be variable, even within institutions, and unsurprisingly most able to be used by clinicians who also contribute to the literature about CCA. It is likely that CCA will soon be nearly universally available as medical device companies are now embedding calculated indices and perfusion targets in their products [10, 11]. This is a unique situation of having indices clinically available before definitive evidence of benefit or practice (consensus) guidelines, in a moment when suspected high rates of interinstitutional and intrainstitutional variability exist both in the application of monitoring as well as in monitoring-guided treatments [12, 13]. There is a distinct possibility that important steps of interpretation, grounded in contextual understanding of CCA and its physiological, technical, and clinical limitations, will be missed. It is unclear how patients will be affected either positively (from wider diffusion of a tool) or negatively (from incorrect or nonoptimized implementation of an incompletely tested tool), and it will be nearly impossible to understand in retrospect. It is also possible that practice will be formed based on literature from one diagnosis being applied to another, from one cohort/pathology to another, and, importantly, from the realities of one center to another, without insight or oversight.

In this context, we wished to convene clinical experts from the CCA research community to inaugurate discovery of the suspected variability and also to report a state of the union of clinical practice of CCA-guided management.

Convention Details

In January of 2023, we (SP, EB, PS, MA) identified, invited, and hosted a virtual convening of experts who met the following criteria: (1) have continuous neuromonitoring at the bedside, (2) display capability of CCA indices information as part of research or clinical protocol, and (3) work as intensive care, medium intensity care, or operating room clinician. These criteria were formed with the understanding that such persons were uniquely positioned to perform clinical care informed by an understanding of the CCA literature. Additionally, we attracted participants via Moberg Analytics' mailing list (users of Moberg 'CNS monitors') to invite self-identified experts. Some experts also recommended colleagues. The mission of the 3-h meeting was to assess the current clinical practice to discover commonalities or variability and spark a moderated discussion to extract insights that influence clinical practice or research initiatives within the context of continuous monitoring of cerebral autoregulation. In total, 49 individuals were invited, mindful of avoiding inclusion of too many individuals from the same institution unless they were known to have independent research or clinical approaches.

A survey was drafted beforehand (SP, MA, EB, PS). The questions covered the general, relevant, clinical, and technological context and probed how, if at all, CCA information was used by the respondents at the time, not focusing intentionally on any particular patient population or pathology. Finally, the questions tried to ascertain the feeling among the participants of the necessity and timing of a phase II or III RCT as well as the main ideas for its protocol. The questions were necessarily centered around PRx (Pearson correlation coefficient between 10-s averages in arterial blood pressure [ABP] and ICP more than 5 min) [3] and COx/HVx (Pearson correlation coefficient between ABP and NIRS-derived regional oxygen saturation index rSO2/ total haemoglobin concentration index THb more than 5 min) [4, 14], given their predominance in the clinical CCA literature.

Prior to the meeting, all individuals were invited to contribute a one-page presentation about their opinions that were compiled and shared with the group. Two presentations about the fundamentals and technical aspects of CCA (PS) and the application within a clinical trial (MA) were given to boost the discussion.

There was representation from 16 countries and 33 institutions. Organizers and participants were not

supported financially by any commercial interests. PS is an original author in the discovery of PRx and the founder of ICM+ [15], a common software used in the community and administered by Cambridge Enterprise Ltd (UK), but holds a full-time, nonclinical, academic position and was a nonvoting participant; EB was also a nonvoting participant as noncurrently practicing.

During the meeting, the survey was presented to the participants one question at a time, followed by a brief discussion on each question and its results. Following the meeting a slightly adjusted survey was sent out to all the 49 invited experts to allow those who could not participate on the day (either due to absence or missing parts of the virtual meeting) to take part. Thirty were able to convene the virtual meeting (27 of whom completed the survey), and an additional 17 were able to only complete the survey. In total, 44 individuals responded to the survey (90%).

Here, we present the audit of the results of the survey along with the summary of the discussions from the meeting. Detailed results are given in the Appendix 2.

Commonalities and Variabilities of Current Clinical Practice

Diversity still exists in where ABP level is zeroed in patients with ICP monitoring (48% at brain level, 50% at right atrial level). The majority of participants do not have individual choice in where to zero ABP level (66% institutional, 30% personal). This is, of course, a crucial point when implementing fixed cerebral perfusion pressure (CPP) targets, according to clinical guidelines [1], but it becomes much less relevant when applying individualized CCA-guided CPP targets.

The majority of participants use ICM+ software for the monitoring of CCA (75%), whereas 9% use CNS monitors. This might represent a bias in the selection of clinical experts, but CNS monitor users were also included in the selection process. Given the efforts to be as inclusive as possible, it is more likely to do with the current lack of CCA software options at the bedside, although, as mentioned earlier, there is now a slowly growing support by industry for these metrics. On the other hand, this might reflect the fact that CCA is very often used within research or by clinicians involved in CCA research, and ICM + has assisted CCA clinical research over the last two decades.

For critically ill patients, only 52% of respondents use a CCA index in clinical decision making, whereas 34% use it as part of a research protocol. Of those who use CCA index in clinical decision making, 39% use it as part of a local clinical protocol and 61% use it without a protocol. PRx is the most used index (64%).

For patients with TBI, 48% of respondents use the 'MAP challenge' suggested by Seattle International Severe Traumatic Brain Injury Consensus Conference consensus guidelines to intermittently assess CA status [2].

Detailed CA Management

In general, seeing impaired CA on a continuous display triggers respondents to review patients clinically (86%) mainly starting with ICP and other brain perfusion markers, looking at ventilator settings and checking PaCO2 levels (45%), looking at ABP and CPP and setting new targets (48%), or more closely reviewing CCA for the next few hours (34%). Very few would do nothing with the obtained information (7%).

Among the 59% that would use CCA to set ABP or CPP targets, most would do it regularly to "optimize" cerebral physiology and as part of a stepwise approach in a multimodal monitoring (MMM)-guided treatment protocol. The second most adopted option is to use the information to decrease the intracranial hypertension therapy (by early ICP control or by decreasing CPP within safe autoregulatory ranges) and to set other targets (ICP, $PaCO_2$). Seven percent would only set ABP/CPP targets using CCA index, only during periods of time when the patient was not autoregulating. Among the responders who use CCA to set ABP or CPP targets, 58% consider the "optimal" value provided by CPP-PRx error bar charts (in the literature referred to as the *U*-shaped CPPopt or ABPopt curve, with it's Minimum location defined as CPPopt or ABPopt values respectively) to set their pressure targets; 58% consider the lower limit of autoregulation derived from the same charts; 51% consider the continuous time trends of ABP, CPP, and CCA index to make their own assessment; 54% consider the "automated" CPPopt/ABPopt/LLA/ULA (where LLA stands for Lower Limit of Autoregulation, and ULA for Upper Limit of Autoregulation) time trends provided by their software or device as the most convenient treatment target.

A total of 59% of all responders would use ABP/CPP-PRx error bar charts to set clinical targets. Of these responders, 43% look at the individual CPPopt/ABPopt curves covering the last 4 h of monitoring, 18% of at least 8 h, and 22% use a specific time period for CPPopt/ABPopt review in which patients' physiology is relatively stable.

Of the responders who do not use a CCA index or CPPopt/ABPopt in clinical practice, and assuming technical capability is not an issue in their center, most (59%) would need an RCT showing benefit to convince them to start. A consensus statement from a group of experts

endorsed by a medical society would convince some to start (28%).

Considerations for RCTs

A total of 27% of responders felt there is already justification for a clinical RCT to show improved brain physiology and/or clinical outcome. The remainder felt that there is still need for effectiveness studies showing improvement of MMM or biomarkers and feasibility studies that include CCA information within MMM-guided bundled treatment protocols.

The majority (57%) of responders would continue to use CCA information in their practice if a RCT of CCA-guided therapy was negative or did not show clear benefits.

A total of 98% of responders would be interested in participating in a CCA-guided clinical RCT. Of those responders, 72% would prefer the intervention to be a direct CPP target range recommendation that is updated every few hours. Around a third of the respondents would want information about the current state of CCA and the CPPopt curve, but without a concrete automated CCA-guided CPP target recommendation (37%) or a single CCA-guided CPP target updated every few hours (35%).

Summary of the Discussion Between Respondents

The majority of experts incorporate knowledge of CCA (whether via MAP challenge or CCA indices), but few felt ready to incorporate automated CPPopt targets in daily practice. There were experts who reasoned that even without high-level evidence to support universal goals of CPP, there was already justification in using CCA-guided individualized goals. Similarly, one third of the community felt that there is enough background knowledge for designing an RCT, whereas the majority felt that further preparatory work is needed to demonstrate safety, feasibility and efficacy. The survey showed that the majority would continue to use CCA information in their practice if an RCT of CCA-guided therapy was negative or did not show clear benefits. This implies that there exists a high trust in the physiologic plausibility of CCA to guide therapy and provide benefit, regardless of the difficulty of proving this on a large and consistent scale. The participants acknowledged the challenges and difficulties in designing and conducting an RCT, but specific ideas of how to overcome those were not discussed in any greater detail at this stage. It was noted that local federal regulatory bodies thresholds for approvals of the algorithms used to calculate the indices and the derived ABP/CPP targets influence the acceptable usage of the technology that enables CCA implementation in clinical care. However, it was also noted that the CCA technology is already commercially available from medical device companies.

In terms of future research efforts, there was agreement that it would be more productive if the community gathered for this scope could agree on targets, interventions, and end points to investigate. Notably, the community felt that pediatric and neonatal interventional studies were necessary, urgent, and particularly attractive because age-varying physiology of these populations would be expected to benefit more from individualized perfusion targets.

Targets and Interventions

For future clinical trials, there was a vigorous discussion about whether CCA monitoring should be evaluated in isolation or as part of MMM to guide tiered, protocolized, individualized therapy. One example of such integrated use might be to detect cerebral ischemia using MMM, and then use a CCA-related index to safely optimize hemodynamic augmentation to treat such ischemia. However, consensus on this issue was incomplete. Those who oppose studying CCA-guided therapy as a single intervention were concerned about the dilution of its effect by other independent and concurrent treatment choices. It was also unclear whether CA-guided recommendations should result in a specific CPP target or simply inform CPP targets as part of overall assessment of clinical physiology. Either way, the results from COGiTATE indicate the need to account for shape and location of the PRx-CPP curve in any future, automated CPP target recommendations. Finally, there was a general agreement regarding the need to identify and evaluate interventions that are effective and safe for optimizing CCA and cerebral perfusion.

End Points

To prove clinical benefit of CCA-guided treatments, traditional end points such as Glasgow Outcome Score (Extended) at 6 months may be too granular and insensitive an outcome for interventions that target CPP or incorporate knowledge of CCA index. Rather, there is likely a role for short-term outcomes such as surrogate serum or imaging biomarkers of brain damage (and their trajectories). Furthermore, for specific diagnoses other than TBI, the in-hospital syndromes or interim outcomes, such as worsening of stroke or bleed, or presence of delayed cerebral ischemia in subarachnoid hemorrhage may be just as, or more, important and certainly more relevant to use then the general, long-term outcomes.

Methodological and Technical Aspects

There remain many questions about technical aspects and workflow. In particular, it was considered, yet unsettled, what the optimal window length of data (i.e., the period) for assessment of the CPPopt should be, how often should a new CPP target be set, and whether the data should be used to target perfusion goals prophylactically, proactively, or reactively (when physiology is deranged). Further, for future clinical trials of automated CCA-guided CPP targets, the community should agree on how to deal with artifacts, if such recommendations are expected to be generated without supervision. This is currently dealt with in very specialized centers, but not all methods are standardized. Given the heterogeneity of available neuromonitors and the thresholds proposed for their derived CA indices in various diseases, there is a great motivation to study better the relationships between different CA indices, with a special attention paid to the uncertainties and errors inherent in the calculation of each.

Limitations

Although the appetite and necessity for prospective trials was discussed, the meeting did not aim to address trials design, analysis strategies, or end points, nor the populations, subpopulations, and numbers to be included. This will form part of future meetings agendas, following to this one.

The reliability and accuracy of the CCA indices was not discussed in depth, but rather considered within the technical aspects of CCA that will require ongoing investigation. Similarly, the advances in technology will likely be able to provide new means for CCA, however, the framework for clinical usage of the new methods will still require standardization of the clinical practice on the concept of continuous availability of CA status, regardless of the technology used. Here, we focused on the clinical practice based on currently available methods.

Despite our best efforts to be inclusive and reach all the experts in the field that met our inclusion criteria (see convention details), we are aware that our selection might have not been exhaustive. If you wish to self-identify yourself as a clinical expert that should be included in the collaborator's list, and you would like to join future CCA initiatives, please email ps10011@cam.ac.uk with your institution and the reason why you feel you should be part of the collaborative effort. Please state "CLINICCA" in the subject of the email.

Conclusions

Much has been written about associations of continuous measures of autoregulation with clinical outcome, and some clinicians have already included CCA in their practice to smaller or larger extent. The results of our convention have shown that there is no apparent standard or common protocols for its clinical implementation shared by the participants. Despite this, there is a certain set of commonalities in clinical practice across experts with a deep understanding of the literature. Future steps include compiling local clinical protocols and seeking a pragmatic consensus. Most are using CA knowledge (in the form of MAP challenge or observation and consideration of indices such as PRx) but stop short of automatically using targets provided by the CPPopt curves. CCA information can trigger a patient clinical review, which might lead to further actions depending on ICP, ventilation, brain perfusion markers, or CA itself. As previously anecdotally suspected, there is a wide variability that remains (inclusive of nonuse of CCA in clinical practice). There is urgency to widely highlight advantages and share pitfalls of CCA interpretation in clinical decision making, while in parallel identifying end points and targets for RCTs, outcome, or effectiveness studies.

Electronic supplementary material

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Authors Contribution

Conceptualization (SP, EB, PS, MA), Methodology (SP, EB, PS, MA), Writing – Original Draft (SP, EB), Writing – Review & Editing (SP, EB, PS, MA, CLINICCA Collaborators). The final manuscript was approved by all authors.

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Conflicts of interest

SP is an Associate Editor of Neurocritical Care; PS receives part of licensing fee for ICM + software (Cambridge Enterprise Ltd, subsidiary of Cambridge University, UK).

Appendix 1: Clinical use of Information on Continuous Monitoring of Cerebral Autoregulation Collaborators

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Appendix 2: Survey Questions and Results

Here we present detailed results of the survey. A total number of 44 persons responded. The survey was divided into three parts: Commonalities and Variabilities of Current Clinical Practice; Detailed CA management; Considerations for Randomized Controlled Trials. The raw results are presented with absolute n of responders (% over the total number of 44) per item.

Part I: Commonalities and Variabilities of Current Clinical Practice

(1) Where do you zero ABP level in patients with ICP monitoring for CPP calculation?

- 21 (48%) Brain level
- 22 (50%) Atrial level
- 1 (2%) N/A

(2) Do you have a choice in where to zero ABP level in individual patients?

- 29 (66%) institutional
- 13 (30%) I can decide
- 2 (4%) N/A

(3) For continuous monitoring of CA, do you use:

- 33 (75%) ICM+
- 4 (9%) CNS
- 0 (0%) Raumedic
- 4 (9%) other (Odin; Sickbay; Mathlab)
- 3 (7%) NA

(4) In critically ill patients, if you have continuous PRx/COx/HVx available at the bedside, what best describes you:

- 9 (20%) use it in decision making—WITH a clinical protocol
- 14 (32%) use it in decision making—WITHOUT a clinical protocol
- 15 (34%) use it as part of a research protocol
- 2 (5%) am open to using it, but do not know how
- 3 (7%) do not use it because there is not enough evidence
- 1 (2%) N/A

(5) Do you use a CA index in clinical decision making in any way? (multiple choices possible):

- 28 (64%) PRx
- 6 (14%) COx/HVx
- 15 (34%) I do not use a CA index in clinical decision making in any way
- 1 (2%) N/A

(6) Do you use the MAP challenge in your patients (with ICP monitoring) to assess cerebral autoregulation status?

- 23 (52%) no
- 21 (48%) yes

Part II: Detailed CA management

(1) The index of CA shows impaired CA over the past few hours, you do(multiple choices possible):

- 3 (7%) Nothing
- 38 (86%) Triggered to start reviewing my patient clinically
- 20 (45%) Look at ventilator and check PaCO2 levels
- 21 (48%) Look at ABP/CPP and set a new ABP/CPP target
- 15 (34%) Report it as something to monitor over the next few hours
- 0 (0%) Another intervention, please specify
- 6 (14%) N/A

(2) If you use a CA index to set patients' ABP/CPP targets, you do it:(multiple choices possible)

- 1 (2%) once during admission to optimize brain physiology
- 22 (50%) updated regularly to optimize brain physiology
- 11 (25%) to decrease the burden of intracranial hypertension therapy whenever possible
- 17 (39%) as part of a stepwise approach in a multimodality monitoring based protocol
- 3 (7%) but only if my patient is not autoregulating
- 11 (35%) also to set other targets (ICP, paCO2 levels)
- 0 (0%) other, specify
- 18 (41%) no, I do not use a CA index to set targets

(3) If you use a CA index to set therapeutic ABP/CPP targets, what do you look at (more answers possible)?

- 15 (34%) optimal value provided by CPP-PRx error bar charts
- 15 (34%) autoregulation range provided by error bar charts, in particular LLA
- 7 (16%) autoregulation range provided by error bar charts, in particular ULA
- 13 (30%) time trends of ABP/CPP and of the index of CA and make my own assessment
- 14 (32%) automated CPPopt/ABPopt/LLA/ULA time trends provided by my software/device
- 20 (46%) N/A
- 0 (0%) Other

(4) If you use the ABP/CPP-PRx error bar charts to set your targets, which periods do you look at:

- 10 (23%) The last 4 h
- 4 (9%) The last 8 h
- 5 (11%) Specific time period where patients' physiology is relatively stable
- 18 (40%) N/A
- 4 (9%) Other (variable interval, 6 h, with 24 h context)

(5) If you don't use a CA Index in clinical practice, and assuming technical capability was not an issue, what would convince you to start?

- 1 (3%) Report of Clinical Practice with protocols published from experts

- 0 (0%) Consensus guideline from a group of experts
- 8 (18%) Consensus guideline from a group of experts—endorsed by a medical society
- 16 (36%) Randomized Controlled Trial(s) showing benefit
- 2 (5%) Other (combination of the above, FDA approval)
- 16 (36%) N/A

(6) If you don't use CPPopt/ABPopt in clinical practice, and assuming technical capability was not an issue, what would convince you to start?

- 1 (3%) Report of Clinical Practice with protocols published from experts
- 0 (0%) Consensus guideline from a group of experts
- 6 (14%) Consensus guideline from a group of experts—endorsed by a medical society
- 20 (45%) Randomized Controlled Trial(s) showing benefit
- 2 (5%) Other (combination of the above, FDA approval)
- 15 (34%) N/A

Part III: Considerations for Randomized Controlled Trials.

(1) Before setting up a clinical RCT, first the following studies should be done (more answers are possible):

- 12 (27%) Not needed, we need a clinical RCT showing improved brain physiology and/or clinical outcome
- 6 (14%) Animal studies, improving our understanding of autoregulation function and drivers
- 18 (41%) Feasibility studies increasing the availability of autoregulation information or targets
- 20 (45%) Feasibility studies with autoregulation information being part of multimodal monitoring guided treatment protocol
- 22 (50%) Effectiveness studies showing improvement of multimodal monitoring, diagnostics or damage markers
- 1 (2%) Other

(2) If a Randomized Controlled clinical Trial of CA guided therapy was negative, or it did not show clear benefits, would you still continue using CA in your practice?

- 25 (57%) yes
- 8 (18%) no
- 10 (23%) depends (study protocol, study quality, study results)

(3) Would you be interested in participating in an CA guided clinical RCT?

- 43 (98%) yes
- 1 (2%) no

(4) If yes for above, what intervention would you be comfortable with? (Multiple choice allowed).

- 15 (34%) Following a direct recommendation for CPP target (updated every X hours)
- 31 (77%) Following a direct recommendation for CPP target range (updated every X hours)
- 16 (36%) Provided information about the current state of autoregulation and the CPPopt curve but **without** a concrete CPP target recommendation(ie values provided but not imposed)
- 1 (2%) Other (incorporating other modalities targets)

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