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REPORTS OF ORIGINAL INVESTIGATIONS

Cerebral autoregulation-based mean arterial pressure targets and delirium in critically ill adults without brain injury: a retrospective cohort study

Cibles de tension artérielle moyenne basées sur l'autorégulation cérébrale et delirium chez les adultes gravement malades sans lésion cérébrale : une étude de cohorte rétrospective

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Abstract

Purpose *Cerebral autoregulation (CA) is a mechanism that acts to maintain consistent cerebral perfusion across a range of blood pressures, and impaired CA is associated with delirium. Individualized CA-derived blood pressure targets are poorly characterized in critically ill patients and the association with intensive care unit (ICU) delirium is unknown. Our objectives were to characterize optimal mean arterial pressure (MAP_{opt}) ranges in critically ill adults without brain injury and determine whether deviations from these targets contribute to ICU delirium.*

Methods *We performed a retrospective cohort analysis of patients with shock of any etiology and/or respiratory failure requiring invasive mechanical ventilation, without a neurologic admitting diagnosis. Patients were screened daily for delirium. Cerebral oximetry and mean arterial pressure data were captured for the first 24 hr from enrolment.*

Results *Forty-two patients with invasive blood pressure monitoring data were analyzed. Optimal mean arterial pressure targets ranged from 55 to 100 mm Hg. Optimal mean arterial pressure values were not significantly different based on history of hypertension or delirium status, and delirium was not associated with deviations from MAP_{opt}. Nevertheless, the majority (69%) of blood*

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pressure targets exceeded the current 65 mm Hg Surviving Sepsis guidelines.

Conclusion *We observed that MAP_{opt} targets across patients were highly variable, but did not observe an association with the incidence of delirium. Studies designed to evaluate the impact on neurologic outcomes are needed to understand the association with individualized mean arterial pressure targets in the ICU.*

Study registration *ClinicalTrials.gov (NCT02344043); first submitted 22 January 2015.*

Résumé

Objectif *L'autorégulation cérébrale (AC) est un mécanisme qui agit pour maintenir une perfusion cérébrale constante pour une gamme de tensions artérielles, et une altération de l'AC est associée au delirium. Les cibles de tension artérielle individualisées dérivées de l'AC sont mal caractérisées chez les patient·es gravement malades et l'association avec le delirium à l'unité de soins intensifs (USI) est inconnue. Nos objectifs étaient de caractériser la tension artérielle moyenne optimale (TAM_{opt}) chez les adultes gravement malades sans lésion cérébrale et de déterminer si les écarts par rapport à ces cibles contribuaient au delirium à l'USI.*

Méthode *Nous avons réalisé une analyse de cohorte rétrospective de patient·es présentant un choc de toute étiologie et/ou une insuffisance respiratoire nécessitant une ventilation mécanique invasive, et n'ayant pas reçu de diagnostic d'atteinte neurologique à l'admission. Les patients ont été dépistés quotidiennement pour le delirium. Les données d'oxymétrie cérébrale et de tension artérielle moyenne ont été saisies pendant les 24 premières heures suivant le recrutement.*

Résultats *Quarante-deux patient·es pour qui des données de monitorage invasif de la tension artérielle étaient disponibles ont été analysé·es. Les cibles optimales de tension artérielle moyenne variaient de 55 à 100 mm Hg. Les valeurs optimales de tension artérielle moyenne n'étaient pas significativement différentes en fonction des antécédents d'hypertension ou de delirium, et le delirium n'était pas associé à des écarts par rapport à la TAM_{opt}. Néanmoins, la majorité (69 %) des cibles de tension artérielle dépassaient celle de 65 mm Hg préconisée par les lignes directrices Surviving Sepsis.*

Conclusion *Nous avons observé que les cibles de TAM_{opt} étaient très variables chez les patient·es, mais nous n'avons pas observé d'association avec l'incidence de delirium. Des études conçues pour évaluer l'impact sur les issues neurologiques sont nécessaires pour comprendre l'association avec les cibles de tension artérielle moyenne individualisées à l'USI.*

Enregistrement de l'étude *ClinicalTrials.gov (NCT02344043); soumis pour la première fois le 22 janvier 2015.*

Keywords cerebral autoregulation · critically ill · delirium · near-infrared spectroscopy · optimal mean arterial blood pressure (MAP_{opt})

Blood pressure targeting to maintain adequate perfusion is a focus of resuscitation efforts in the intensive care unit (ICU). Clinical practice guidelines provide fixed targets, including the Surviving Sepsis recommendation to maintain a mean arterial pressure (MAP) of 65 mm Hg.[1] Debate has ensued surrounding best practices, as a MAP of 65 mm Hg may not be sufficient to maintain adequate perfusion in all patients.[2] Improved neurologic outcomes have been seen in patients who sustained higher MAPs over their ICU stay after cardiac arrest[3] and spinal cord injury.[4] Nevertheless, in a recent interventional study, a 77 mm Hg *vs* 63 mm Hg MAP target did not improve three-month cognitive outcomes in cardiac arrest survivors.[5] The application of a one-size-fits-all approach may lead to inappropriate perfusion at an individual level, masking the benefit in individuals who have elevated perfusion requirements.[6,7]

Cerebral autoregulation (CA) is the mechanism that acts to maintain appropriate cerebral perfusion despite systemic blood pressure fluctuations. Impaired CA is linked with acute neurologic dysfunction, where duration of disturbed cerebral autoregulation is associated with the development and duration of delirium in critically ill patients.[8,9] Intact CA is associated with specific MAP values, and CA monitoring can be used to compute personalized optimal blood pressure targets (optimal MAP; MAP_{opt}) that maintain CA. In cardiac surgery, deviations from MAP_{opt} peri- and postoperatively are associated with delirium.[10,11] Further, individualized MAP targeting during surgery has reduced rates of postoperative delirium.[12–14]

While feasible to determine MAP_{opt} targets using noninvasive neuromonitoring in the ICU,[15–18] the use of CA monitoring in clinical practice is still under investigation.[9,19] Few studies have sought to characterize MAP_{opt} targets in the ICU and are limited to patients with brain injury.[16,17,20] Further, the impact of deviations from individualized MAP targets on ICU delirium are unknown. Our goal was to characterize noninvasively derived MAP_{opt} targets using cerebral oximetry in critically ill patients with shock and/or respiratory failure without brain injury, and to perform an exploratory analysis comparing deviations from MAP_{opt} with delirium. This analysis was performed on a nested cohort of patients in whom duration

of disturbed CA was associated with the presence and duration of ICU delirium.[8] We hypothesized that MAP_{opt} targets would exceed 65 mm Hg and be further elevated in patients with a history of hypertension. Additionally, we hypothesized that deviations from MAP_{opt} would be associated with increased likelihood of the development and duration of ICU delirium.

Materials and methods

Study design and participant recruitment

We retrospectively analyzed a nested cohort from the main Cerebral Oxygenation and Neurologic Outcomes Following Critical Illness 1 (CONFOCAL-1) study, a single centre prospective cohort study (ClinicalTrials.gov, ID: NCT02344043) in Kingston, ON, Canada, for which the full protocol has been previously published.[21] The Queen's University Health Sciences and Affiliated Hospitals Research Ethics Board (Kingston, ON, Canada) approved this study according to ethical principles, regulations, and guidelines, including the Food and Drugs Act, the International Conference on Harmonisation Good Clinical Practice Guidelines, and the Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Our study aimed to characterize CA-based blood pressure targets for the general medical and surgical ICU population. Eligibility extended to adult patients ($\geq$ 18 yr) admitted to a 33-bed general, surgical, and trauma ICU between March 2014 and September 2016, with shock of any etiology and/or respiratory failure requiring mechanical ventilation for an expected period of $>$ 24 hr. Only patients admitted within the previous 24 hr were eligible. Shock was defined as the requirement of the following vasopressors and inotropes: dopamine $\geq$ 7.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, dobutamine $\geq$ 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$, norepinephrine $\geq$ 5 $\mu g \cdot min^{-1}$, phenylephrine $\geq$ 75 $\mu g \cdot min^{-1}$, epinephrine at any dose, milrinone at any dose (if used in conjunction with another agent), vasopressin $\geq$ 0.03 $U \cdot min^{-1}$ (if used in conjunction with another agent).[21] Exclusion criteria included life expectancy $<$ 24 hr, primary central nervous system diagnosis, or previous diagnosis of cognitive impairment/dementia, as listed on medical records.

Sample size

Our nested cohort was composed of CONFOCAL-1 patients with data from invasive blood pressure monitoring. This retrospective study was exploratory in nature and an *a priori* power calculation was not performed.

Data collection

Clinical and demographic information was collected at patient enrolment including admitting diagnosis and comorbidities. Histories of hypertension and alcohol use disorder were determined based on chart review. Illness severity was quantified using the APACHE II score. Regional cerebral oxygenation (rSO_2) data were collected using the ForeSight^{TM} near-infrared spectroscopy oximeter (Edwards Lifesciences, Irvine, CA, USA). One 5-cm monitor was centred on the patient's forehead and rSO_2 data were captured at 0.5 Hz for 24 hr. Oximeter screens were concealed to ensure treating clinicians were unaware of rSO_2 values. Physiologic variables (i.e., heart rate, MAP) were extracted from the ICU monitors (GE Solar, New York, NY, USA) using commercial software (Bedmaster, Excel Medical Electronics, Jupiter, FL, USA) and stored at Queen's Centre for Advanced Computing (Kingston, ON, Canada).

Delirium screening

Trained researchers used the Confusion Assessment Method (CAM)-ICU to screen patients for delirium once daily for up to 30 days. Patients were reported to be comatose (Richmond Agitation Sedation Scale -4 or -5), delirious, or nondelirious on each day. To calculate proportion of time spent delirious, only noncomatose days were included in the denominator as patients could not be assessed for delirium on days when comatose. To compare the proportion of time delirious with area outside the MAP_{opt}, patients who were comatose for their whole ICU stay were excluded as the proportion of time spent delirious would be zero. Intensive care unit discharge was reported as the day discharge was ordered, as patients did not always leave on this day because of low ward bed availability.

Cerebral autoregulation and optimal mean arterial pressure analysis

Prior to cerebral oximetry index calculation, MAP data were cleaned of artifacts using an algorithm[22] adapted for use in an ICU population.[23,A] The algorithm was modified to incorporate the removal of MAP values $<$ 30 mm Hg and $>$ 200 mm Hg because of physiologic implausibility and to incorporate more lenient thresholds for acceptable minute-to-minute MAP fluctuations. Graphical depictions of MAP traces were then reviewed independently by two researchers. Based on clinical

[A] Code available from URL: https://github.com/jasmine-jk/ICU-MAP-Cleaning (accessed May 2023).

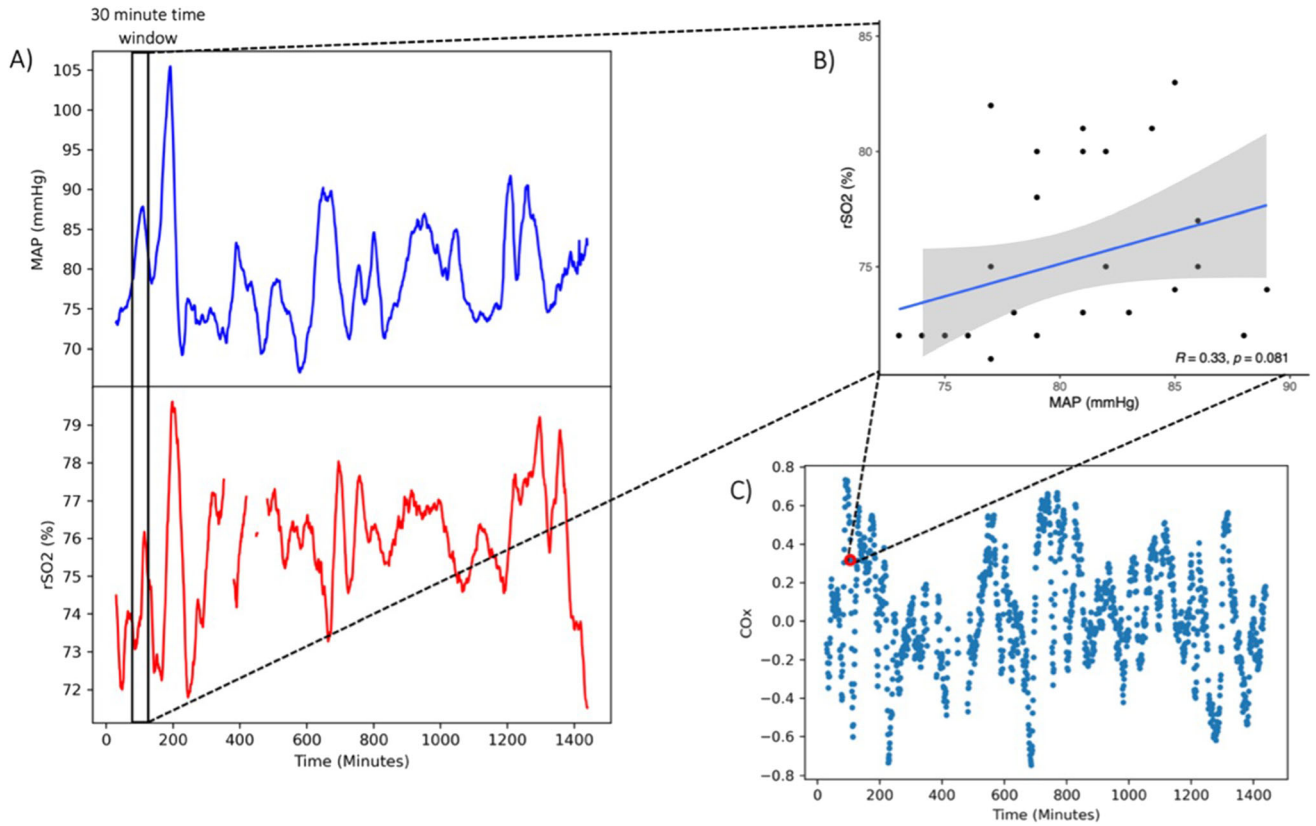

Fig. 1 Method for calculating the cerebral oximetry index. A) Twenty-four hours of mean arterial pressure (MAP) and regional cerebral oxygenation (rSO_2) data from one patient. B) Sample Spearman Rho correlation calculated for 30 min of MAP and rSO_2 data. C) All cerebral oximetry index values calculated for a single patient within the 24-hr recording period.
COx = cerebral oximetry index; MAP = mean arterial pressure; rSO_2 = regional cerebral oxygenation

judgement, patients were excluded from data analysis if significant contamination was present after data cleaning. A representative example of excluded MAP data is shown in Electronic Supplementary Material (ESM) eFig. 1.

The cerebral oximetry index (COx) was used to assess CA as described previously.[8] The COx is defined as the time-varying correlation coefficient between cerebral oxygenation and blood pressure. To summarize, time-rolling Spearman Rho correlation coefficients were calculated between MAP and rSO_2 in 30-min time windows, advanced by one-minute intervals across the recording period (Fig. 1). Positive COx values ($P < 0.0001$) indicated disturbed CA, while negative or near-zero values indicated intact CA. A 30-min time window and P value of 0.0001 were chosen for CA analysis based on previous analysis showing that these thresholds optimized the ability to discriminate between delirious and nondelirious patients.[8]

The COx was then used to derive individual patient MAP_{opt} values using custom algorithms designed in R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and Python™ version 6.4.5 (Python Software Foundation, Wilmington, DE, USA) as described previously.[15] Briefly, MAP_{opt} is the MAP range in which CA is theoretically preserved. The optimal mean arterial pressure was calculated as mean MAP for which COx = 0, where ± 1 standard deviation (SD) represents upper and lower MAP_{opt} limits. Our current method does not require a complete CA curve to calculate a MAP range in which CA is preserved because dynamic measurements of CA mean that patients may not necessarily enter danger zones within the recording period. All patients included in this study had identifiable MAP ranges where CA was considered intact.

The area outside MAP_{opt} was calculated as the area (time multiplied by magnitude of deviations) outside of MAP_{opt}. For example, a 3-mm Hg deviation for ten minutes would give the same value as a 30-mm Hg deviation for one minute. The area within MAP_{opt} was calculated as the time multiplied by the magnitude above the lower limit of the MAP_{opt} range. The proportion of area outside MAP_{opt} was then calculated by dividing the area outside MAP_{opt} by the total recorded area (i.e., area within MAP_{opt} and area outside MAP_{opt}) to account for variation in recording lengths (ESM eFig. 2).[B]

[B] The code is available from URL: https://github.com/jasmine-jk/ICU-MAPopt.git (accessed May 2023).

Statistical analysis

We compared clinical and demographic data between "ever delirious" and "never delirious" patients using Fisher's exact test for categorical data and the Mann–Whitney *U* test for continuous data. Bonferroni correction was applied to correct for multiple comparisons of demographic data ($a = 0.05/16 = 0.003$). We used the Mann–Whitney *U* test to compare MAP_{opt} values between subgroups based on delirium status and history of hypertension. We used multiple logistic regression analysis to assess the independent contribution of area outside MAP_{opt} to presence/absence of delirium, controlling for history of chronic hypertension and alcohol use disorder. Goodness of fit was assessed using McFadden's pseudo R^2. We performed simultaneous multiple linear regression analysis to determine the contribution of area outside of MAP_{opt} to proportion of days of delirious, controlling for history of hypertension, alcohol use disorder, and illness severity (i.e., APACHE II score). We calculated the proportion of days delirious as the number of days delirious divided by the duration of ICU stay not comatose, censored at 30 days. For all regression analyses, covariates including alcohol use disorder, history of hypertension, and illness severity were chosen prior to analysis based on their association with delirium.[24] To prevent selective outcome reporting, we report all models analyzed.

Results

Clinical and demographic patient characteristics

From March 2014 to September 2016, 1,155 patients were assessed for eligibility and 104 were enrolled (Fig. 2). Forty-eight of 104 enrolled patients had blood pressure data available. Six patients were excluded after applying the MAP cleaning algorithm because of significant MAP signal contamination, resulting in MAP_{opt} analysis for 42 patients. Two patients remained comatose for their entire ICU stay and could not be evaluated for delirium. Baseline characteristics for the cohort are shown in Table 1 and are grouped based on delirium status. Patients with missing demographic data were excluded. Twenty-five (63%) patients were "ever-delirious," experiencing delirium at least once while in the ICU, while fifteen were "never-delirious." We found no statistically significant differences ($P > 0.003$) in baseline comorbidities, admitting diagnoses, or illness severity at admission. The median [interquartile range (IQR)] vital sign recording length was 23 [19–24] hr. The mean (SD) MAP across the recording period was 78 (15) mm Hg.

Distribution of optimal mean arterial pressure targets across patients

We successfully identified MAP_{opt} targets in 42/48 (88%) patients. The median [IQR] MAP_{opt} was 75 [70–81] mm Hg, with values ranging from 55 to 100 mm Hg. The median lower limit was 68 [65–73] mm Hg and median upper limit was 83 [75–87] mm Hg. The average MAP_{opt} range was 14 mm Hg, with 29/42 (69%) patients having MAP_{opt} ranges that did not encompass 65 mm Hg. Individual MAP_{opt} data indicated heterogeneity as shown in Fig. 3.

Optimal mean arterial pressure targets based on history of hypertension and intensive care unit delirium

Average MAP_{opt} was calculated for patients with and without a history of hypertension. The median [IQR] MAP_{opt} for each group was 74 [71–81] mm Hg and 75 [70–80] mm Hg, respectively ($P = 0.83$). The variability of MAP_{opt} within groups is shown in Fig. 4A. There were no significant differences in lower ($P = 0.83$) or upper ($P = 0.55$) limits of MAP_{opt} (ESM eFig. 3A, B), as well as differences in MAP_{opt} between "ever" delirious and "never" delirious patients ($P = 0.18$), shown in Fig. 4B. Delirium status was not significantly associated with lower MAP_{opt} limit ($P = 0.11$) or upper MAP_{opt} limit ($P = 0.21$) (ESM eFig. 3C, D).

Cumulative deviation from optimal mean arterial pressure and delirium

In our nested cohort, the mean (SD) proportion of area outside the MAP_{opt} was 36 (9)%. We controlled for risk factors of delirium development including history of alcohol use disorder and illness severity. Further, we controlled for history of hypertension as chronic hypertension is associated with right-shifted CA curves. Multiple logistic regression indicated no significant association of area outside MAP_{opt} (odds ratio [OR], 0.96; $P = 0.26$), history of hypertension (OR, 1.15; $P = 0.83$), or history of alcohol use disorder (OR, 2.61; $P = 0.42$) with delirium status (Table 2). Overall, the model did not account for a significant amount of variance ($\chi^2 = 2.2$; $P = 0.53$). We also assessed the association between the area outside MAP_{opt} and the proportion of ICU stay spent delirious using linear regression. Our model accounted for a significant amount of the variance in proportion of time spent delirious ($R^2 = 0.36$; $P = 0.003$). The area outside MAP_{opt} ($b = -0.002$; $P = 0.54$) and history of hypertension ($b = -0.08$; $P = 0.32$) did not significantly predict proportion of stay delirious. A history of alcohol use disorder ($b = 0.46$; $P = 0.0003$) and illness

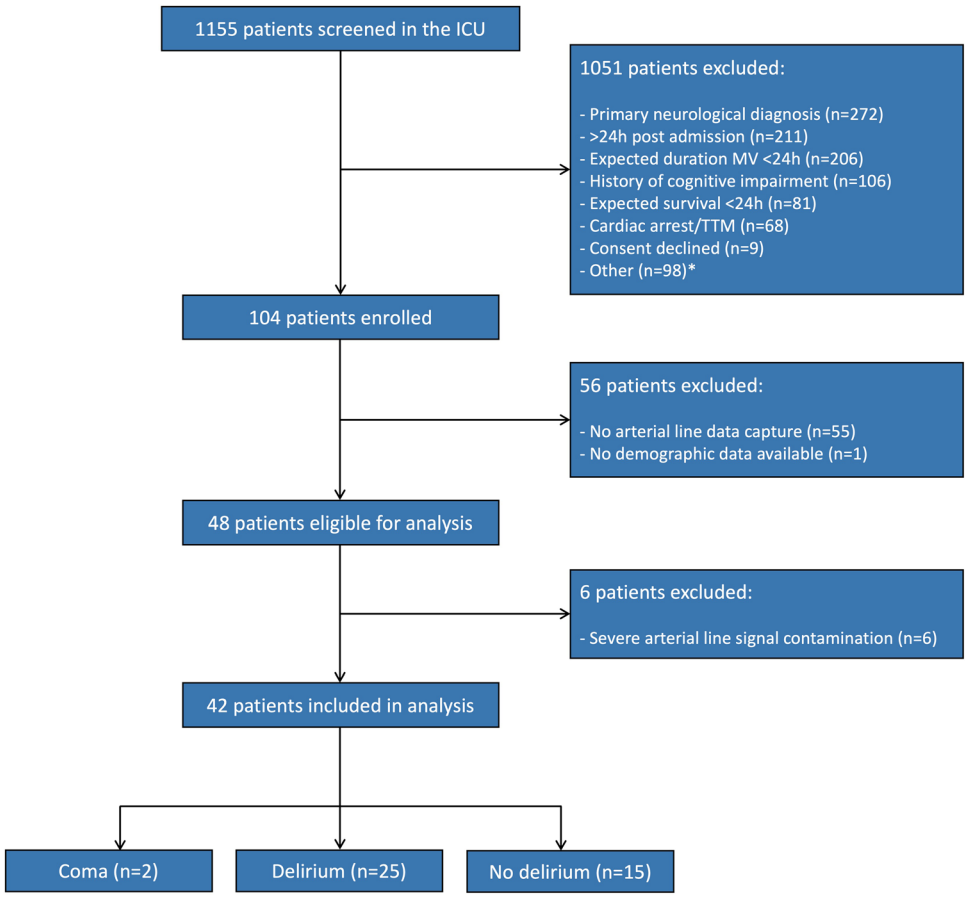

Fig. 2 CONSORT flow diagram for study recruitment and data analysis. *Other reasons for patient exclusion included unavailability of staff/equipment, family unapproachable for research consent, and previous documented refusal to participate in research. ICU = intensive care unit; MV = mechanical ventilation; TTM = target temperature management

severity ($b = 0.01$; $P = 0.03$) were associated with increased duration of delirium (Table 2).

Discussion

We evaluated CA-based MAP_{opt} targets in a nested cohort of 42 critically ill adults without brain injury that were admitted with shock and/or respiratory failure. The MAP_{opt} was variable, ranging from 55 to 100 mm Hg with a median [IQR] of 75 [70–81] mm Hg. Controlling for history of hypertension and alcohol use disorder, we did not observe an association between area outside MAP_{opt} and the presence of delirium or the proportion of days spent delirious.

The observed MAP_{opt} of our cohort is comparable to values derived noninvasively using near-infrared spectroscopy in critically ill adults with neurologic diagnoses. In patients who were acutely comatose secondary to brain injury, a median [IQR] MAP_{opt} of 90 [85–100] mm Hg was reported.[16] In another study of patients with hypoxic ischemic brain injury after cardiac arrest, the observed mean (SD) MAP_{opt} was 76 (7) mm Hg.[17] On the other hand, a study examining patients after cardiac arrest observed that those with good neurologic outcomes had a median MAP_{opt} of 87 [82–88] mm Hg compared with 82 [74–92] mm Hg in those with poor neurologic outcomes.[20] Therefore, average MAP_{opt} targets appear to be similar in critically ill patients with or without brain injury. The average MAP_{opt} range was 15 mm Hg, a blood pressure target range that is more feasible than attempting to target a single MAP value.

Interestingly, ICU guidelines suggest maintaining a MAP of 65 mm Hg for patients, and the majority of MAP_{opt} targets of this cohort exceeded current guidelines, raising the possibility that hypoperfusion may be occurring in a large number of critically ill patients. As such, current ICU practice may impact cerebral perfusion and subsequent cognitive outcomes through targeting a suboptimal MAP. Concern of hypoperfusion with a MAP of 65 mm Hg was addressed in the SEPSISPAM study, where researchers pharmacologically targeted patients' MAP within the recommended guideline of 65–70 mm Hg or a higher value of 80–85 mm Hg.[25] The primary outcome was 28-day mortality, for which no significant difference was observed between groups;

Table 1 Demographic and clinical characteristics of all patients for which optimal mean arterial pressure was calculated

Clinical feature or demographic	Total $N = 42$	Delirium $N = 25$	No delirium $N = 15$	Coma $N = 2$	P value[†]
Age (yr), median [IQR]	68 [58–79]	68 [59–79]	73 [50–78]	69 [67–70]	0.46
Male sex, *n*/total *N* (%)	28/42 (67%)	19/25 (76%)	7/15 (47%)	2/2 (100%)	0.04
Comorbidities					
Hypertension, n/total *N* (%)	25/42 (60%)	14/25 (56%)	9/15 (60%)	2/2 (100%)	1.00
Diabetes, n/total *N* (%)	11/42 (26%)	5/25 (20%)	5/15 (33%)	1/2 (50%)	0.70
Tobacco use, n/total *N* (%)	9/42 (21%)	6/25 (24%)	2/15 (13%)	1/2 (50%)	1.00
Alcohol use disorder, n/total *N* (%)	5/42 (12%)	4/25 (16%)	1/15 (7%)	0/2 (0%)	0.63
Admitting diagnosis					
Respiratory, n/total *N* (%)	14/42 (33%)	6/25 (25%)	8/15 (53%)	0/2 (0%)	0.09
Sepsis, n/total *N* (%)	6/42 (14%)	6/25 (25%)	0/15 (0%)	0/2 (0%)	0.07
Cardiac, n/total *N* (%)	7/42 (23%)	5/25 (20%)	1/15 (7%)	1/2 (50%)	0.38
Trauma, n/total *N* (%)	3/42 (7%)	2/25 (8%)	1/15 (7%)	0/2 (0%)	1.00
Gastrointestinal, n/total *N* (%)	7/42 (23%)	2/25 (8%)	4/15 (27%)	1/2 (50%)	0.17
Vascular, n/total *N* (%)	3/42 (7%)	2/25 (8%)	1/15 (7%)	0/2 (0%)	1.00
Other, n/total *N* (%)*	2/42 (5%)	2/25 (8%)	0/15 (0%)	0/2 (0%)	0.52
Mechanical ventilation, *n*/total *N* (%)	41/42 (98%)	25/25 (100%)	15/15 (100%)	2/2 (100%)	N/A
Vasoactive agents, *n*/total *N* (%)	25/42 (60%)	12/25 (48%)	11/15 (73%)	2/2 (100%)	0.26
ICU LOS (days), median [IQR]	7 [5–13]	7 [5–13]	10 [7–14]	8 [7–9]	0.03

Patients are divided according to the presence ("ever" delirious) or absence ("never" delirious) of delirium, or comatose for the evaluation period during their intensive care unit stay. Age and length of stay (LOS) measurements are reported as median [IQR]

*Other = benzodiazepine withdrawal, acute kidney injury/encephalopathy requiring dialysis

[†]Statistical testing only performed between delirious and nondelirious groups

ICU LOS = intensive care unit length of stay; IQR = interquartile range

however, actual MAP values exceeded 65–70 mm Hg in the low MAP target group. In several studies examining fixed high *vs* low MAP targets on 3-, 6-, and 12-month neurologic outcomes[26–28] there were no differences between groups. In our study, up to 30% of patients had MAP_{opt} targets containing 65 mm Hg. A lack of difference in outcomes with fixed high *vs* low MAP targets may be explained by the heterogeneity in MAP_{opt} between patients. In an observational study, greater than 80% of time spent outside MAP_{opt} was associated with 3- and 6-month mortality.[16] Additional work is needed to determine whether the use of individualized targets, rather than a single fixed target, improves neurologic outcomes.

Chronic hypertension has been shown to cause right-shifted CA curves, thereby requiring elevated MAP to maintain CA.[29] In our study, the MAP_{opt} did not differ based on history of hypertension. Our sample size was small, and there was marked variability within groups, with MAP_{opt} ranging from 55 to 85 mm Hg without hypertension and 65 to 100 mm Hg with hypertension. At a population level, chronic hypertension leads to right shifts in CA curves, although many factors may contribute, including time from diagnosis, severity, and level of management.

Previous research indicates that age, sex, frailty, illness severity, hypertension, medications including sedatives and analgesics, and alcohol use disorder are risk factors for the development of delirium.[24,30–32] Given the multifactorial nature of delirium, we controlled for covariates in our analyses. Nevertheless, our sample size precluded us from incorporating a comprehensive array of delirium risk factors. Our results are consistent with a MAP targeting trial after cardiac arrest, where individualized targeting for the first 36 hr increased cerebral oxygenation but did not improve neurologic outcomes.[26] Our results contradict findings in cardiac surgery where intraoperative MAP targeting based on CA monitoring reduced postoperative delirium.[13] This was a small exploratory retrospective study; subgroups may exist that warrant different MAP targets to prevent both hyper- and hypoperfusion. Further work is needed to parse out potential differences based on deviations below *vs* above individualized targets, and to understand whether deviations from MAP targets to maintain CA has a greater impact on severity rather than solely the presence or absence of ICU delirium. Although

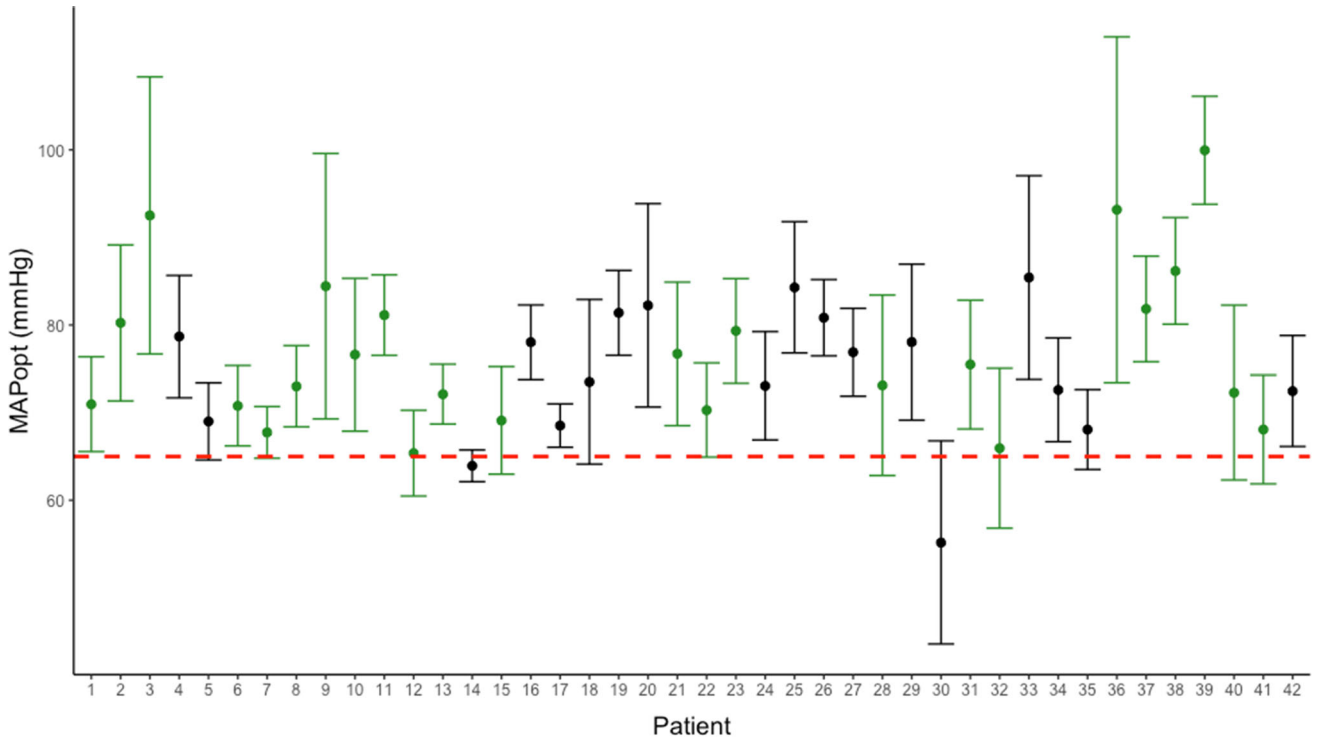

Fig. 3 Individualized mean arterial pressure targets by patient based on cerebral autoregulation monitoring data. Circles indicate patients' optimal mean arterial pressure (MAP_{opt}) and vertical lines represent each patient's MAP_{opt} range. Dotted red line represents the 2021 Surviving Sepsis MAP target of 65 mm Hg.[1]
Black = no history of hypertension; green = history of hypertension; MAP = mean arterial pressure; MAP_{opt} = optimal mean arterial pressure

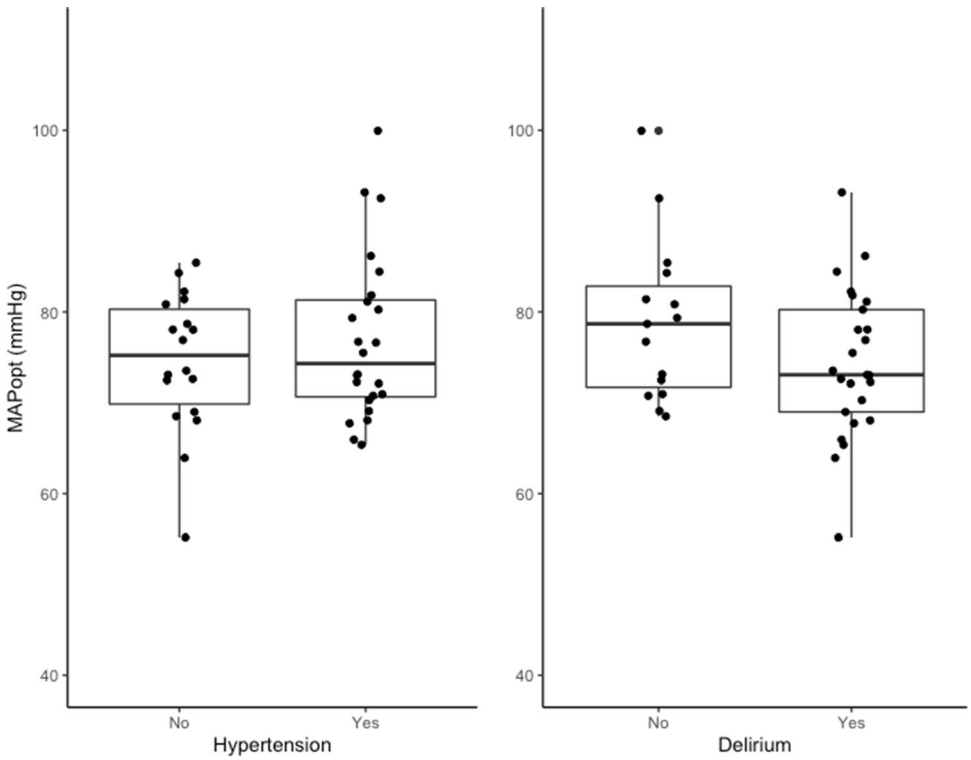

Fig. 4 Optimal mean arterial pressure values of patients based on A) history of chronic hypertension and B) delirium status in the intensive care unit
MAP_{opt} = optimal mean arterial pressure

Table 2 Logistic and linear regression analysis examining the association between the area outside of optimal mean arterial pressure with presence of delirium and proportion of intensive care unit stay being delirious

Outcome	Delirium presence/absence		Proportion of time spent delirious	
Measure	OR (95% CI)	*P* value	*b* (95% CI)	*P* value
Area outside MAP_{opt} (%)	0.96 (0.89 to 1.03)	0.26	−0.002 (−0.010 to 0.006)	0.54
History of hypertension	1.15 (0.30 to 4.42)	0.83	−0.08 (−0.24 to 0.08)	0.32
History of alcohol use disorder	2.61 (0.33 to 54.72)	0.42	0.46 (0.22 to 0.70)	0.00036
Illness severity (APACHE II score)	—	—	0.01 (0.002 to 0.03)	0.03
	Pseudo R^2 = 0.04 (χ^2 = 2.2, *P* = 0.53)		R^2 = 0.36 (*P* = 0.0027)	

CI = confidence interval; ICU = intensive care unit; MAP_{opt} = optimal mean arterial pressure; OR = odds ratio

we have observed that many individuals in our cohort had a MAP_{opt} higher than the typical target of 65 mm Hg, targeting a higher MAP must be balanced against the risks of higher vasopressor doses, which can be associated with tachyarrhythmias, hyperglycemia, and end-organ ischemia.[33] A systematic review of two randomized control trials comparing low *vs* high MAP targets found no difference in mortality between groups; however, a secondary analysis found that high MAP targets increased risk of new-onset supraventricular arrhythmia.[34] Therefore, further research is needed to optimize vasopressor use at an individual level to minimize exposure to adverse events from both hypoperfusion and pharmacologic side-effects.

This study has several limitations. It was retrospective in design, and the analysis was exploratory in nature. In addition, the sample was small, and therefore may be underpowered to detect an effect. This also limited the number of covariates we could include in the regression analysis. Delirium is influenced by several factors, including age, sex, frailty, and medication use (i.e., sedative and analgesics) and as such requires us to control for covariates that may predispose individuals. Our sample size may not have been sufficient to properly control for differences in terms of sex, admitting diagnoses, and use of vasoactive agents in delirious *vs* nondelirious groups. Further, invasive blood pressure monitoring was restricted to the initial 24 hr after enrolment. Cerebral autoregulation curves are impacted by a patient's physiologic state, and as such MAP_{opt} targets may fluctuate over time. While the overarching hypothesis of our program of research is that early cerebral ischemia (i.e., during the first day of ICU admission) is a key risk factor for the subsequent development of delirium, we acknowledge that events beyond the first 24 hr may contribute to delirium risk as well, including sedative/analgesic drugs and new ICU-acquired infections. Finally, delirium assessments were restricted to binary classification (i.e., present or absent). To overcome these limitations, this analysis will be replicated in a prospective, observational, multicentre study, CONFOCAL-2 (ClinicalTrials.gov ID: NCT03141619) of 500 patients and will be powered to incorporate six additional covariates. In addition, monitoring will be performed for the first 72 hr. Finally, we will use the CAM-ICU-7[35] to capture delirium severity and will examine whether cumulative delirium severity across ICU stay is impacted by CA-derived parameters. We will also consider the use of a composite outcome of delirium to account for coma and death precluding delirium assessment.

Noninvasive CA monitoring is not a standard practice in the ICU. This study contributes to the growing body of literature that aims to characterize personalized MAP targets in critically ill adults using noninvasive neuromonitoring, and to examine the association between impaired CA and neurocognitive outcomes. A main focus in the literature is on the extremes of outcomes including mortality and severe cognitive impairment. While studies have shown comparable mortality rates with low *vs* high MAP targets, 65 mm Hg may be at the lower end of what is required to ensure adequate end-organ perfusion in the majority of patients. In some studies, higher MAP thresholds of 73–75 mm Hg result in better renal outcomes.[36,37] Similar requirements may be needed to preserve cognitive function, tailored based on an individual's CA curve. Defining optimal rSO_2 presents significant challenges given the variability in absolute values based on factors including skin colour, oximeter manufacturer, and probe placement.[38–40] As such, the derivation of individualized blood pressure targets to preserve CA provides an avenue for optimizing cerebral perfusion. Delirium is one of the most consistent and potentially modifiable risk factors for post-ICU cognitive impairment.[41] Intensive care unit survivors experience mild to moderate cognitive impairment that impacts quality of life, from instrumental activities of daily living to return to the workplace, highlighting the importance of

understanding how to improve recovery through effective neuromonitoring and hemodynamic management.

Conclusion

In this exploratory analysis, MAP targets did not differ based on history of hypertension or delirium status. We observed variability in individual MAP_{opt} values, ranging from 55 to 100 mm Hg. Importantly, 69% of individual's target MAP ranges exceeded the current 65 mm Hg recommended in the Surviving Sepsis guidelines. Controlling for two covariates of delirium development, we found that deviations from personalized MAP targets were not associated with the presence or duration of delirium. Studies designed to understand the association between individualized MAP targeting and neurologic outcomes in the ICU are needed.

Author contributions *Jasmine M. Khan* and *J. Gordon Boyd* contributed to all aspects of this manuscript, including study conception and design; acquisition, analysis, and interpretation of data; and drafting the article. *Abigail Shore*, *Kevin F. H. Lee*, *Michael D. Wood*, and *David M. Maslove* contributed to acquisition, analysis, and interpretation of data. *Miranda Hunt* and *Ilinca Georgescu* contributed to the acquisition of data. *John Muscedere* contributed to conception and design of the study.

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