Title

Targeting Mean Arterial Pressure During Cardiopulmonary Bypass Using Cerebral Autoregulation Monitoring to Reduce Postoperative Delirium: A Nested Substudy

Trial Registration

The parent trial to this nested trial is registered at www.clinicaltrials.gov (NCT 00981474)

Funding

NIH RO1 HL092259

Johns Hopkins Clinician Scientist Award

Roles and Responsibilities

Charles Hogue is PI of the parent trial.

Charles Brown is PI of the nested substudy

Important Dates

8/21/2012: IRB and protocol approval to begin nested substudy, with incident delirium as the primary outcome

7/8/2014: Protocol revision to change primary outcome of the nested substudy to incident delirium as defined by a consensus committee, based on renewal grant application for the parent study (R01 HL092259).

Background and Rationale

Delirium in the postoperative setting is common and associated with significant morbidity and cost. Although there are multiple proposed causes of delirium, recent evidence has pointed to the importance of adequate cerebral perfusion in maintaining cognitive function. However, the role of cerebral hypoperfusion in postoperative delirium has not been thoroughly investigated. During surgery and anesthesia, hemodynamics can vary markedly resulting in a risk for reduced cerebral perfusion pressure and cerebral ischemia. Unfortunately, there are no currently available clinical methods for monitoring the adequacy of cerebral perfusion during surgery. Rather, blood pressure targets during and after surgery are empirically set. Under normal circumstances, cerebral blood flow (CBF) is autoregulated to keep a steady supply of oxygenated blood to the brain over a range of blood pressures. In the elderly, the presence of hypertension, diabetes, and cerebral vascular disease may shift the lower blood pressure limit of autoregulation. Thus, current perioperative blood pressure management practices may result in cerebral hypoperfusion and possibly risk for delirium.

Individualizing blood pressure targets to be above a patient's lower autoregulatory threshold might provide a means to avoid cerebral hypoperfusion during and after CPB. Monitoring of cerebral autoregulation with a moving linear regression correlation coefficient between cerebral perfusion pressure and middle cerebral artery TCD-measured blood flow velocity (mean velocity index) has been validated in

volunteers and in patients with head trauma, carotid artery stenosis, acute ischemic stroke, and subarachnoid hemorrhage. When autoregulation is lost, flow velocity has a correlation approaching 1 with cerebral perfusion pressure at low frequencies, but when autoregulated, the correlation approaches zero or is even negative. This method provides a way to monitor autoregulation continuously at the bedside in contrast to the intermittent ("snap shot") measurements provided by other methods (e.g., PET, inert gas washout). This feature allows for assessment of CBF autoregulation in individual patients rather than estimating a patient's autoregulatory threshold based on summary data obtained from a group of patients. This ability is important in surgical patients, as CBF autoregulation is dynamic and potentially influenced by many perioperative perturbations, including rewarming from hypothermia, volatile anesthetics (dose dependently), and anemia.

Objectives

To assess whether targeting MAP during cardiopulmonary bypass to a level above an individual's lower autoregulatory threshold during bypass reduces the frequency of postoperative delirium, as assessed with a structured examination, compared with the use of standard blood pressure management.

Trial Design

Nested randomized controlled trial

Study Setting

A cardiac surgery program in a quaternary care hospital

Eligibility Criteria

This is a nested study in Dr. Hogue's trial (NCT 00981474)) so only patients enrolled in this trial are eligible. Generally, inclusion criteria will be male or female patients, ≥55 years old, undergoing primary or re-operative CABG and/or valvular surgery or ascending aorta surgery that requires CPB who are at high risk for neurologic complications (stroke or encephalopathy) as determined by a Johns Hopkins Encephalopathy Risk score which includes of history of stroke, presence of carotid artery bruit, hypertension, diabetes, and age that generally excludes patients in the lowest quartile of risk. This prediction algorithm, devised from data analysis by the investigative team, identifies probability of an adverse neurologic outcome based on patient-related factors, including age, prior stroke, diabetes, hypertension, or the presence of a carotid bruit.

Women of childbearing potential will have a urine pregnancy test done prior to surgery to insure that they are not pregnant. Patients without a TCD window are excluded from the study.

Patients will be ineligible for this study if they have any of the following exclusion criteria:

1. contraindication to MRI imaging (e.g., permanent pacemaker, cerebral arterial vascular clips);
2. AST, ALT and Alkaline phosphitase obtained before surgery which is more than twice the upper limit of institutional normal value and which, in the opinion of the principal investigator, is believed to be related to hepatic dysfunction;
3. chronic renal failure, including requiring renal dialysis.
4. emergency surgery;

5. inability to attend outpatient visits;
6. visual impairment or inability to speak and read English
7. Baseline delirium

Autoregulation Monitoring

CBF autoregulation will be monitored continuously by members of the investigative team. The patient's forehead will be cleansed with the supplied alcohol sponge and wiped dry. Then, NIRS monitoring electrodes will be calibrated, as specified by the manufacturer, and placed on the patient's forehead. We will perform TCD monitoring (DWL, Compumedics DWL, El Paso, TX) of the right and left middle cerebral arteries using two 2.5-MHz transducers fitted on a headband and positioned over the temporal bone windows to obtain bilateral continuous measurement of baseline velocity. Depth of insonation will be varied between 35 and 52 mm until representative spectral middle cerebral artery flow is identified. Arterial pressure from an indwelling cannula (started for clinical indication), along with TCD signals from the middle cerebral arteries and the near-infrared spectroscopy signals, will be sampled with an analog-to-digital converter using ICM+ software. Digital rScO2 signals from the NIRS monitor will be transferred directly to a laptop computer. Blood pressure, TCD, and rScO2 signals will then be time integrated as non-overlapping 10-sec mean values, equivalent to applying a moving average filter with a 10-sec time window and re-sampling at 0.1 Hz. This operation eliminates high-frequency noise from the respiratory and pulse frequencies, according to the Nyquist theorem, allowing detection of oscillations and transients that occur below 0.05 Hz. A continuous, moving Pearson correlation coefficient will be calculated between mean arterial pressure and TCD CBF velocity of the middle cerebral arteries, rendering the variable mean velocity index (Mx). Similar methods will be performed to calculate the Pearson correlation coefficient between mean arterial pressure and cerebral oximetry signals, rendering the variable cerebral oximetry index, and between mean arterial pressure and relative total hemoglobin signals, generating the hemoglobin volume index (see Cerebrovascular Reactivity Measured by Near-infrared Spectroscopy). Consecutive, paired, 10-sec averaged values from 300-sec duration will be used for each calculation, incorporating 30 data points for each index. Mx and COx values for each patient will be placed into 5 mmHg MAP bins and displayed on the laptop computer.

Interventions

Control Group: mean arterial pressure is maintained during surgery, including CPB, using institutional standard of care.

Intervention Group: mean arterial pressure during CPB is targeted to be kept above the patient's lower CBF autoregulatory threshold based on continuous monitoring of mean velocity index, as per the parent study.

For the intervention group, when MAP is below the LLA based on Mx the patients will be treated with phenylephrine boluses (100 mcg) until stabilized, and isoflurane concentrations will be reduced with a minimum of 0.5%. One-unit boluses of vasopressin can be given intravenously if MAP is not responsive to phenylephrine. When repeated doses of either drug are needed over a short period, an intravenous infusion of the drug will be started after first ensuring the fidelity of the arterial catheter. Isoflurane concentrations will be increased up to 1% and bolus doses (50 mcg to 100 mcg) of nitroglycerin will be given if needed for high MAP. The same algorithm will be used for hemodynamic management in Controls but will be based on standard MAP targets, not autoregulation monitoring.

Other Perioperative Care

Anesthesia and Patient Monitoring: Arterial blood pressure will be measured via a canula inserted into the radial or femoral artery placed for clinical purposes. Anesthetic drugs will be standardized and will consist of propofol (1–2 mg/kg for induction of anesthesia), fentanyl (5–20 μg/kg), isoflurane, and skeletal muscle relaxants. During CPB, isoflurane will be administered via the membrane oxygenator, with a minimum concentration of 0.5% and maximum concentration of 2%. Sedation after surgery will be started when sternal wires are placed and will consist of propofol 20–75 μg/kg/min.

Cardiopulmonary Bypass: A 40-μm filter will be placed in the arterial line from the CPB circuit. Blood flow during CPB will be maintained between 2.0 and 2.4 L/min/m^2 using nonpulsatile flow. Nasopharyngeal temperature will be measured during surgery and the temperature nadir recorded. Arterial blood gases will be recorded 30 min after the start of CPB and every 60 min thereafter. The patients will be managed using α-stat pH management. Hemoglobin will be kept >8.0 g/dL with transfusion of packed red blood cells. Blood glucose will be measured at the onset of CPB and at least every 60 min thereafter. Regular humulin insulin will be given by continuous infusion when glucose is >110 mg/dL. Rewarming will be at an arterial inflow temperature of ≤37°C. Nasopharyngeal temperature will not exceed 36°C. Surgical field CO_2 insufflation will be performed. Cardiotomy suction will be returned to the CPB circuit after being processed with a cell saver device for patients undergoing CABG surgery or directly to the CPB circuit for open chamber procedures, as is our usual practice.

Outcomes

We will assess delirium once a day for a total of 3 times between postoperative days 1-4, using standard delirium assessments as described below.

Confusion Assessment Method (CAM) is a standardized method that is designed to allow trained non-psychiatrists to diagnose delirium. It shows high inter-rater reliability, and has high sensitivity (94-100%) and specificity (90-95%) as compared to the gold standard of psychiatric diagnosis. (Inouye et al. 1990) The CAM diagnostic algorithm is based on assessing the four cardinal features of delirium: 1) acute onset and fluctuating course, 2) inattention, 3) disorganized thinking, and 4) altered level of consciousness.

Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is a validated instrument to diagnose delirium in critically ill intubated patients in the intensive care unit, including those who are non-verbal due to mechanical ventilation. Inter-rater reliability is high (kappa 0.79-0.95) and has high sensitivity (0.95-1.0) and specificity (0.89-0.93) as compared to the gold standard of psychiatric diagnosis. (Ely 2001) This test will be used for intubated patients in the ICU.

Delirium Rating Scale- Revised-1998 (DRS-R-98) is a 16-item scale that has been validated as a measure of delirium severity. Inter-rater reliability is high (Interclass correlation coefficient = 0.99), and the scale is one of the few that has been validated against a dementia group. (Trzepacz et al. 2001)

The primary outcome is any incidence of delirium from the CAM, CAM-ICU, or DRS-R-98 assessments.

Secondary outcomes are maximum score on the DRS-R-98 and number of days of delirium.

In July 2014, this is revised, with the primary outcome being changed to a diagnosis of delirium by consensus panel. The rationale is that the investigative team believes the consensus panel will be more accurate and there is additional funding to support effort. All assessment data gathered on each day of assessment will be reviewed in a delirium consensus panel of generally three delirium experts led by Dr. Neufeld. The panel will adjudicate each case for final diagnostic assignment using Diagnostic and

Statistical Manual (DSM-V) diagnostic criteria for delirium. The panel will retrospectively review prior delirium assessments using the same methodology.

Timeline

Assessment Schedule	PRE-OP	DOS before CPB	DOS CPB	DOS after CPB	ICU	POD 1	POD 2	POD 3	POD 4
Informed Consent	X								
Medical history/Physical Exam	X								
Randomization		X							
Autoregulation Measurement		X	X	X					
Delirium Assessment					X	X	X	X	X

Sample Size

Assuming a 50% incidence of delirium in the control group with a 40% reduction in incidence in the intervention group, 206 patients would be required to demonstrate a difference with 80% power.

Allocation

Patients will be prospectively randomized after anesthesia induction, but before CPB, using an internet-based system (managed by the Johns Hopkins School of Public Health Department of Biostatics).

Allocation Concealment

No study members have access to the next randomization code.

Masking

Clinicians caring for the patients will participate in managing blood pressure in the Blood Pressure Intervention Group and, thus, cannot be masked. Patients and individuals conducting the delirium assessments will be masked to the intraoperative management group.

Data Management

Patient information relevant to this study will be recorded on case report forms customized for this study. Only the PI and authorized staff according to the list of Authorized Study Personnel are entitled to make entries on the case report form. Completed case report forms will be dated and signed by the PI or Sub-PI.

Personal patient data will be kept confidential. Case report forms or other documents will identify a patient by initials and number only. The PI will keep in his/her file a Patient Identification and Enrollment List. To allow compliance with GCP principles, each patient will be asked for consent regarding the access to source documents for monitoring, audits, and inspections. The agreement, also covering the use of the data for analyses, must be documented in writing, together with the written ICF for study participation. Data will be transferred from the case report form to a study database. This database will include only the patient study number and will be devoid of patient identifying information. All information obtained during the conduct of this study will be regarded as confidential. Manuscripts prepared for publication will be in accordance with the policies of The Johns Hopkins Medical Institutions.

Statistical Methods

We will compare Intervention and Control groups for proportion of patients with delirium. We will estimate the unadjusted (without any other variable in the model) and adjusted risk of delirium by comparing the two study groups using the chi-squared test or regression models. We will consider adjusting for baseline differences in groups. Delirium severity and number of days of delirium will likely be skewed and so comparisons will be made using categorical definitions, rank-sum tests, or regression.

Data Monitoring

A Data and Safety Monitoring Board (DSMB) is appointed as part of the parent study. The DSMB members will not be direct participants in the study and they must attest to not having any conflicts of interest with the study or any of its investigators. The DSMB will be charged with oversight of the study's safety and integrity and assessing the risk versus benefits of continuing the study if such questions arise. The DSMB will meet at least bi-annually in person or by conference call or more often, if necessary, based on the progression of the study, including any arising events as communicated by the PI. The DSMB will continue to meet until the completion of the study. The DSMB will review patient recruitment and patient follow-up, compliance with the protocol including protocol violations, timeliness and completeness of data entry, compliance with patient confidentiality and HIPPA regulations, and communications of adverse events to the IRB. The DSMB members should immediately review the data provided by the statistician in order to make any requests for additional information or analysis in a time frame that can allow for such requests to be completed before the scheduled DSMB meeting. Members of the DSMB must maintain confidentiality of the study data until otherwise instructed.

Adverse Events

For this study, an adverse event (AE) is any untoward medical occurrence (e.g., sign, symptom, disease, syndrome, intercurrent illness, or abnormal laboratory finding) that emerges or worsens relative to baseline during the study periods, regardless of the suspected cause. Untoward medical events that occur from the time the subject signs the ICF to the time of surgery are not considered AEs and should be recorded under medical history. AEs encountered during or after surgery will be recorded on the appropriate AE section of the CRF. All AEs will be evaluated by the PI for their intensity, frequency, relationship to study, and outcome. The intensity of both serious and non-serious AEs will be graded as mild, moderate, or severe. The definitions are as follows: 1) mild, transient event—does not require medical intervention; the normal clinical course for a subject undergoing cardiac surgery is not changed; AND/OR the subject experiences discomfort, but no disruption of normal daily activity; 2) moderate—event may require medical intervention; induces moderate deviation from the normal clinical course for a subject undergoing cardiac surgery; AND/OR the subject experiences sufficient discomfort to reduce or affect normal daily activity; and 3) severe—event requires significant medical intervention and constitutes a marked deviation from the normal

clinical course for a subject undergoing cardiac surgery AND/OR the subject is incapacitated and unable to perform normal daily activities.

An AE should be classified as **SERIOUS** if: 1) it resulted in death (i.e., the AE caused or led to death); 2) it was life threatening (i.e., the AE placed the subject at immediate risk of death); 3) it required or prolonged inpatient hospitalization (i.e., the AE required at least a 24 h inpatient hospitalization or prolonged a hospitalization beyond the expected length of stay); 4) it was disabling (i.e., the AE resulted in a substantial disruption of the patient's ability to carry out normal life functions); or 5) it did not meet any of the serious criteria listed above but potentially jeopardized the patient or required medical or surgical intervention to prevent one of the outcomes listed above. Adverse events will be reported to the IRB, recorded in the study database, and reviewed at the weekly investigators' meeting. Adverse events also will be reviewed at the quarterly Data Safety and Monitoring Board meeting. Serious AEs will be reported to NIH personnel.

Consent

Before the start of any study-related procedure, a signed and dated IRB-approved informed consent form (ICF) will be obtained and documented in the patient's medical record. The investigator must 1) inform each patient accordingly and allow each patient sufficient time to decide whether or not to participate in the study; 2) give patients and relatives the opportunity to inquire about details of the study and to answer any questions regarding the study; and 3) ensure that the ICF is approved by the IRB when an amendment to the study protocol is made.

A patient is free to withdraw consent for participation in the study at any time, without prejudice to further treatment. Every effort will be made to obtain complete follow-up information on subjects who discontinue from the study prematurely. The reason(s) for a subject's discontinuation must be clearly documented in the subject's medical records and in the case report form (CRF). A patient's participation in the study may be discontinued at any time at the discretion of the PI.

Dissemination

A major objective of this study is to disseminate to the medical community new information. We propose to fulfill this aim by presentations at national and international meetings and conventional publications in the medical literature. Full results of the study will be published as soon as possible, consistent with principles of peer-reviewed publication. National meetings of the AHA, American Stroke Association, Society of Thoracic Surgeons, and the Society of Cardiovascular Anesthesiologists are excellent venues for presenting clinical study results.