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Effect of Targeting Mean Arterial Pressure During Cardiopulmonary Bypass by Monitoring Cerebral Autoregulation on Postsurgical Delirium Among Older Patients

A Nested Randomized Clinical Trial

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Supplemental content

IMPORTANCE Delirium occurs in up to 52% of patients after cardiac surgery and may result from changes in cerebral perfusion. Using intraoperative cerebral autoregulation monitoring to individualize and optimize cerebral perfusion may be a useful strategy to reduce the incidence of delirium after cardiac surgery.

OBJECTIVE To determine whether targeting mean arterial pressure during cardiopulmonary bypass (CPB) using cerebral autoregulation monitoring reduces the incidence of delirium compared with usual care.

DESIGN, SETTING, AND PARTICIPANTS This randomized clinical trial nested within a larger trial enrolled patients older than 55 years who underwent nonemergency cardiac surgery at a single US academic medical center between October 11, 2012, and May 10, 2016, and had a high risk for neurologic complications. Patients, physicians, and outcome assessors were masked to the assigned intervention. A total of 2764 patients were screened, and 199 were eligible for analysis in this study.

INTERVENTION In the intervention group, the patient's lower limit of cerebral autoregulation was identified during surgery before CPB. On CPB, the patient's mean arterial pressure was targeted to be greater than that patient's lower limit of autoregulation. In the control group, mean arterial pressure targets were determined according to institutional practice.

MAIN OUTCOMES AND MEASURES The main outcome was any incidence of delirium on postoperative days 1 through 4, as adjudicated by a consensus expert panel.

RESULTS Among the 199 participants in this study, mean (SD) age was 70.3 (7.5) years and 150 (75.4%) were male. One hundred sixty-two (81.4%) were white, 26 (13.1%) were black, and 11 (5.5%) were of other race. Of 103 patients randomized to usual care, 94 were analyzed, and of 102 patients randomized to the intervention 105 were analyzed. Excluding 5 patients with coma, delirium occurred in 48 of the 91 patients (53%) in the usual care group compared with 39 of the 103 patients (38%) in the intervention group ($P = .04$). The odds of delirium were reduced by 45% in patients randomized to the autoregulation group (odds ratio, 0.55; 95% CI, 0.31-0.97; $P = .04$).

CONCLUSIONS AND RELEVANCE The results of this study suggest that optimizing mean arterial pressure to be greater than the individual patient's lower limit of cerebral autoregulation during CPB may reduce the incidence of delirium after cardiac surgery, but further study is needed.

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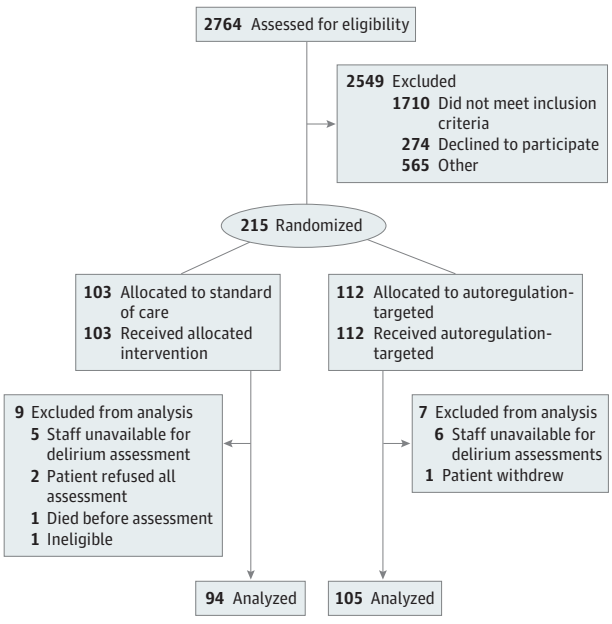
Delirium is common after cardiac surgery, affecting up to 52% of patients, depending on the method of assessment.[1] The importance of this complication is increasingly recognized owing to its association with short-term morbidity,[2] health resource utilization,[3] cognitive decline,[4] and long-term mortality.[5] However, few intraoperative interventions have been shown to reduce the risk of postoperative delirium.

In cardiac surgery, reduced cerebral perfusion may be important in the pathogenesis of delirium because extremes of blood pressure are common, with the potential for unrecognized cerebral ischemia especially in patients with clinically known or undiagnosed cerebrovascular disease. The current standard of care for managing blood pressure during cardiopulmonary bypass (CPB) is for mean arterial blood pressure (MAP) targets to be chosen empirically based mostly on historical practices. An alternative individualized method for targeting appropriate MAP has been proposed using real-time, individualized monitoring of cerebral autoregulation,[6] a process that maintains cerebral blood flow during changes in MAP to protect the brain from both ischemia and hyperemia. A wide, interindividual range of MAPs at the lower limit of cerebral blood flow autoregulation has been found,[7] supporting the hypothesis that hypotension is an individual and not population-based definition. These results further suggest that many patients may be exposed to the risk of hypoperfusion if empirical MAP targets are below the actual lower limit of autoregulation.[8,9] Although the contribution of reduced cerebral perfusion to postoperative delirium has been investigated in several observational[10,11] and interventional studies[12,13] with somewhat conflicting results, earlier studies have used empirical cutoffs of MAP to define hypotension, leaving open the question of whether estimation of adequate cerebral perfusion in those studies was accurate.

Figure 1. Patient Enrollment



Key Points

Question Does targeting mean arterial pressure during cardiopulmonary bypass by monitoring cerebral autoregulation reduce the incidence of delirium compared with usual care?

Findings In this nested randomized clinical trial of 199 participants, the incidence of delirium (excluding coma) was significantly greater in the usual care group (53%) than in the group in which mean arterial pressure was targeted using cerebral autoregulation monitoring (38%).

Meaning Targeting mean arterial pressure during cardiopulmonary bypass using cerebral autoregulation monitoring may reduce the incidence of post–cardiac surgery delirium.

We conducted a nested study within an ongoing randomized clinical trial in which MAP during CPB was targeted to be greater than the lower limit of autoregulation for individual patients. Our primary hypothesis was that individualized targeting of MAP during CPB would reduce the incidence of delirium.

Methods

Study Design

This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline. A patient flow diagram is shown in **Figure 1**. This was a nested prospective study (initiated by C. H. B.) within an ongoing parent clinical trial (primary investigator, C. W. H.). The primary aim of the parent trial was to determine whether targeting MAP during CPB to be greater than an individual's lower limit of autoregulation would reduce the composite outcome of stroke, cognitive decline, and ischemic brain lesions on postoperative magnetic resonance imaging compared with standard of care (MAP based on usual clinical care). Enrollment for this nested study with delirium as a primary outcome began in 2012, year 4 of the parent study (when C. H. B. started joined the faculty of the Johns Hopkins University School of Medicine), and ended in 2016, when the senior author (C.W.H.) accepted a position at another institution, where the substantially different patient population and delirium assessment team would have made combining results at the 2 institutions difficult. Safety and conduct of the study was overseen by a data and safety monitoring board convened for the parent trial. The trial protocol is available in Supplement 1. This study was approved by the Johns Hopkins institutional review board. Written informed consent was obtained from patients before surgery by study personnel.

Patients

Patients at Johns Hopkins Medicine in Baltimore, Maryland, were enrolled between October 11, 2012, and May 10, 2016. Data were analyzed between July 2017 and March 2018.

Inclusion criteria were age 55 years or older; undergoing primary or reoperative coronary artery bypass graft with or

without valvular surgery, or ascending aorta surgery that required CPB; and high risk for neurologic complications (stroke or encephalopathy) as determined by a Johns Hopkins risk score,[14] which includes of history of stroke, carotid artery bruit, hypertension, diabetes, and age and generally excluded patients in the lowest quartile of risk. Exclusion criteria were contraindications to magnetic resonance imaging; hepatic dysfunction (aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase elevated to twice the upper limit of the reference range); chronic renal failure, including requiring dialysis; inability to attend outpatient visits; non–English speaking; severe visual impairment; and emergency surgery. Patients without windows for transcranial Doppler analysis were excluded. Patients with delirium at baseline were also excluded from this substudy. Data on race, defined by patient report or medical record, were collected to examine treatment interactions.

Randomization and Masking

Patients were randomized 1:1 using computerized randomization. After enrollment, research assistants accessed the statistical automated website for treatment assignment. Patients, surgeons, anesthesiologists, outcome assessors, and the statistician were masked to the assigned intervention; the perfusionist was not masked.

Procedures

Cerebral Autoregulation Monitoring

Transcranial Doppler monitoring of the middle cerebral arteries (Doppler Box, DWL; Compumedics) was performed using two 2.5-MHz transducers. Digitized arterial blood pressure and transcranial Doppler signals were processed using ICM software (University of Cambridge). Arterial blood pressure and Doppler signals were time-integrated and resampled as 10-second mean values, to remove pulse, rollerhead, 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 cerebral blood flow velocity values was calculated to generate the mean velocity index (Mx). Mean velocity index was updated every 60 seconds from an overlapping, moving 300-second window and paired with the mean arterial pressure value from the same 300-second window.[6] Mean velocity index values are plotted as a function of MAP in 5-mm Hg bins in a continuously updating graph at the bedside. Blood pressure in the autoregulation range is indicated by an Mx value that approaches zero (there is no correlation between flow velocity and MAP), whereas an Mx approaching 1 indicates dysregulated cerebral blood flow (flow velocity and MAP are correlated). The lower limit of autoregulation was determined by the senior author (C.W.H.) before CPB based on the highest MAP where Mx increased from less than 0.4 to 0.4 or greater.[15] When Mx did not cross 0.4 clearly, the lower limit of autoregulation was defined as the blood pressure with the lowest Mx (the MAP with the best autoregulation). After the procedure, the product of the magnitude and duration of time that MAP was the lower limit of autoregulation or lower as determined by the senior author was calculated (mm Hg × h).[9,16] Thus, information from autoregulation monitoring included MAP at the lower limit of autoregulation, and magnitude and duration of time of MAP less than the lower limit of autoregulation.

Intervention and Comparison

In the autoregulation group, the patient's MAP at the lower limit of autoregulation was determined just before CPB, based on monitoring beginning at the start of the procedure. The patient's MAP was maintained by perfusionists at above the specified MAP at the lower limit of autoregulation by using phenylephrine boluses (100 µg) and reductions in isoflurane concentrations as needed (generally maintained >0.5%). If MAP was not responsive to phenylephrine, 1-unit boluses of vasopressin could be given followed by infusion of a vasopressor. For high MAP, perfusionists increased isoflurane concentrations up to 1% and administered nitroglycerin. In the standard-care group, the patient's MAP during CPB was maintained using usual MAP targets, typically greater than 60 mm Hg, using the same protocol. The intervention was discontinued after separation from CPB, because we hypothesized that the most variability in MAP would occur during CPB.

Perioperative Management

General anesthesia was induced and maintained with fentanyl (5-20 µg kg^{-1}), propofol (0.5-2.0 mg kg^{-1}), and isoflurane. Cardiopulmonary bypass was performed with a nonocclusive roller pump, a membrane oxygenator, and an arterial line filter 40 µm or less. Nonpulsatile flow was maintained between 2.0 and 2.4 L/min m^{-2}, with α-stat pH management. Partial pressure of carbon dioxide was maintained between 35 and 45 mm Hg. Rewarming was based on institutional standards with a goal of maintaining pharyngeal temperature less than 37°C. Sedation after surgery was maintained with propofol until readiness for extubation or for 24 hours postoperatively.

Primary Outcome

The primary outcome of this study was predefined as any incidence of delirium after surgery. Originally, delirium was defined using assessment by research assistants, but the definition was changed to consensus panel diagnosis using *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*)[17] criteria when additional funding became available. Patients with coma at all assessments were censored. Secondary outcomes included maximum score on the Delirium Rating Scale-Revised-1998 (DRS-R-98)[18] severity scale and number of delirium days. These analyses were exploratory, so there was no adjustment for multiple comparisons.

Delirium was assessed daily on 3 of the first 4 postoperative days using the Confusion Assessment Method (CAM)[19] and CAM-ICU,[20] followed by consensus panel adjudication using *DSM-5* criteria. The CAM assessment was performed by trained research assistants and included a structured cognitive examination and open-ended queries of patients, nurses, families, and medical records for evidence of delirium. For intubated patients in the intensive care unit, the CAM-ICU was used. For days (up to postoperative day 4) on which patients were not assessed in person, a validated medical record review was

used.[21] Delirium severity was assessed using the DRS-R-98.[18] Coma was assessed using the Richmond Agitation Sedation Scale (RASS),[22] with a score of -4 or -5 indicating coma. Patients who were comatose on all assessments were classified as having coma in this analysis. The once-daily delirium assessments were limited to the first 4 postoperative days because of evidence that more than 90% of delirium occurs within this time.[23]

Delirium assessors underwent formal training by an expert psychiatrist (K.N.), with co-evaluation of patients every 2 weeks. During the study, κ statistics for agreement between assessors were from 0.7 to 0.8, consistent with substantial agreement. For adjudication, all delirium evaluation data were presented by research assistants to a panel with substantial clinical and research expertise in delirium, consisting of 4 consultation psychiatrists (including K.J.N. and O.J.B.) and 1 geriatric psychiatrist. The *DSM-5* criteria for delirium were rated separately by each panel member using a standardized approach.[24]

Statistical Analysis

Baseline patient and surgical characteristics were compared using *t* tests, Wilcoxon rank sum tests, Fisher exact tests, and χ^2 tests. The effect of the MAP intervention on the primary outcome was assessed using a χ^2 test and logistic regression models. All analyses were based on intention-to-treat principles. Delirium severity was categorized into quintiles, because it was highly skewed. The effect of the intervention on quintile of delirium severity and number of days of delirium was assessed using ordinal logistic regression. Differences in subgroups defined post hoc were assessed using *P* values for interaction.

The sample size was calculated before enrollment assuming a delirium incidence of 50%[1,3] in the standard group and 30% in the autoregulation group, a difference that we thought to be clinically significant. With 87% power, 122 patients in each randomized group would be required to detect this difference in delirium frequency at a confidence level of 0.05, whereas with 80% power, 103 patients in each group would be required. Enrollment in this study was stopped with analyzable data on 199 patients.

Sensitivity analyses included (1) adding patients who were comatose at all in-person assessments to the delirium group, because some argue that coma is a severe form of acute brain injury[25]; (2) adding medical record–review diagnosed delirium to account for days with no in-person assessment; and (3) using the CAM or CAM-ICU assessment of delirium, not the consensus panel adjudication.

Analyses were conducted using SAS 9.2 (SAS Institute, Inc) with 2-sided hypotheses testing; $P < .05$ was considered significant.

Results

During the study period, 2764 patients were screened for eligibility in the parent trial, of whom 215 patients were enrolled and randomized between October 11, 2012, and May 10, 2016. Delirium assessments were available on 199 patients, of whom 94 patients were randomized into the standard group and 105 patients into the autoregulation group. Of the 199 patients included, mean (SD) age was 70.3 (7.5) years old and 150 (75.4%) were male. One hundred sixty-two (81.4%) were white, 26 (13.1%) were black, and 11 (5.5%) were of other race.

Patient and surgical characteristics are listed in **Table 1**. Baseline variables appeared generally similar between the autoregulation and standard groups.

All patients underwent CPB. As shown in **Table 2**, mean (SD) flow on CPB was similar between groups (standard care, 4.4 [0.6]; intervention, 4.4 [0.6]), but there was more phenylephrine administered in the intervention group (1.8 [0.5-3.6], vs 1.2 [0.3-2.3] mg). The mean (SD) MAP at the lower limit of autoregulation was 67.3 (11.1) mm Hg (range, 35.0-97.5) and was similar between the standard care (68.7 [11.3] mm Hg) and autoregulation-targeted groups (66.0 [10.9] mm Hg, $P = .10$). The autoregulation-based intervention was effective in reducing the duration and magnitude that a patient's MAP was below the individual limit of autoregulation. Overall, 41 of 199 (20.6%) patients had evidence of dysautoregulation, with the average index of autoregulation greater than 0.4 across MAP, a frequency similar to previous observations.[15]

The primary delirium outcome by treatment group is listed in **Table 3** and shown in **Figure 2**. The incidence of delirium (excluding coma) was 52.7% (48 of 91) in the standard-treatment group compared with 37.9% (39 of 103) in the autoregulation group ($P = .04$). The odds of delirium were reduced by 45% in patients randomized to the autoregulation group (odds ratio [OR], 0.55; 95% CI, 0.31-0.97; $P = .04$).

Delirium severity was assessed as a secondary exploratory outcome using the maximum score on the DRS-R-98.[18] There was no statistically significant difference between groups in the median DRS-R-98 scores (Table 3), but the odds of being in a higher quintile of delirium severity were 41% lower for patients in the autoregulation group compared with patients in the standard group (Table 3). The number of days of delirium was greater in the standard group (median [IQR] 1 [0-2] days) compared with the autoregulation group (median [IQR] 0 [0-1] days) ($P = .05$). The odds of an additional day of delirium were 42% lower for patients in the autoregulation group compared with patients in the standard group. (OR, 0.58; 95% CI, 0.35-0.99).

Sensitivity analyses were considered using different definitions of delirium. As shown in Table 3, the inferences were unchanged in each of these sensitivity analyses. In exploratory subgroup analyses, no significant interactions were observed between patient age, sex, Mini-Mental State Examination,[26] or logistic EuroSCORE[27] and the primary outcome of delirium.

Discussion

Our results suggest that optimizing MAP to be greater than an individual patient's lower limit of cerebral autoregulation during CPB may reduce the incidence of postoperative delirium.

There is currently no agreement on the appropriate MAP for individual patients during CPB. In practice, these targets

Table 1. Patient and Perioperative Characteristics for Patients Randomized to Standard Care vs Autoregulation-Targeted Management of Mean Arterial Pressure During Cardiopulmonary Bypass

Characteristic	Standard Care (n = 94)	Autoregulation-Targeted (n = 105)
Age, mean (SD), y	70.3 (7.6)	70.3 (7.5)
Male, No. (%)	73 (77.7)	77 (73.3)
Race, No. (%)		
White	78 (83.0)	84 (80.0)
Black	11 (11.7)	15 (14.3)
Other	5 (5.3)	6 (5.7)
Education, median (IQR), y	16 (12-17)	16 (12-17)
MMSE, median (IQR)	27 (26-29)	28 (26-29)
Comorbidities, No. (%)		
Previous stroke	4 (4.3)	7 (6.7)
Hypertension	89 (94.7)	96 (91.4)
Atrial fibrillation	24(25.5)	30 (28.6)
Myocardial infarction	27 (28.7)	36 (34.3)
COPD	13 (14.0)	7 (6.7)
Obstructive sleep apnea	23 (24.7)	16 (15.2)
Tobacco use (current)	8 (8.7)	6 (7.6)
Diabetes	44 (46.8)	50 (47.6)
Anemia	39 (41.9)	45 (43.3)
Medications, No. (%)		
Aspirin	81 (86.2)	79 (75.2)
Angiotensin-converting enzyme inhibitor	32 (34.0)	40 (38.1)
Angiotensin II receptor blocker	20 (21.3)	16 (15.2)
β-Blocker	69 (73.4)	82 (78.1)
Calcium channel blocker	26 (27.7)	31 (29.5)
Statin	83 (88.3)	88 (83.8)
Platelet aggregation inhibitor	23 (24.5)	20 (19.1)
Insulin	30 (31.9)	34 (32.4)
Logistic EuroSCORE, median (IQR)	5.3 (2.8-9.6)	4.4 (2.3-10.40)
Surgery, No. (%)		
CAB	44 (46.8)	57 (54.8)
CAB + valve	19 (20.2)	15 (14.4)
Valve	24 (25.5)	29 (27.9)
Other	7 (7.5)[a]	3 (2.9)
Cardiopulmonary bypass duration, median (IQR), min	114.5 (80-146)	115 (90-153)
Aortic cross-clamp duration, median (IQR), min	76.5 (53-97)	69.5 (57-91)
Aortic clamping in addition to single cross-clamp	11 (12)	23 (22)
Minimum nasopharyngeal temperature, median (IQR), °C	32.8 (30.3-34.3)	32.0 (30.0-34.0)
Transfusion, median (IQR), U	1 (0-4)	2 (0-5)
Reoperation	10 (11)	6 (6)

Abbreviations: CAB, coronary artery bypass; COPD, chronic obstructive pulmonary disease; IQR, interquartile range; MMSE, Mini-Mental State Examination.

[a] This group includes the only patient who underwent circulatory arrest (12 minutes without cerebral protection).

are empirically chosen based on institutional and practitioner preferences. Fundamentally, a MAP as low as 50 mm Hg is believed adequate based on classic teaching that this represents the lower limit of cerebral blood flow autoregulation.[28] Higher MAPs, though, may be necessary for many patients undergoing cardiac surgery given the high prevalence of hypertension and cerebrovascular disease in this population.[7]

Monitoring cerebral blood flow autoregulation during surgery provides an alternative method to identify the MAP required for adequate cerebral perfusion in individual patients. Using such monitoring, it has been shown that the lower limits of cerebral blood flow autoregulation vary widely between individuals (40 to 90 mm Hg) during CPB.[7] Thus, arbitrarily choosing MAP targets may result in hypoperfusion in patients with an elevated lower limit of autoregulation. In observational studies, we have demonstrated that the magnitude and duration that MAP is outside the limits of autoregulation is associated with acute kidney injury and major morbidity and mortality after cardiac surgery.[9,16] However, these observational studies are limited by the potential for confounding. In the present study, we found that a targeted strategy to maintain the MAP above the lower

Table 2. Characteristics of Management During Cardiopulmonary Bypass for Patients Randomized to Standard Care vs Autoregulation-Targeted Management of Mean Arterial Pressure

Characteristic of Management	Standard Care (n = 94)	Autoregulation-Targeted (n = 105)	*P* Value
Phenylephrine, median (IQR), mg	1.2 (0.3-2.3)	1.8 (0.5-3.6)	.02
Vasopressin administration, No. (%)	6 (6.4)	9 (8.6)	.56
Cardiopulmonary bypass flow, mean (SD), L/min	4.4 (0.6)	4.4 (0.6)	.92
Isoflurane, mean (SD), %	0.76 (0.27)	0.77 (0.31)	.71
Arterial pressure during cardiopulmonary bypass, mean (SD), mm Hg	71.3 (7.6)	73.9 (6.7)	.01
Arterial pressure at the lower limit of autoregulation, mean (SD), mm Hg	68.7 (11.3)	66.0 (10.9)	.10
Product of the duration of time and mean arterial pressure below the lower limit of autoregulation, median (IQR), mm Hg × h[a]	9.5 (3.7-19.5)	5.3 (2.0-13.4)	.002

Abbreviation: IQR, interquartile range.

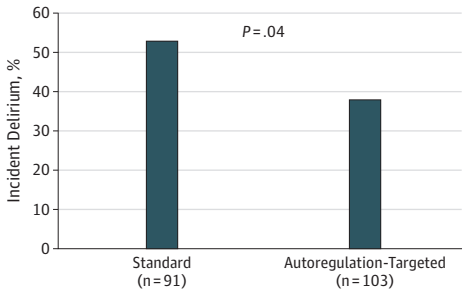
[a] Calculated as the product of duration of time and magnitude of bood pressure that mean arterial pressure was below the lower limit of autoregulation.

Table 3. Delirium Outcomes by Treatment Group

Outcome	Standard Care	Autoregulation-Targeted	OR (95% CI)	*P* Value
Primary outcome				
Delirium incidence, No./total No. (%)	48/91 (52.7)	39/103 (37.9)	0.55 (0.31-0.97)	.04
Secondary outcomes				
Delirium severity (DRS-R-98), median (IQR)	8 (5-13)	7 (4-10)	NA	.10
Delirium severity (quintile of DRS-R-98) No. (%)			0.59 (0.36-0.98)	.04
1	14 (15.6)	20 (19.4)	NA	
2	15 (16.7)	25 (24.3)	NA	
3	15 (16.7)	21 (20.4)	NA	
4	19 (21.1)	18 (17.5)	NA	
5	27 (30.0)	19 (18.5)	NA	
No. of days of delirium, median (IQR)	1 (0-2)	0 (0-1)	NA	.05
Increasing No. of days of delirium, OR	NA	NA	0.58 (0.35-0.99)	.04
Sensitivity analyses of alternative definitions of delirium, No./total No. (%)				
Consensus panel adjudication + coma	51/94 (54.3)	41/105 (39.1)	0.54 (0.31-0.95)	.03
Consensus panel adjudication + medical record review	53/91 (58.2)	45/103 (43.7)	0.56 (0.32-0.98)	.04
Research assistant CAM assessment	53/91 (58.2)	39/103 (37.9)	0.44 (0.25-0.78)	.005

Abbreviations: CAM, confusion assessment method; DRS-R-98, Delirium Rating Scale-Revised-1998; IQR, interquartile range; NA, not applicable; OR, odds ratio.

Figure 2. Delirium Incidence by Randomization Group



Mean arterial pressure during cardiopulmonary bypass was managed according to standard care or autoregulation-targeted goals. Delirium incidence by randomization group is shown.

limit of autoregulation reduced the incidence of postoperative delirium. Although the mean MAP was only slightly higher in the intervention group, the MAP below the lower limit of autoregulation was substantially reduced in the intervention group.

It is well accepted that patient risk factors are paramount in susceptibility to delirium, but the interactions between these factors and superimposed perioperative insults are multifactorial.[29] Several studies have implicated hypotension as a contributor to delirium. A randomized clinical trial of patients undergoing cardiac surgery found that MAP targets of 70 to 80 mm Hg compared with 50 to 60 mm Hg reduced the incidence of delirium.[12] However, the study was small, and delirium was assessed by the Mini-Mental State Examination, which is not validated for this purpose. A pre-post study examining an intervention to optimize cerebral hemodynamics also demonstrated a reduction in delirium, although the study was not randomized and the delirium assessment was not standardized.[13] Other studies in cardiac surgery have shown conflicting results.[10,11] Two recent studies reported an association of delirium with impaired cerebral autoregulation after cardiac surgery[30] and in patients with shock,[31] but neither study assessed the lower limit of autoregulation.

Strengths and Limitations

Strengths of this study include a novel method of targeting adequate cerebral perfusion in individual patients using real-time cerebral autoregulation monitoring, which could be extended to various types of surgery and postoperative care. The delirium assessments were conducted by an experienced group, in accordance with *DSM-5* criteria. However, there are several limitations to consider. This was a single-center nested study, and delirium was not the primary outcome for the parent trial. Thus, these results should be considered preliminary and need to be confirmed in a broad population. The delirium assessment was sensitive, although our methods and estimates of delirium incidence are similar to those of other prominent researchers in the field.[1] We have also shown that patients in this study with delirium had greater postoperative cognitive decline, thus supporting the validity of our delirium assessment.[4] There was some disagreement in delirium rating between the CAM criteria and the consensus panel. The reasons for and significance of these differences are unclear. This trial only focused on maintaining MAP above the lower limit of autoregulation, although cerebral hyperperfusion from MAP above the upper limit of autoregulation may also be associated with delirium.[32] We used autoregulation indices derived from Doppler measurements, which are labor intensive. However, other indices derived from near infrared spectroscopy data are also validated and more feasible.[6] We are unable to determine which intervention during CPB contributed to our findings of improved delirium outcomes, although administration of phenylephrine was most significant between groups. We provided guidance to perfusionists on strategies to maintain MAP greater than target MAP; thus the results of this study are pragmatic in nature and reflect different target MAPs rather than a proscriptive protocol on perfusion practice.

Conclusions

The findings of our trial suggest that individualizing MAP during CPB based on cerebral autoregulation monitoring may be effective in reducing the incidence of postoperative delirium. These results should be confirmed in a multicenter trial, and the benefit of extending this monitoring throughout surgery or in the intensive care unit requires further research.

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Acquisition, analysis, or interpretation of data: Neufeld, Tian, Probert, LaFlam, Max, Hori, Nomura, Shah, Zehr, Cameron, Bienvenu, Gottesman, Kraut, Brady, Hogue.
Drafting of the manuscript: Brown, Hogue.
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