BJA

British Journal of Anaesthesia, 126 (5): 967–974 (2021)

doi: 10.1016/j.bja.2020.12.043
Advance Access Publication Date: 23 March 2021
Neuroscience and Neuroanaesthesia

NEUROSCIENCE AND NEUROANAESTHESIA

Cerebral autoregulation in the operating room and intensive care unit after cardiac surgery

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Abstract

Background: Cerebral autoregulation monitoring is a proposed method to monitor perfusion during cardiac surgery. However, limited data exist from the ICU as prior studies have focused on intraoperative measurements. Our objective was to characterise cerebral autoregulation during surgery and early ICU care, and as a secondary analysis to explore associations with delirium.

Methods: In patients undergoing cardiac surgery (n=134), cerebral oximetry values and arterial BP were monitored and recorded until the morning after surgery. A moving Pearson's correlation coefficient between mean arterial proessure (MAP) and near-infrared spectroscopy signals generated the cerebral oximetry index (COx). Three metrics were derived: (1) globally impaired autoregulation, (2) MAP time and duration outside limits of autoregulation (MAP dose), and (3) average COx. Delirium was assessed using the 3-Minute Diagnostic Interview for CAM-defined Delirium (3D-CAM) and the Confusion Assessment Method for the ICU (CAM-ICU). Autoregulation metrics were compared using χ^2 and rank-sum tests, and associations with delirium were estimated using regression models, adjusted for age, bypass time, and logEuroSCORE.

Results: The prevalence of globally impaired autoregulation was higher in the operating room *vs* ICU (40% *vs* 13%, P<0.001). The MAP dose outside limits of autoregulation was similar in the operating room and ICU (median 16.9 mm Hg×h; inter-quartile range [IQR] 10.1–38.8 *vs* 16.9 mm Hg×h; IQR 5.4–35.1, P=0.20). In exploratory adjusted analyses, globally impaired autoregulation in the ICU, but not the operating room, was associated with delirium. The MAP dose outside limits of autoregulation in the operating room and ICU was also associated with delirium.

Conclusions: Metrics of cerebral autoregulation are altered in the ICU, and may be clinically relevant with respect to delirium. Further studies are needed to investigate these findings and determine possible benefits of autoregulation-based MAP targeting in the ICU.

Keywords: cardiac surgery; cerebral autoregulation; delirium; geriatrics; intensive care unit

Received: 28 January 2020; **Accepted:** 24 December 2020

Editor's key points

- Cardiac surgery patients were monitored to determine whether impairments in cerebral autoregulation indices occurred more frequently in the ICU relative to the operating theatre.
- Globally impaired cerebral autoregulation occurred more frequently in the operating theatre than the ICU, although the duration of cerebral autoregulation outside the upper and lower limits of autoregulation was comparable for the operating theatre and ICU.
- A greater duration of cerebral autoregulation outside the lower and upper limits of autoregulation was associated with delirium.
- This association between cerebral autoregulation indices and delirium requires further study, particularly in the ICU setting.

A fundamental principle in the perioperative care of patients undergoing cardiac surgery is to target adequate mean arterial pressure (MAP) to maintain end-organ perfusion and in particular brain perfusion.[1] However, there is no agreement on what constitutes an adequate MAP to maintain end-organ perfusion, with a systematic review identifying more than 40 definitions of hypotension in the perioperative literature.[2] Hence, clinicians often utilise empiric MAP targets, with modification based on individual patient profiles. Further, the challenge of targeting adequate MAP during cardiac surgery is not limited to the operating room, but also extends to the early ICU period, where fluctuations in MAP are common.[3]

Monitoring cerebral autoregulation may provide insight into adequate MAP for individual patients or physiologic states of impairment in cerebral blood flow regulation.[4,5] There are several important metrics derived from cerebral autoregulation monitoring. First, the MAP at an individual's lower and upper limits of autoregulation (LLA and ULA, respectively) can be identified, outside of which cerebral hypo- or hyperperfusion may occur. Second, because of global impairment in cerebral autoregulation that is present at all MAPs in some patients, the LLA and ULA cannot be identified. Finally, an estimate of average autoregulation (across different time periods and changes in MAP) can be calculated.

Our previous studies demonstrate the possible clinical significance of these metrics. During cardiopulmonary bypass, the MAP at the LLA varies widely among patients.[6] The product of the magnitude and duration of MAP (which we further refer to as dose) that is less than the LLA during cardiopulmonary bypass is associated with acute kidney injury, morbidity, and mortality.[7,8] Alternatively, the MAP dose greater than ULA is associated with postoperative delirium.[9] Importantly, the results of a recent clinical trial suggest a MAP greater than the LLA during cardiopulmonary bypass may reduce delirium incidence.[10] Impaired autoregulation may also be associated with cognitive decline after surgery.[11]

Studies to date primarily focus on the intraoperative period, and in the ICU, cerebral autoregulation has not been well characterised, especially with respect to postoperative delirium. Studies in the cardiac surgery ICU found associations between average[12,13] or cumulative dysfunction of autoregulation[14] and postoperative delirium, however, neither the prevalence of impaired autoregulation nor the dose of MAP outside limits of autoregulation were reported. Another study found an association between deviations from optimal MAP in the operating room and early ICU period and delirium on postoperative day 2.[15]

To address these gaps in understanding the burden and clinical significance of cerebral autoregulation in the ICU, we conducted an observational study in cardiac surgery patients. We hypothesised that patients would experience a substantial MAP dose outside the limits of cerebral autoregulation in the ICU that is greater than when compared with the operating room. In exploratory and secondary analyses, we also examined whether metrics of cerebral autoregulation in the operating room and the ICU would be associated with delirium.

Methods

This study was approved by the Johns Hopkins Institutional Review Board (Baltimore, MD, USA) (IRB00086547). Patients provided written informed consent. The first and last author had full access to all data and take responsibility for their integrity and analysis. This manuscript adheres to applicable Equator guidelines.

Study design and patients

Data analysed were abstracted from an ongoing observational study examining autoregulation characteristics in patients undergoing cardiac surgery. All clinical management (including BP management) was based on usual care, and autoregulation monitoring was not used for clinical decision-making. Patients were enrolled between October 2017 and August 2019 at a single academic medical centre. Inclusion criteria were >18 yr old and undergoing isolated or combined coronary artery bypass, valve, aortic, or myectomy surgery. Exclusion criteria were lung or heart transplant or planned insertion of a ventricular assist device.

Cerebral autoregulation monitoring

Patients were monitored in the operating room after arterial catheter placement and connection to an INVOS cerebral oxygen monitor (Medtronic Inc., Minneapolis, MN, USA) using bilateral sensors above the eyebrows on the forehead, as per clinical use instructions. Monitoring continued in the ICU until the morning after surgery. The acquisition and analysis of MAP and near-infrared spectroscopy (NIRS) signals have been described.[4] Arterial BP signals were digitised using an analogue-to-digital converter. Digitised signals were acquired and processed with a personal computer using ICM+ software (Cambridge Enterprise Ltd., Cambridge, UK). Arterial BP and regional oxygen saturation (rSO_2) from the INVOS cerebral oximeter (Medtonic, Dublin, Ireland) were time-integrated and resampled as 10-s mean values, to remove pulse and respiratory frequency variations and preserve low frequency waveforms associated with autoregulatory vascular reactivity. Next, a continuous, moving Pearson correlation coefficient between 30 consecutive, paired MAP and rSO_2 signals was calculated to generate the cerebral oximetry index (COx).[4] The COx was updated every 10 s from an overlapping, moving 300-s window and paired with the MAP value from the same 300-s window. COx values are plotted as a function of MAP in 5 mm Hg bins (Fig. 1a), and BP in the autoregulation range is indicated by a COx value approaching zero (no correlation between changes in rSO_2 and MAP), while a COx approaching 1

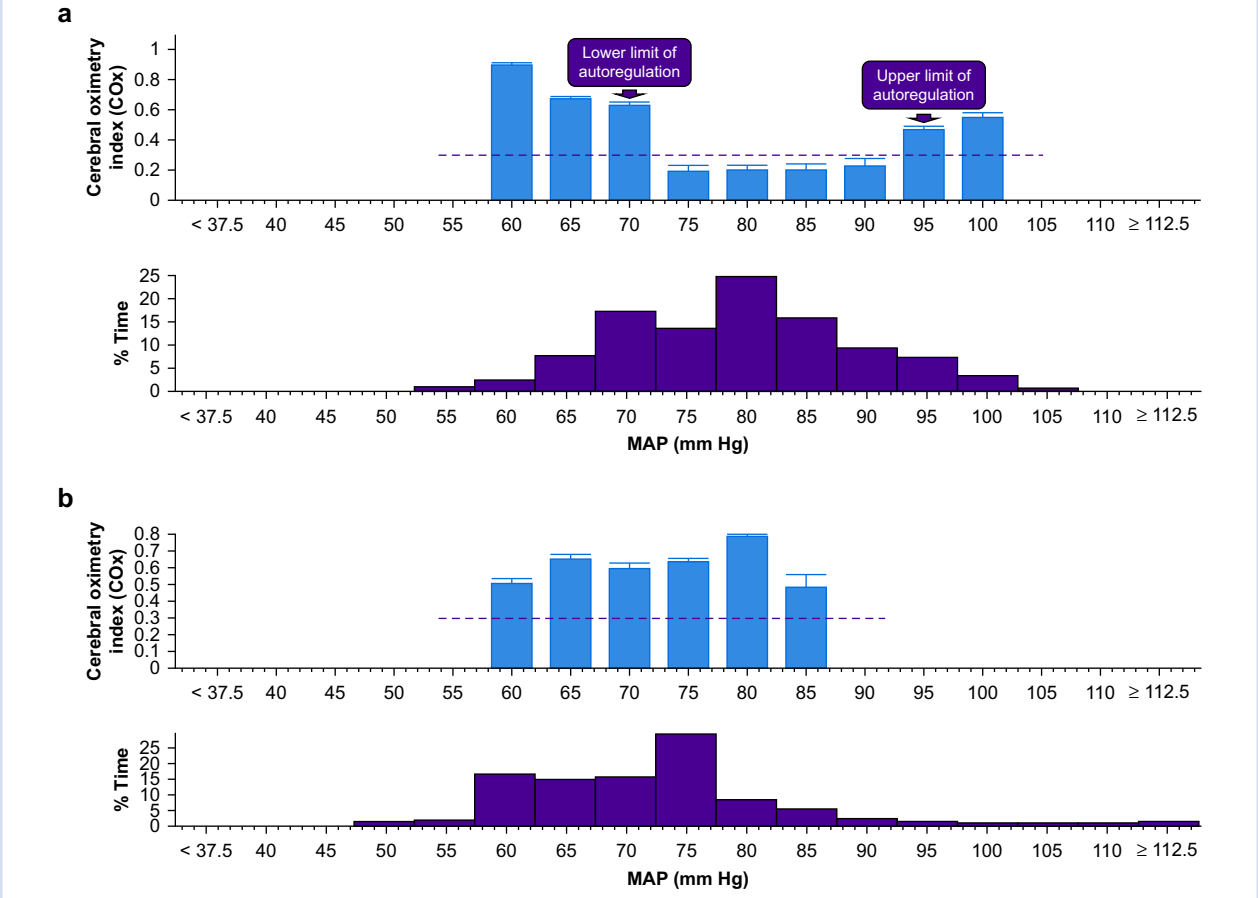

Fig 1. Cerebral autoregulation monitoring. (a) Cerebral oximetry index of autoregulation for each 5 mm Hg bin of mean arterial poressure. The arrows indicate the MAP at the lower and upper limits of autoregulation, where the cerebral oximetry index increases to >0.3. A histogram of % time at each MAP allows visualisation and calculation of the dose of MAP outside the limits of autoregulation. (b) A patient with globally impaired cerebral autoregulation, defined by all estimates of the cerebral oximetry index >0.3 (dashed line).

indicates dysregulation (correlation between changes in rSO_2 and MAP). Prior studies have demonstrated the validity of NIRS-based measurement of cerebral autoregulation in comparison with methods using transcranial Doppler (TCD)-based approaches.[4,16] The lower and upper limits of autoregulation (LLA and ULA, respectively) were defined using an automated curve-fitting algorithm[17] as the MAP at which the COx decreased from ≥0.3 to <0.3 or increased from <0.3 to ≥0.3, respectively, as MAP increased, in accordance with previous methodology[8] (Fig. 1a). All estimates from the curve-fitting algorithm were confirmed using visual inspection and were derived from the entire period of monitoring in the operating room and ICU. Monitoring data from each patient's left and right sides were averaged. Globally impaired autoregulation was defined when all estimates of COx in each 5 mm Hg bin on the left or right side were greater than the COx-specific cutoff of 0.3[18] (Fig. 1b).

Assessment of delirium

Trained research staff conducted delirium assessments daily during three of the first four postoperative days using the 3-Minute Diagnostic Interview for CAM-defined Delirium (3D-CAM) (reported sensitivity and specificity >94%).[19] The timing of the delirium assessment was based on our prior studies[20] and on a study demonstrating that >90% of delirium occurs during this time.[21] Training included written materials on 3D-CAM administration, videos depicting standardised assessment, observation of patient assessments, and supervised administration. For intubated patients, trained ICU nurses administer the Confusion Assessment Method for the ICU (CAM-ICU) several times per day, including administration of the Richmond Agitation-Sedation Scale as per the CAM-ICU protocol,[22] and these assessments were used to identify delirium in intubated patients. All delirium assessors were masked to autoregulation data.

Perioperative clinical management and data

Perioperative care was according to usual practice. Anaesthesia was induced and maintained with fentanyl (5–20 μg kg^{-1}), propofol (0.5–2 mg kg^{-1}), a neuromuscular blocking agent, and isoflurane. Dexmedetomidine, ketamine, or both infusions were used per anaesthesiologist discretion. During

Table 1 Patient and surgical characteristics.

	Cardiac surgery patients N=134
Age (yr), median (IQR)	65 (58–71)
Male, *n* (%)	100 (74.6)
Race, *n* (%)	
Caucasian	107 (79.9)
African-American	22 (16.4)
Other	5 (3.0)
Comorbidities, *n* (%)	
Prior stroke	7 (5.2)
Hypertension	105 (78.4)
Congestive heart failure	40 (29.9)
Peripheral vascular disease	18 (13.4)
COPD	13 (9.7)
Tobacco (prior)	74 (55.2)
Diabetes mellitus	53 (39.6)
Log EuroSCORE, median (IQR)	3.45 (1.72–6.09)
Baseline medications	
Aspirin-based inhibitors of platelet aggregation, *n* (%)	101 (75.4)
Beta blockers, *n* (%)	96 (71.6)
Calcium channel blockers, *n* (%)	44 (32.8)
Angiotensin converting enzyme-inhibitors, *n* (%)	33 (24.8)
Angiotensin II-receptor blockers, *n* (%)	24 (18.1)
Statin, *n* (%)	107 (79.9)
Surgery, *n* (%)	
CAB	82 (61.2)
CAB+valve	14 (10.5)
Valve	28 (20.9)
Aortic	10 (7.5)
Cardiopulmonary bypass duration (min), median (IQR)	109 (83–138)
Lowest temperature on bypass (°C), median (IQR)	33.8 (32–34.6)
Time to extubation (h), median (IQR)	4 (0–7.5)
LOS-ICU (h), median (IQR)	43 (23.8–69.8)
Epinephrine in the ICU on day of surgery, *n* (%)	109 (81.3)
Maximum dose of epinephrine in the ICU on day of surgery among patients receiving epinephrine (μg kg^{-1} min^{-1}), median (IQR)	0.05 (0.03–0.06)
Norepinephrine in the ICU on day of surgery, *n* (%)	49 (36.6)
Maximum dose of norepinephrine in the ICU on day of surgery among patients receiving norepinephrine (μg kg^{-1} min^{-1}), median (IQR)	0.06 (0.03–0.09)

CAB, coronary artery bypass surgery; COPD, chronic obstructive pulmonary disease; EuroSCORE, European System for Cardiac Operative Risk Evaluation; IQR, inter-quartile range; LOS-ICU, length of stay in the ICU.

bypass, flow was maintained between 2.0 and 2.4 L min^{-1} m^{-2}, and MAP targets were established based on discussions among the surgeon, anaesthesiologist, and perfusionist. MAP targets in the ICU were 65–90 mm Hg, and inotropes were weaned based on estimates of adequate perfusion. Sedation after surgery was with propofol or dexmedetomidine until readiness for extubation.

Patient and perioperative characteristics were collected by review of the electronic medical record (EMR) by research staff. Comorbidities were defined as present/absent and medications were recorded from the EMR. Surgical and anaesthetic characteristics were abstracted from the surgical and anaesthetic records, respectively. ICU characteristics were abstracted from the flow sheets and the EMR.

Statistical analysis

Data for this analysis were obtained as part of an ongoing cohort study. Before analysis, we conducted a power analysis based on comparisons of dose of MAP outside the limits of autoregulation in the operating room and the ICU. Based on a dose of 15 (9) mm Hg×h in the operating room, we estimated that we would have >80% power to detect a 33% difference in dose in the ICU, using a significance threshold of $P<0.05$. As secondary and exploratory analyses of observational data, we examined associations of autoregulation metrics with delirium.

The statistical approach was established before the analysis, based on prior methods from our research group, but was not registered. Three cerebral autoregulation metrics were derived. First, the percentage of patients with globally impaired autoregulation in the operating room and the ICU was calculated. Second, the MAP at the LLA and ULA was defined using all intra- and postoperative data, and the total dose that MAP was <LLA or >ULA was calculated for each perioperative period. (Note, the mathematical definition of the dose is $\sum_{i=0}^{N}(Magnitude_i \times \Delta Time)$ [mm Hg×h], where h stands for hour, $\Delta Time$ is the time resolution (h), and $Magnitude_i$ are the individual values for magnitude of MAP deviation <LLA or >ULA.) Separately, the dose was normalised by monitoring time, with results expressed in units of '(mm Hg×h) h^{-1}'. Third, the average index of autoregulation was calculated as the average of all COx values.

Patient characteristics and autoregulation metrics were compared using Student's *t*-test, Wilcoxon rank sum test, Fisher's exact test, and χ^2 test. In exploratory analyses, logistic regression was used to quantify the association between postoperative delirium and (1) globally impaired autoregulation, (2) MAP dose outside limits of autoregulation, and (3) average index of autoregulation. The distribution of MAP dose outside limits of autoregulation was skewed, so these values were considered as quintiles in regression models. Models were adjusted for age and logistic EuroSCORE (both with complete data) based on *a priori* decisions, and bypass time was added subsequently. There was no loss to follow-up.

Results

Patient characteristics

A total of 134 patients were enrolled and a patient flow diagram is shown (Figure S1). The median age of patients was 65 yr (inter-quartile range [IQR] 58–71), and 75% were male (Table 1). Delirium was identified in 16.4% (22/134) of patients (Day 1: nine patients, Day 2: five patients, Day 3: 12 patients, Day 4: six patients). Compared with non-delirious patients, delirious patients were similar in their age and in the duration of cardiopulmonary bypass. However, the delirious patients had a higher logEuroSCORE, were more likely to be female, and have diabetes mellitus compared with non-delirious patients (Table S1). The duration of arterial BP and rSO_2 monitoring in the operating room was 4.8 (1.1) h (range 3.0–8.9 h). In the ICU, the duration of arterial BP monitoring was 15.9 (2.6) h (range 7.3–20.2 h) and rSO_2 monitoring 14.8 (3.2) h (range 5.4–19.7 h; some patients removed rSO_2 monitors prematurely).

Globally impaired autoregulation

The number of patients with globally impaired autoregulation (COx>0.3 at all MAPs) on at least one monitoring side (i.e. left/right) was greater in the operating room (53 [40%]) compared with in the ICU (18 [13%]; $P<0.001$). In the operating room, the prevalence of globally impaired autoregulation was greater in delirious compared with non-delirious patients, but this difference was not statistically significant (Fig. 2a). However, in the ICU, globally impaired autoregulation occurred significantly more often in delirious compared with non-delirious patients (Fig. 2b). In regression models, the odds of delirium were higher for patients with globally impaired *vs* not impaired autoregulation in the ICU in unadjusted models (odds ratio [OR] 3.1, 95% confidence interval [CI] 1.03–9.5, $P=0.045$) and models adjusted for age, duration of bypass, and logEuroSCORE (OR 4.0, 95% CI 1.2–13.7, $P=0.03$) (Table S2).

MAP dose outside the limits of cerebral autoregulation

Of the 134 patients monitored in the operating room and ICU, an LLA was identified in 105 patients and a ULA was identified in 65 patients. The remaining patients with interpretable curves exhibited globally impaired autoregulation (discussed in previous section) or the COx did not increase above 0.3 at the lower, upper, or both limits of autoregulation.

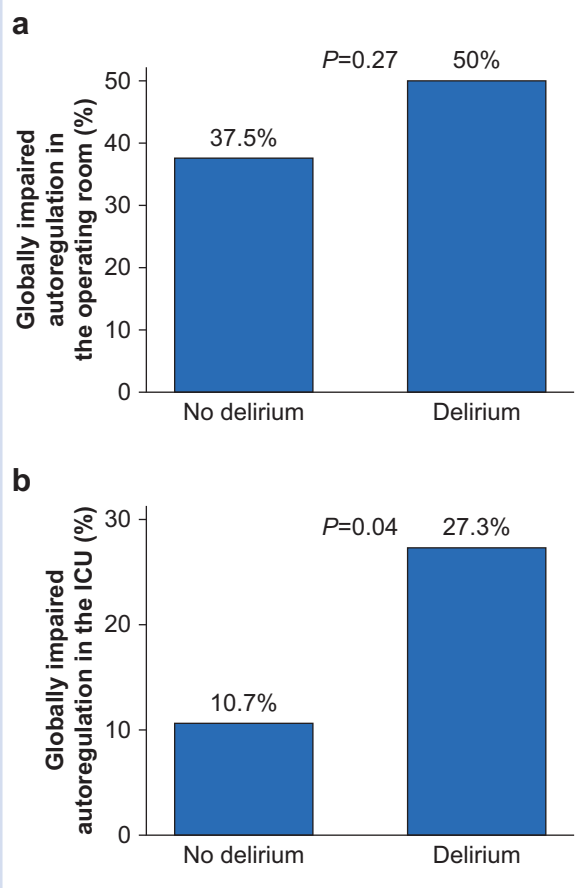

Fig 2. Globally impaired autoregulation in delirious and non-delirious patients. Globally impaired autoregulation ($n=134$) by delirium status in both the operating room (a) and the ICU (b). Globally impaired autoregulation is defined as all estimates of the index of autoregulation (COx) in each 5 mm Hg bin greater than the COx cutoff which distinguishes intact from impaired autoregulation.

The total MAP dose outside the upper and lower limits of cerebral autoregulation was similar in the operating room and in the ICU (Table 2). However, the contribution of MAP<LLA *vs* MAP>ULA was different. Specifically, the dose of MAP<LLA was greater in the operating room compared with the ICU, whereas for MAP>ULA there was no difference between the two monitoring periods. When the total MAP dose was normalised by the duration of monitoring to account for the approximately three-fold longer monitoring times in the ICU, all estimates of MAP dose outside the limits of cerebral autoregulation were greater in the operating room (Table 2).

The MAP dose outside the limits of cerebral autoregulation was greater in delirious *vs* non-delirious patients in the operating room (37.5 mm Hg×h, IQR 19.5–64.1 *vs* 16.2 mm Hg×h, IQR 9.7–29.2, $P=0.005$) (Fig. 3a), although was not significant in the ICU (26.7 mm Hg×h, IQR 13.8–47.9 *vs* 14.5, IQR 4.2–32.4, $P=0.07$) (Fig. 3b). In the operating room, the odds of delirium were higher for each quintile of increasing MAP dose outside the limits of cerebral autoregulation in both unadjusted models (OR 1.77, 95% CI 1.14–2.74, $P=0.01$) and models adjusted for age, duration of bypass, and logEuroSCORE (OR 1.75, 95% CI 1.10–2.77, $P=0.02$). Similarly, in the ICU, the odds of delirium were higher for each quintile of increasing MAP dose outside the limits of cerebral autoregulation in both unadjusted models (OR 1.53, 95% CI 1.02–2.32, $P=0.04$) and models adjusted for age, duration of bypass, and logEuroSCORE (OR 1.80, 95% CI 1.11–2.91, $P=0.02$ (Table S3).

Average index of autoregulation

The mean COx was greatest (i.e. weakest autoregulation) in the operating room (0.29 [0.17]) compared with in the ICU (0.19 [0.11]; $P<0.001$). There was no difference in average COx for delirious compared with non-delirious patients in either the operating room (0.28 [0.20] *vs* 0.29 [0.16], $P=0.67$) or ICU (0.21 [0.13] *vs* 0.19 [0.11], $P=0.52$).

Discussion

This study demonstrates the potential value of cerebral autoregulation monitoring in the ICU after cardiac surgery. In the ICU, the MAP dose outside the limits of cerebral autoregulation, although comparable in magnitude to the intraoperative period, was driven by a longer duration of exposure. In exploratory analyses, both globally impaired autoregulation and the MAP dose outside the limits of cerebral autoregulation in the ICU were associated with delirium, although the incidence of delirium was lower than in prior studies,[10,20] and confirmatory studies are needed to support the latter results.

Identifying an adequate MAP to ensure cerebral perfusion is a challenge for surgical patients, and cerebral autoregulation monitoring may identify personalised MAP targets and other quantification of cerebral autoregulation. In the operating room, individualised targets for adequate MAP have proved to be clinically meaningful in observational studies[8,9,18] and a randomised trial.[10]

Although the value of cerebral autoregulation monitoring in the operating room is becoming evident, characteristics of autoregulation in the ICU have not been well investigated, although our data suggest they are clinically relevant. The

Table 2 The product of magnitude and duration of mean arterial pressure outside the limits of autoregulation.

Cerebral autoregulation metric		Operating room	ICU	P-value
Product of magnitude and duration of MAP outside the limits of cerebral autoregulation (i.e. MAP<LLA+MAP>ULA[a]) median (IQR)	Total (mm Hg×h)	16.9 (10.1–38.8)	16.9 (5.4–35.1)	0.20
	Normalised per hour of monitoring (mmHg×h per hour)	4.1 (2.4–7.3)	1.1 (0.4–2.2)	<0.001
Product of magnitude and duration of MAP<LLA only,[a] median (IQR)	Total (mm Hg×h)	12.7 (6.8–28.3)	9.3 (1.8–22.8)	0.01
	Normalised per hour of monitoring (mm Hg×h per hour)	3.1 (1.6–5.6)	0.5 (0.1–1.4)	<0.001
Product of magnitude and duration of MAP>ULA only,[a] median (IQR)	Total (mm Hg×h)	5.3 (2.8–13.1)	5.3 (1.2–15.6)	0.74
	Normalised per hour of monitoring (mm Hg×h per hour)	1.1 (0.6–2.7)	0.4 (0.1–0.9)	<0.001

IQR, inter-quartile range; LLA, lower limit of autoregulation; ULA, upper limit of autoregulation.
[a] Defined as the product of magnitude×time [i.e. $\sum_{i=0}^{N}(Magnitude_i \times \Delta Time)$]) that the MAP was below the lower limit of autoregulation, above the upper limit of autoregulation or both combined together. Both total values (mmHg×h) and values normalised per hour of monitoring (mmHg×h per hour) are presented. The normalised values reflect the greater duration of recording in the ICU.

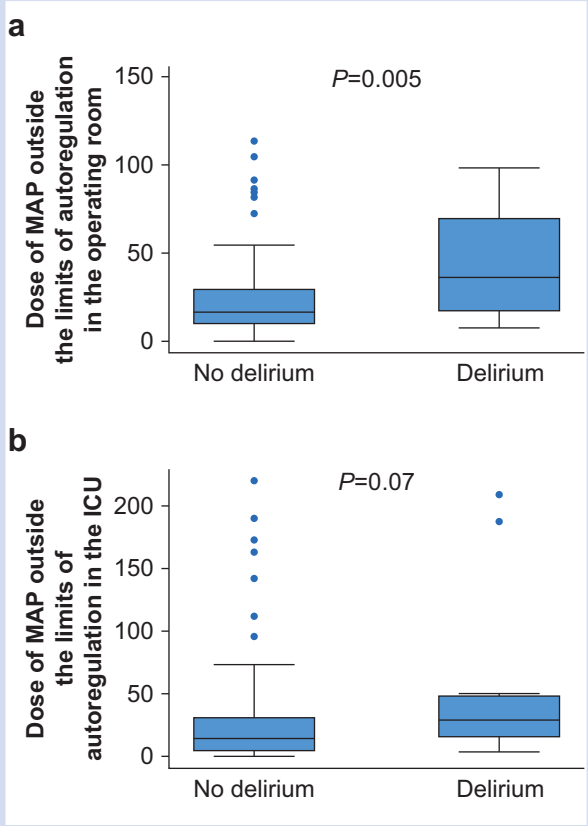

Fig 3. The product of magnitude and duration of mean arterial presssure outside the limits of autoregulation in delirious and non-delirious patients. The dose of MAP outside the limits of cerebral autoregulation by delirium status (n=110) in both the operating room (a) and the ICU (b). The dose of MAP outside the limits of cerebral autoregulation refers to the product of magnitude and duration of MAP below the lower limit of autoregulation (LLA) and above the upper limit of autoregulation (ULA). In Panel b, three outlier values >220 are depicted at 220 for purposes of scale.

prevalence of globally impaired autoregulation was 13% in the ICU. These patients are likely sensitive to small changes in MAP, as a result of reduced ability to regulate cerebral blood flow across MAPs. Previous results in the operating room demonstrated an association of globally impaired autoregulation with stroke,[23] and the current results demonstrate an association of globally impaired autoregulation in the ICU with delirium. Interestingly, more patients had globally impaired autoregulation in the operating room than in the ICU, the reasons for which are unclear but could include drugs, inflammation, or temperature. Regardless, the pathophysiology of, and treatments for, globally impaired autoregulation deserve further study.

The total dose of MAP outside the limits of cerebral autoregulation was similar in the ICU and operating room, implying that potential cerebral malperfusion extends into the early phase of ICU care. However, the intensity (total dose normalised by time of monitoring) was less in the ICU and driven more by MAP>ULA. The total dose reflects summation of potential malperfusion, while the intensity reflects dose per hour. In both the operating room and ICU, total dose of MAP outside the limits of autoregulation was associated with delirium. These results are conceptually similar to a study in which the cumulative duration of cerebral autoregulation dysfunction in the ICU was associated with delirium.[14] Although prior studies identified the average index of autoregulation in the ICU as a risk factor for delirium,[12,13] the current study did not. Differences in the estimation of autoregulation and periods of monitoring make the results difficult to compare directly.

A strength of this study is cerebral autoregulation monitoring in the ICU, which is a logical extension of prior operating room studies. Although brain injury may be common in the operating room, optimising postoperative management through the continuum of care is also likely important given neuropsychological sequelae of critical illness.[24] The autoregulation monitoring used clinically-feasible technology and the limits of autoregulation were estimated using transparent algorithms.[17] There are several limitations. Foremost, delirium was assessed once daily on three of the first four postoperative days using the 3D-CAM or clinical CAM-ICU assessments (in intubated patients). Some delirium may have been missed, which is reflected in two-to three-fold less delirium than we have reported previously.[20] Reasons for less delirium

compared with our prior studies include the brief nature of the 3D-CAM *vs* full CAM, less extensive cognitive testing during the assessment, no consensus committee for adjudication, and less queries to nurses and family about episodic delirium. This important limitation supports the need for confirmatory studies of these findings. However, any measurement bias should not be differential by autoregulation characteristics. Autoregulation data were only recorded through the morning of postoperative day 1. This design ensured that autoregulation measurements preceded a delirium diagnosis, but periods of MAP outside the limits of autoregulation may have been missed, and future studies should monitor for longer. Only the frontal cortex was monitored, so regional autoregulation information is unavailable. No brain injury biomarkers were collected, although such data could have provided insights into mechanistic relationships between delirium and autoregulation. Indeed, studies in cardiac and noncardiac surgery demonstrated associations of markers of oxidative stress[25] and neuronal injury[25–27] with delirium. Finally, the sample size limited the number of covariates in regression models and may not be sufficient to detect a difference in average index of autoregulation by delirium.

Cerebral autoregulation monitoring in the cardiac surgery ICU may provide information to individualise MAP targets and optimise cerebral autoregulation. Larger studies are needed to examine relationships with delirium to determine whether cerebral autoregulation monitoring in the ICU could guide management.

Authors' contributions

Acquisition of data: MN, YN, MW
Analysis of data: MN, YN, EC, BB, CHB
Interpretation of data: all authors
Revised the work for important intellectual content, approved the final version, and agrees to be accountable for all aspects of the work: all authors
Drafted the work: CHB

Acknowledgements

We acknowledge the efforts of Michelle Parish, Elizabeth White, and Mirinda Anderson White of the Johns Hopkins Department of Anesthesiology and Critical Care Medicine Clinical Research Core, who were instrumental in the conduct of the study.

Declarations of interest

KJN has received funding from Hitachi Corporation and funding from Merck & Co Inc. PS receives a portion of licensing fees for software ICM+. KB is listed as co-inventor of patents related to autoregulation monitoring that have been awarded and assigned to Johns Hopkins University. CH has received funding from Medtronic and consulted for Medtronic, Merck, & Edwards. CB has consulted for and participated in a data share agreement with Medtronic Inc. The remaining authors declare that they have no conflicts of interest.

Funding

National Institute on Aging (grant number K76 AG057020; to CHB) and Johns Hopkins Magic that Matters Foundation Grant to CHB).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2020.12.043.

References

1. Grocott HP. Blood pressure during cardiopulmonary bypass: how low is too low? *Anesth Analg* 2012; **114**: 488–90
2. Bijker JB, van Klei WA, Kappen TH, van Wolfswinkel L, Moons KG, Kalkman CJ. Incidence of intraoperative hypotension as a function of the chosen definition: literature definitions applied to a retrospective cohort using automated data collection. *Anesthesiology* 2007; **107**: 213–20
3. Stephens RS, Whitman GJ. Postoperative critical care of the adult cardiac surgical patient. part I: routine postoperative care. *Crit Care Med* 2015; **43**: 1477–97
4. Brady K, Joshi B, Zweifel C, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke* 2010; **41**: 1951–6
5. Brady KM, Lee JK, Kibler KK, et al. Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. *Stroke* 2007; **38**: 2818–25
6. Joshi B, Ono M, Brown C, et al. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg* 2012; **114**: 503–10
7. Ono M, Arnaoutakis GJ, Fine DM, et al. Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit Care Med* 2013; **41**: 464–71
8. Ono M, Brady K, Easley RB, et al. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *J Thorac Cardiovasc Surg* 2014; **147**: 483–9
9. Hori D, Brown C, Ono M, et al. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. *Br J Anaesth* 2014; **113**: 1009–17
10. Brown CH, Neufeld KJ, Tian J, et al. Effect of targeting mean arterial pressure during cardiopulmonary bypass by monitoring cerebral autoregulation on postsurgical delirium among older patients: a nested randomized clinical trial. *JAMA Surg* 2019; **154**: 819–26
11. Goettel N, Burkhart CS, Rossi A, et al. Associations between impaired cerebral blood flow autoregulation, cerebral oxygenation, and biomarkers of brain injury and postoperative cognitive dysfunction in elderly patients after major noncardiac surgery. *Anesth Analg* 2017; **124**: 934–42
12. Caldas JR, Panerai RB, Bor-Seng-Shu E, et al. Dynamic cerebral autoregulation: a marker of post-operative delirium? *Clin Neurophysiol* 2019; **130**: 101–8
13. Chan B, Aneman A. A prospective, observational study of cerebrovascular autoregulation and its association with delirium following cardiac surgery. *Anaesthesia* 2018; **74**: 33–44
14. Lee KF, Wood MD, Maslove DM, Muscedere JG, Boyd JG. Dysfunctional cerebral autoregulation is associated with delirium in critically ill adults. *J Cereb Blood Flow Metab* 2019; **39**: 2512–20

15. Hori D, Max L, Laflam A, et al. Blood pressure deviations from optimal mean arterial pressure during cardiac surgery measured with a novel monitor of cerebral blood flow and risk for perioperative delirium: a pilot study. *J Cardiothorac Vasc Anesth* 2016; **30**: 606–12
16. Blaine Easley R, Kibler KK, Brady KM, et al. Continuous cerebrovascular reactivity monitoring and autoregulation monitoring identify similar lower limits of autoregulation in patients undergoing cardiopulmonary bypass. *Neurol Res* 2013; **35**: 344–54
17. Aries MJ, Czosnyka M, Budohoski KP, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. *Crit Care Med* 2012; **40**: 2456–63
18. Ono M, Joshi B, Brady K, et al. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. *Br J Anaesth* 2012; **109**: 391–8
19. Marcantonio ER, Ngo LH, O'Connor M, et al. 3D-CAM: derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: a cross-sectional diagnostic test study. *Ann Intern Med* 2014; **161**: 554–61
20. Brown CH, Probert J, Healy R, et al. Cognitive decline after delirium in patients undergoing cardiac surgery. *Anesthesiology* 2018; **129**: 406–16
21. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. *Ann Surg* 2009; **249**: 173–8
22. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med* 2001; **29**: 1370–9
23. Joshi B, Brady K, Lee J, et al. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. *Anesth Analg* 2010; **110**: 321–8
24. Pandharipande PP, Girard TD, Ely EW. Long-term cognitive impairment after critical illness. *N Engl J Med* 2014; **370**: 185–6
25. Lopez MG, Hughes CG, DeMatteo A, et al. Intraoperative oxidative damage and delirium after cardiac surgery. *Anesthesiology* 2020; **132**: 551–61
26. Fong TG, Vasunilashorn SM, Ngo L. Association of plasma neurofilament light with postoperative delirium. *Ann Neurol* 2020; **88**: 984–94
27. Casey CP, Lindroth H, Mohanty R, et al. Postoperative delirium is associated with increased plasma neurofilament light. *Brain* 2020; **143**: 47–54

Handling editor: Michael Avidan