Hypotension After Cardiac Operations Based on Autoregulation Monitoring Leads to Brain Cellular Injury

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Background. **Individualizing blood pressure targets could improve organ perfusion compared with current practices. In this study we assess whether hypotension defined by cerebral autoregulation monitoring vs standard definitions is associated with elevation in the brain-specific injury biomarker glial fibrillary acidic protein plasma levels (GFAP).**

Methods. **Plasma GFAP levels were measured in 121 patients undergoing cardiac operations after anesthesia induction, at the conclusion of the operation, and on postoperative day 1. Cerebral autoregulation was monitored during the operation with the cerebral oximetry index, which correlates low-frequency changes in mean arterial pressure (MAP) and regional cerebral oxygen saturation. Blood pressure was recorded every 15 minutes in the intensive care unit. Hypotension was defined based on autoregulation data as an MAP below the optimal MAP (MAP at the lowest cerebral oximetry index) and based on standard definitions (systolic blood pressure decrement >20%, >30% from baseline, or <100 mm Hg, or both).**

Results. **MAP (mean ± standard deviation) in the intensive care unit was 74 ± 7.3 mm Hg; optimal MAP was 78 ± 12.8 mm Hg ($p = 0.008$). The incidence of hypotension varied from 22% to 37% based on standard definitions but occurred in 54% of patients based on the cerebral oximetry index ($p < 0.001$). There was no relationship between standard definitions of hypotension and plasma GFAP levels, but MAP of less than optimal was positively related with postoperative day 1 GFAP levels (coefficient, 1.77; 95% confidence interval, 1.27 to 2.48; $p = 0.001$) after adjusting for GFAP levels at the conclusion of the operation and low cardiac output syndrome.**

Conclusions. **Individualizing blood pressure management using cerebral autoregulation monitoring may better ensure brain perfusion than current practice.**

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Blood pressure after cardiac operations is kept at a level that ensures organ perfusion while minimizing mediastinal blood loss. Guidance for hemodynamic management in patients after cardiac operations based on individualized physiologic end points may provide a strategy for balancing these goals. Our group has reported the clinical feasibility of monitoring of cerebral blood flow (CBF) autoregulation in patients during cardiopulmonary bypass (CPB). CBF autoregulation determinations occur in real time using signal processing of raw noninvasively measured regional cerebral oxygen saturation ($rSco_2$) data obtained with near-infrared spectroscopy (NIRS) in relation to mean arterial pressure (MAP). Using this approach, MAP at the lower limit of autoregulation is quite broad (ie, 40 to 90 mm Hg) and difficult to predict from the patient's medical or demographic data [1]. Although emerging data suggest that

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targeting MAP during the operation based on autoregulation monitoring might preserve organ perfusion better than empirically chosen blood pressure targets, little data exist on the utility of CBF autoregulation of MAP in the intensive care unit (ICU) [2–4].

Glial fibrillary acidic protein (GFAP) is an astrocyte cytoskeleton protein with high specificity for the brain [5]. Elevation in plasma GFAP levels has been reported in adults with traumatic brain injury, stroke, and after cardiac arrest [6–8]. Although operative outcome, such as stroke, may require a large sample size and postoperative cognitive dysfunction requires sophisticated testing and scoring over months of follow-up, monitoring plasma GFAP levels may provide an objective and sensitive method for identifying brain injury.

The purpose of this study was to assess whether blood pressure management in patients recovering in the ICU from cardiac operations is associated with changes in plasma GFAP levels. We hypothesize that an individualized definition of hypotension, defined as MAP below optimal pressure based on cerebral oximetry index (COx) autoregulation monitoring, is associated with an elevation in postoperative plasma GFAP levels. In contrast, we speculate that hypotension based on standard definitions is insensitive for identifying plasma GFAP elevations.

Material and Methods

From July 2013 to July 2014, 121 patients undergoing cardiac operations requiring CPB at The Johns Hopkins Hospital were enrolled in an on-going prospective randomized clinical trial evaluating whether individualizing MAP targets during CPB based on real-time cerebral autoregulation monitoring is associated with improved neurologic outcomes compared with the standard of care where MAP targets that are empirically chosen (NCT00981474). The current study represents an analysis of data collected from that trial. The authors remain blinded to treatment assignment in the parent trial.

Inclusion criteria for enrollment are patient age 55 years or older, an operation with CPB, and high risk for neurologic complications as determined by a Johns Hopkins Encephalopathy Risk score [9]. Patients were excluded by (1) contraindication to magnetic resonance imaging, (2) evidence of liver injury, (3) hemodialysis, (4) emergency operation, (5) inability to attend outpatient visits, and (6) visual impairment or inability to speak and read English. All procedures received the approval of The Johns Hopkins Medical Institutions Institutional Review Board, and all patients were provided with written informed consent.

Hemodynamic Management and Anesthesia

Routine patient monitoring included arterial pressure measured from a radial artery. General anesthesia was induced and maintained with midazolam, fentanyl, and isoflurane, and pancuronium or vecuronium were given for skeletal muscle relaxation. CPB was initiated after administration of heparin to achieve an activated clotting time exceeding 480 seconds. The CPB flow was nonpulsatile flow and maintained between 2.0 and 2.4 L/min/m^2. Temperature management during CPB was determined by the surgeon. The patients were managed with alpha-stat pH management and with a continuous in-line arterial blood gas monitor that was calibrated hourly.

Postoperatively, blood pressure was continuously monitored in the ICU and recorded every 15 minutes by computerized record systems. Low cardiac output syndrome was defined as the use of inotropes for 24 hours or new intraaortic balloon pump insertion.

NIRS-Based Autoregulation Monitoring

NIRS Invos 5100 sensors (Covidien, Boulder, CO) were placed on the patient's forehead before induction of anesthesia. Analog arterial pressure signals from the operating room hemodynamic monitor were processed with a DT9800 data acquisition module (Data Translation Inc, Marlboro, MA). These signals and the raw digital NIRS signals, were analyzed using ICM+ software (University of Cambridge, Cambridge, United Kingdom), as described previously [10, 11]. Arterial blood pressure and NIRS signals were filtered to focus on the frequency of slow vasogenic waves, which are relevant to autoregulation. The signals were filtered as nonoverlapping 10-second mean values that were time-integrated, which is equivalent to having a moving average filter with a 10-second time window and resampling at 0.1 Hz, eliminating high-frequency components resulting from respiration and pulse waveforms. Additional high-pass filtering was applied with a DC cutoff set at 0.003 Hz. A continuous, moving Pearson's correlation coefficient between changes in MAP and $rSco_2$ were calculated rendering the variable COx.

Consecutive, average COx within a 10-second window was collected as 30 data points to monitor each COx in a 300-second window. COx approaches 1 when the MAP is outside the limits of autoregulation indicating pressure-passive CBF. In contrast, COx approaches 0 or is negative when MAP is within the CBF autoregulation range. The average COx measurements from the CPB period were placed into 5 mm Hg bins. Optimal MAP (OptMAP) was defined as the MAP at the lowest COx because it is the MAP with the least correlation with CBF (Fig 1).

Plasma GFAP Analysis

Arterial blood (3 mL) was collected into ethylenediaminetetraacetic acid–containing glass tubes after anesthesia induction, at the conclusion of the operation, and in the ICU on postoperative day 1 for plasma GFAP measurement. Within 2 hours of collection, the samples were centrifuged at 1,500*g* for 8 minutes, and the serum was separated and stored at –80°C. GFAP assays were performed as previously described [12] using an electrochemiluminescent sandwich immunoassay platform (MesoScale Discovery, Gaithersburg, MD) and were analyzed on a Sector Imager 2400 (MesoScale Discovery) according to the manufacturer's protocol. The lower limit of quantification was 0.04 ng/mL, and the interassay