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Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium

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Editor's key points

- Cerebral hyperperfusion attributable to arterial pressure above an upper limit of autoregulation could contribute to delirium after cardiopulmonary bypass (CPB).
- Cerebral autoregulation was measured using cerebral oximetry, and postoperative delirium was prospectively assessed in cardiac surgery patients.
- Mean arterial pressure above the upper limit of cerebral autoregulation during CPB was associated with increased risk of delirium.

Background. Mean arterial pressure (MAP) below the lower limit of cerebral autoregulation during cardiopulmonary bypass (CPB) is associated with complications after cardiac surgery. However, simply raising empiric MAP targets during CPB might result in MAP above the upper limit of autoregulation (ULA), causing cerebral hyperperfusion in some patients and predisposing them to cerebral dysfunction after surgery. We hypothesized that MAP above an ULA during CPB is associated with postoperative delirium.

Methods. Autoregulation during CPB was monitored continuously in 491 patients with the cerebral oximetry index (COx) in this prospective observational study. COx represents Pearson's correlation coefficient between low-frequency changes in regional cerebral oxygen saturation (measured with near-infrared spectroscopy) and MAP. Delirium was defined throughout the postoperative hospitalization based on clinical detection with prospectively defined methods.

Results. Delirium was observed in 45 (9.2%) patients. Mechanical ventilation for >48 h [odds ratio (OR), 3.94; 95% confidence interval (CI), 1.72–9.03], preoperative antidepressant use (OR, 3.0; 95% CI, 1.29–6.96), prior stroke (OR, 2.79; 95% CI, 1.12–6.96), congestive heart failure (OR, 2.68; 95% CI, 1.28–5.62), the product of the magnitude and duration of MAP above an ULA (mm Hg h; OR, 1.09; 95% CI, 1.03–1.15), and age (per year of age; OR, 1.01; 95% CI, 1.01–1.07) were independently associated with postoperative delirium.

Conclusions. Excursions of MAP above the upper limit of cerebral autoregulation during CPB are associated with risk for delirium. Optimizing MAP during CPB to remain within the cerebral autoregulation range might reduce risk of delirium.

Clinical trial registration. clinicaltrials.gov NCT00769691 and NCT00981474.

Keywords: cardiac surgery; cardiopulmonary bypass; cerebral autoregulation; delirium

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Mean arterial pressure (MAP) targets during cardiopulmonary bypass (CPB) are arbitrarily chosen based mostly on historical practices.[1 2] These practices are grounded largely on older data showing that cerebral blood flow (CBF) autoregulation remains functional during CPB when alpha-stat pH management is used.[2–4] Consequently, MAP as low as 50 mm Hg is viewed as well-tolerated because CBF is perceived not to be compromised. More recently, our group has found that the lower limit of CBF autoregulation in patients monitored continuously during CPB ranges between 40 and 90 mm Hg and that the actual limit is difficult to predict based on preoperative arterial pressure and patient medical history.[5–7] We have found that higher magnitudes and longer durations of MAP below the lower limit of autoregulation are associated with a higher risk of complications.[8 9]

One approach to address potential organ hypoperfusion during CPB might be to simply raise current MAP targets to a higher level.[10] However, empirically raising MAP targets during CPB might result in arterial pressure that is above the upper limit of autoregulation (ULA) in some patients. In such

cases, CBF would increase proportionately with MAP and could cause cerebral hyperperfusion that may lead to microvascular changes, alterations in the blood–brain barrier, cerebral oedema, and perhaps a more subtle presentation of cerebral dysfunction.[11–13] Delirium is one manifestation of cerebral dysfunction that has been associated with subsequent adverse events.[14 15] In nonsurgical settings, cerebral hyperperfusion is the proposed mechanism for delirium in patients with hypertensive emergencies.[16] However, little information is available on whether MAP above an ULA during CPB adversely affects patient outcomes. In this study, we hypothesized that the magnitude and duration of MAP above the upper limit of CBF autoregulation during CPB is associated with postoperative delirium.

Methods

From April 2008 to January 2013, patients undergoing cardiac surgery with CPB were enrolled in prospective studies of CBF autoregulation monitoring as described.[5–9 17] The current study represents a retrospective analysis of these data.

All procedures received the approval of the Institutional Review Board (Committee 1) of The Johns Hopkins Medical Institutions (protocol number NA_00027003), and all patients provided written informed consent.

Perioperative care

Patients received routine institutional care, including continuous, direct, radial artery arterial pressure monitoring. Midazolam, fentanyl, isoflurane, and pancuronium or vecuronium were used for anaesthesia and muscle relaxation. Nonpulsatile flow between 2.0 and 2.4 litre min^{-1} m^{-2} was used for CPB. Isoflurane concentration was maintained between 0.5 and 1.0% through the gas inflow of the oxygenator. Alpha-stat pH management was used, and oxygenation and normocarbia were ensured by continuous in-line arterial blood gas monitoring that was calibrated hourly. Arterial pressure targets were chosen empirically based on institutional standard of care. Phenylephrine was administered to treat low arterial pressure based on institutional standards.

Near-infrared spectroscopy-based autoregulation monitoring

Two sensor pads connected to a near-infrared spectroscopy (NIRS) monitor (INVOS™, Covidien Somanetics™, Boulder, CO, USA) were placed on the patient's forehead before induction of anaesthesia. Our signal processing and analysis has been described elsewhere.[5–9 17] Arterial pressure signals from the operating room haemodynamic monitor were digitalized by a data acquisition module (DT9800, Data Translation, Inc., Marlboro, MA, USA); these data, along with digital NIRS-derived regional cerebral oxygen saturation ($rScO_2$) signals, were transferred to a laptop computer using the ICM+ software (University of Cambridge, Cambridge, UK). The signals were then filtered as non-overlapping 10 s mean values that were time-integrated. This method, which is equivalent to having a moving average filter with a 10 s time window and resampling at 0.1 Hz, eliminates high-frequency components caused by respiration and pulse waveforms. Additional high-pass filtering was applied with a DC cutoff set at 0.003 Hz to remove slow drifts associated with haemodilution at initiation of CPB. The monitor calculates a continuous, moving Pearson's correlation coefficient between MAP and $rScO_2$ using a sliding 300 s window updated every 10 s, rendering the variable cerebral oximetry index (COx). COx provides a reliable surrogate of CBF for autoregulation monitoring.[6 18] When CBF is within the autoregulatory range, COx approaches zero or is negative. However, when MAP is below or above the limits of autoregulation, COx increases towards 1. Average COx data were placed in 5 mm Hg MAP bins. We define the limit of autoregulation as that MAP when COx increases from <0.3 to >0.3 with low or high MAP (Fig. 1).

Patient outcomes

Each patient's medical history, medications, and intraoperative and postoperative course were recorded in a study-specific database. The record included complications affecting major organs, as defined by the Society of Thoracic Surgeons National Cardiac Surgery Database (www.sts.org), and acute kidney injury. Baseline serum creatinine was defined as the last value collected before surgery, as measured in the Clinical Chemistry Laboratory of Johns Hopkins Hospital (Roche Diagnostics, Indianapolis, IN, USA). The estimated glomerular filtration rate (eGFR) was calculated using the simplified Modification of Diet in Renal Disease formula.[19] Acute kidney injury was diagnosed based on the RIFLE criteria: (i) *Risk*, defined as an increase in plasma creatinine $\times 1.5$ or decrease in eGFR by $>25\%$ from baseline; (ii) *Injury*, defined as an increase in plasma creatinine $\times 2$ or a decrease in eGFR by $>50\%$ from baseline; and (iii) *Failure*, defined as an increase in plasma creatinine $\times 3$, plasma creatinine ≥ 350 μmol $litre^{-1}$, an acute increase in plasma creatinine of ≥ 44 μmol $litre^{-1}$ from baseline, or new renal replacement therapy.[20] Patients meeting any of the RIFLE criteria were considered to have acute kidney injury. Operative death was defined as death that occurred during the hospitalization in which the operation was performed, even if it was after 30 days, or death that occurred after discharge from the hospital but within 30 days of the procedure.

Assessment for delirium

After patients underwent cardiac surgery, clinical nurses (with clinical training to care for cardiac surgery patients) identified possible neurologic problems (stroke, delirium, confusion, agitation, change in mental status, seizure, coma, or slowness to awaken after surgery) on a daily basis and communicated this information to a charge nurse or nurse practitioner as previously described.[6] Research personnel queried the charge nurse (for patients in the intensive care unit) and reviewed daily patient progress sheets (prepared by nurse practitioners for patients on the floor) for evidence of any new neuropsychiatric symptoms. Delirium was defined as the presence of any of the following observations by clinical staff: delirium, confusion,