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

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Abstract

Background—Individualizing blood pressure targets could improve organ perfusion compared to current practices. In this study we assess whether hypotension defined by cerebral autoregulation monitoring versus 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 surgery after anesthesia induction, at the conclusion of surgery, and on post-operative day 1 (POD1). Cerebral autoregulation was monitored during surgery with the cerebral oximetry index (COx), which correlates low frequency changes in mean arterial pressure (MAP) and regional cerebral oxygen saturation. Blood pressure was recorded every 15 minutes in the ICU. Hypotension was defined based on autoregulation data as MAP < optimal MAP (MAP at lowest COx), and based on standard definitions (systolic blood pressure decrement > 20%, > 30% from baseline, and/or < 100mmHg).

Results—MAP (mean±SD) in the ICU was 74±7.3 mmHg; optimal MAP was 78±12.8 mmHg (p=0.008). The incidence of hypotension varied from 22% to 37% based on standard definitions, but it occurred in 54% of patients based on COx (p<0.001). There was no relationship between standard definitions of hypotensions and plasma GFAP levels, but MAP < optimal was positively related with POD1 GFAP levels (Coef, 1.77; 95%CI, 1.27-2.48; p=0.001) after adjusting for GFAP levels at the conclusion of surgery and low cardiac output syndrome.

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

Keywords

Cardiopulmonary bypass; Cerebral protection; Circulatory hemodynamics; Organ perfusion; Perioperative care

Introduction

Blood pressure after cardiac surgery is kept at a level that ensures organ perfusion while minimizing mediastinal blood loss. Guidance for hemodynamic management in patients after cardiac surgery based on individualized physiologic end-points may provide a strategy for balancing these goals. Our group has reported on 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 non-invasively measured regional cerebral oxygen saturation (rScO₂) data obtained with near infrared spectroscopy in relation to mean arterial pressure (MAP). Using this approach, MAP at the lower limit of autoregulation is quite broad (ie, 40 to 90 mmHg) and difficult to predict based on patients medical or demographic data. While emerging data suggests that targeting MAP during surgery based on autoregulation monitoring, might preserve organ perfusion better than empirically chosen blood pressure targets, little data exists on the utility of CBF autoregulation of MAP in the intensive care unit (ICU).⁽¹⁻³⁾

Glial fibrillary acidic protein (GFAP) is an astrocyte cytoskeleton protein with high specificity for the brain. ⁽⁴⁾ Elevation in plasma GFAP levels has been reported in adults with traumatic brain injury, stroke, and after cardiac arrest. ⁽⁵⁻⁷⁾ While operative outcome such as stroke may require 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 the patients recovering from cardiac surgery in the ICU is associated with changes in plasma GFAP levels. We hypothesize that individualized definition of hypotension defined as MAP below optimal pressure based on CO_x autoregulation monitoring is associated with elevation in postoperative plasma GFAP levels. In contrast, we speculate that hypotension based on standard definitions is insensitive for identifying plasma GFAP elevations.

Materials and Methods

From July 2013 to July 2014, 121 patients undergoing cardiac surgery 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 neurological outcomes compared to 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, surgery with CPB, and high risk for neurologic complications as determined by a Johns Hopkins Encephalopathy Risk score.(8) Patients were excluded based for: 1) contraindication to MRI 2) evidence of liver injury; 3) hemodialysis; 4) emergency surgery; 5) inability to attend outpatient visits; and 6) visual impairment or inability to speak and read English. All procedures received the approval of the Institutional Review Board of The Johns Hopkins Medical Institutions and all patients were provided with written informed consent.

Hemodynamic Management and Anesthesia

The patient had routine monitoring that included arterial pressure measured from a radial artery. General anesthesia was induced and maintained with midazolam, fentanyl, isoflurane, and pancuronium or vecuronium were given for skeletal muscle relaxation. Cardiopulmonary bypass was initiated after administration of heparin to achieve an ACT > 480s. The CPB flow was non-pulsatile flow and maintained between 2.0L/min/m² to 2.4L/min/m². 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.

Post-operatively, 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 usage of inotropes for 24 hours or new intra-aortic balloon pump insertion.

Near Infrared Spectroscopy Based Autoregulation Monitoring

Near-infrared spectroscopy (NIRS) sensors (Invos 5100, Covidien, Boulder, CO) were placed on the patient's forehead prior to induction of anesthesia. Analog arterial pressure signals from the operating room hemodynamic monitor were processed with a data acquisition module (DT9800, Data Translation Inc, Marlboro, MA, USA). These signals and the raw digital NIRS signals, were analyzed using ICM+ software (University of Cambridge, Cambridge, United Kingdom) as described previously. (9, 10) The signals were filtered as non-overlapping 10-s mean values that were time-integrated, which is equivalent to having a moving average filter with a 10-s time window and resampling at 0.1Hz, 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 rScO₂ were calculated rendering the variable cerebral oximetry index (COx). Consecutive, average COx within a 10-s window was collected as 30 data points to monitor each COx in a 300s window. COx approaches 1 when 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 5mmHg bins. Optimal MAP (OptMAP) was defined as the MAP at the lowest COx as it is the MAP with the least correlation with CBF (Figure 1).

Plasma GFAP Analysis

Three milliliters of arterial blood was collected into EDTA containing glass tubes after anesthesia induction, at the conclusion of surgery, and in the ICU on post-operative day 1

for plasma GFAP measurement. Within two hours of collection, the samples were centrifuged at 1500g for 8 minutes and the serum was separated and stored at -80°C. GFAP assays were performed as previously described(11) using an electrochemiluminescent sandwich immunoassay platform (MesoScale Discovery [MSD], Gaithersburg, MD) and were analyzed on a Sector Imager 2400 (MSD) according to the manufacturer's protocol. The lower limit of quantification was 0.04 ng/mL and the inter-assay variance at the LLOQ was <10%.

Data Analysis

The normality of the distribution of the data was assessed by the Kolmogorov-Smirnov test. For continuous variables, data that were normally distributed were analyzed by the Student t-test. Data that were non-normally distributed were logarithmically transformed and were analyzed by Mann-Whitney test if not normally distributed. Categorical variables were analyzed by Chi squared test and Fisher's exact test when 20% or more cells had expected value of less than 5. Test for correlation was performed by Pearson's correlation and Spearman's correlation for data that were not normally distributed. P-values less than 0.05 were considered statistically significant. The average MAP in the ICU was calculated from the time of ICU admission to the time that the last blood sample for GFAP was obtained. The average blood pressures during this interval were compared with the baseline blood pressure measured during the pre-operative office visit to define hypotension in the ICU. Hypotension was defined based on the most commonly used criteria derived from a previously published systematic review: either a > 20% decline in systolic blood pressure (sBP) from baseline, or a > 30% decline in sBP from baseline, and/or systolic blood pressure less than 100mmHg.(12) The patients were also dichotomized into two groups based on whether or not their average MAP in the ICU during the period of surveillance was below the OptMAP. The area under the curve of the MAP below OptMAP (AUC<OptMAP:mmHg_h) was calculated as the sum of the product of the difference from the OptMAP and the time interval of the blood pressure measurement in the ICU, which was 15 minutes (0.25 hours). Factors that were associated with elevation in plasma GFAP levels on post-operative day 1 were assessed using linear regression. Patient demographics and perioperative variables (Table 1 and 2) with p<0.1 based on univariate analysis were included in the model. All analysis was performed using Stata (Version 13.1, Stata Corp, College Station, TX) and Prism 5 (GraphPad Software Inc., La Jolla, CA, USA)

Results

Patient demographics and perioperative variables are listed in Tables 1 and 2. During CPB, the OptMAP defined by cerebral autoregulation monitoring was 78±12.8 mmHg, while the average MAP was 75±6.5 mmHg (p=0.11). The average MAP in the ICU was 74±7.3 mmHg (p=0.008 vs OptMAP). Forty-five (37.2%) patients had an average sBP < 20% from baseline, and 27 (22.3%) patients had a > 30% lower average sBP from baseline and/or an average sBP <100mmHg (p<0.001). In sixty-five (53.7%) patients, the average MAP in the ICU was below OptMAP. Out of 45 patients who had an average sBP < 20% from baseline, 30 (66.7%) patients had MAP < OptMAP while 15 (33.3%) had MAP > OptMAP in the ICU (p=0.038). Out of 27 patients who had a > 30% lower average sBP from baseline and/or

an average sBP <100mmHg, 20 (74.1%) patients had MAP < OptMAP while 7 (25.9%) patients had MAP > OptMAP (p=0.017).

There was an increase in plasma GFAP levels (median immediately after surgery compared with baseline (0.023ng/ml vs. 0.034ng/ml, p<0.001). Plasma GFAP levels were increased on post-operative day1 compared with baseline (0.023ng/ml vs. 0.044ng/ml, p<0.001), and immediately after surgery (p=0.29). There were no differences in plasma GFAP levels (median, IQR) on post-operative day 1 in hypotensive patients when defined with standard definitions (sBP < 20% from baseline, 0.051 ng/mL, 0.031-0.116 vs. > 20% from baseline, 0.043 ng/mL, 0.025-0.075, p=0.32) and (sBP <30% baseline or < 100 mmHg: 0.044 ng/mL; 0.029 to 0.078 vs. >30% or systolic > 100 mmHg: 0.047 ng/mL; 0.029 to 0.081; p=0.97). Plasma GFAP levels on post-operative day 1 for patients with and without average MAP < OptMAP based on COx monitoring is shown in Figure 2. Plasma GFAP levels (median, IQR) were higher in the group with MAP < OptMAP compared to the group with average MAP > OptMAP in the ICU (0.064 ng/mL; 0.035 to 0.116 vs. 0.035 ng/mL; 0.016 to 0.059; p< 0.001). The sum of the product of the magnitude and duration of the blood pressure spent below OptMAP (AUC<OptMAP) for those with average MAP < OptMAP was higher than for patients with average MAP > OptMAP (168 mmHg $\times$ h; 91.3 to 269.0 vs. 8.75 mmHg $\times$ h; 3.5 to 22.1; p<0.001) (Figure 3). There was a positive correlation between AUC<OptMAP and plasma GFAP at post-operative day 1 (Figure 4). After adjusting for plasma GFAP levels at the conclusion of surgery, AUC<OptMAP was correlated with plasma GFAP levels measured on post-operative day 1 in a linear regression model (Coef, 1.002; standard error, 1.0007; 95% confidence interval [CI], 1.0006 to 1.0035, p=0.007). That is, for every 1mmHg $\times$ hr spent below the MAP, there is a 0.2% increase in plasma GFAP level on post-operative day 1.

Patients with low cardiac output syndrome, had higher plasma GFAP levels on post-operative day 1 compared with patients without low cardiac output syndrome (0.078 ng/mL, 0.051-0.124 vs. 0.040 ng/mL, 0.022-0.078; p=0.015). Of the 17 patients with low cardiac output syndrome, 13 (76.5%) had average MAP < OptMAP in the ICU while 52 (50.0%) patients without low cardiac output syndrome had average MAP < OptMAP in the ICU (p=0.065). Preoperative NYHA classification was not associated with preoperative plasma GFAP levels (p=0.46) or plasma GFAP levels on post-operative day 1 (p=0.99).

The results of the multivariable linear regression analysis are shown in Table 3. After adjusting for plasma GFAP level at the conclusion of surgery and low cardiac output syndrome, average MAP in the ICU below the optimal MAP were positively correlated with plasma GFAP levels on post-operative day 1.

Comment

There is no consensus on the definition of perioperative hypotension. In a systematic review, Bijker et al.(12) identified 130 publications that used the term intraoperative hypotension in the text. Of these reports, there were 140 different definitions of hypotension. Further, the various definitions for hypotension were empirically derived and not based on physiologic end-points. Using the three most common clinical definitions, we found no relationship

between hypotension and plasma GFAP levels measured on post-operative day 1. In contrast, patients who had average MAP in the ICU below their OptMAP based on COx monitoring during CPB had significantly higher plasma GFAP levels on post-operative day 1 compared with patients whose MAP remained above the optimal level in the ICU. Further, the product of the magnitude and the duration that MAP was below OptMAP (AUC<OptMAP) had positive correlation with plasma GFAP levels indicating a dose-response of MAP < OptMAP and brain cellular injury.. After adjusting for plasma GFAP levels measured at the conclusion of surgery, average MAP<OptMAP and low cardiac output syndrome were independently associated with higher plasma GFAP levels on post-operative day 1. These results indicate that monitoring COx based optMAP , but not hypotension defined by standard definition, may better ensure brain perfusion.

In prior investigations our group has found that the lower limit of CBF autoregulation during CPB has wide inter-individual variability and is difficult to predict based on medical history or preoperative blood pressure. Thus, many patients are exposed to varying periods of time during surgery where their MAP is below the lower limit of autoregulation. In this study we demonstrate that periods of MAP<OptMAP are common in the post-operative period. We have previously shown that excursions of MAP below the lower limit of CBF autoregulation during CPB are biologically significant, impacting visceral organ perfusion. Ono et al. (1,2) for example, found that the magnitude and duration that MAP is below the lower limit of autoregulation during cardiac surgery, based on COx monitoring, was an independent predictor of post-operative acute kidney injury and major organ morbidity and operative mortality after cardiac surgery. More recently we have found that blood pressure excursions above the upper limit of cerebral autoregulation were associated with post-operative delirium.(3) Further, we have found that dysfunctional cerebral autoregulation is associated with post-operative stroke.(13) The results of the present study extends these findings to the postoperative ICU suggesting that the usual standard of care of choosing empiric definitions of hypotension may not ensure optimal brain perfusion for all patients.

A sensitive and specific biomarker of brain ischemic injury would have great value in the early diagnosis of both severe and subtle neurological complications after cardiac surgery as well as providing an end-point for clinical neuroprotection investigations. In the past, S100 β and neuron specific enolase have been proposed as biomarkers for this purpose for patients undergoing cardiac surgery but significant extra-cerebral contamination limits there specificity for diagnosing brain injury.(14-16) Glial fibrillary acidic protein is a astrocyte cytoskeleton protein with high specificity for the brain.(4) Astrocytes are the most abundant cellular component in the brain that have many important functions including modulation of synaptic plasticity, glutamate re-uptake, neuronal repair after ischemic injury, and maintaining blood brain barrier integrity.(4) Elevation in plasma GFAP levels has been reported in adults with traumatic brain injury, stroke, and after cardiac arrest.(5-7) In a series of pediatric patients, Bembea et al. (11) reported high GFAP during extracorporeal membrane oxygenation which was significantly associated with acute brain injury and death. Rapid availability of plasma GFAP measures could expand the potential of this protein for guiding perioperative patient management.

Our study is associated with several limitations. First, blood pressure measurements in the ICU were obtained every 15 minutes and not continuously. Thus, we cannot ensure that patients may have had periods of $MAP < OptMAP$ in the intervening periods between measurements. Further, our definition of OptMAP is based on data obtained during CPB. Our study cannot address whether OptMAP in the non-physiologic conditions of CPB and during anesthesia are similar to those that might occur in the ICU, where other factors such as $PaCO_2$ could influence autoregulation.. Further, although we adjust for plasma GFAP levels at the conclusion of surgery in our analysis, we cannot ensure that brain cellular injury we detected occurred exclusively in the postoperative period. Due to small incidence of stroke and delirium, the association between these neurological clinical end-point and plasma GFAP levels cannot be accurately determined.

In conclusion, these results show that empiric post-operative blood pressure management maybe imprecise for ensuring brain perfusion after cardiac surgery. We demonstrate that many patients have elevated plasma GFAP levels even when blood pressure is clinically within an acceptable range. Individualizing blood pressure management using COx cerebral autoregulation monitoring may provide a more precise method for blood pressure management potentially limiting cerebral hypoperfusion injury.

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Figure 1.

Cerebral oximetry index (COx) results obtained during cardiopulmonary bypass placed in 5mmHg bins. Optimal MAP was defined as that MAP with the lowest COx. As MAP moves away from the optimal MAP, COx increases indicating trends towards pressure dependent changes in cerebral blood flow. In this example, the optimal MAP is 80 mmHg. (Black Arrow)

Figure 2.

Box and whisker plot comparing plasma GFAP levels on post-operative day 1 for patients who had average MAP (ICU) above the optimal MAP, and patients who had average MAP (ICU) below the optimal MAP. ($p < 0.001$) The horizontal line in the shaded box represents the median value, and the shaded box represents the interquartile range. The error bars below and above the shaded area represents $\pm 1.5 \times$ the interquartile range; points beyond the error bar are outliers.

Figure 3.

Box and whisker plot comparing the product of magnitude and duration of MAP below optimal MAP (AUC<OptMAP) in patients who had average MAP (ICU) above the optimal MAP and for patients who had average MAP (ICU) below the MAP. ($p < 0.001$) The horizontal line in the shaded box represents the median value, and the shaded box represents the interquartile range. The error bars below and above the shaded area represents $\pm 1.5 \times$ the interquartile range; points beyond the error bar are outliers.

Figure 4.

Spearman's correlation ratio between plasma GFAP levels on postoperative day 1 and the product of magnitude and duration of blood pressure below the optimal MAP. ($r=0.31$, $p<0.001$)

Table 1

Patients demographic data.

	Patient Demographic
	n=121
Age [†]	71±8.1 (70-72)
Gender (Male)	46 (38.0%)
Hypertension (%)	101 (83.5%)
Diabetes (%)	71 (58.7%)
CHF (%)	18 (14.9%)
Peripheral Vascular Disease (%)	19 (15.7%)
COPD (%)	13 (10.7%)
Aspirin (%)	93 (76.9%)
Statin (%)	71 (58.7%)
ARB (%)	21 (17.4%)
ACE Inhibitor (%)	49 (40.5%)
Ca Blocker (%)	31 (25.6%)
Beta Blocker (%)	71 (58.7%)
Diuretics (%)	48 (39.7%)
Current Smoker (%)	10 (8.3%)
Previous Smoker (%)	57 (47.1%)
Prior CEA (%)	7 (5.8%)
Prior CVA (%)	10 (8.3%)
NYHA	
I	33 (27.3%)
II	57 (47.1%)
III	25 (20.7%)
IV	6 (4.9%)
Hemoglobin (g/dl) [‡]	12.2±1.74 (11.9-12.6)
Surgery	
CABG	66 (54.5%)
CABG+AVR/MVR	25 (20.7%)
AVR/MVR	22 (18.2%)
Others	8 (6.6%)
Postoperative Stroke (%)	4 (3.3%)
Postoperative Delirium (%)	14 (11.6%)
Hospital Stay (days) [‡]	7 (6-10)

Data are listed as number and percent of patients for dichotomous variables with the exception of age listed as

[†] mean±SD (95% Confidence Interval) and duration of in-hospital stay that is listed as

[‡] median (interquartile range).

Table 2

Perioperative variables.

	Perioperative variables
	n=121
Systolic Blood Pressure (mmHg) [†]	
Baseline	135±20.8 (131-138)
ICU	112±11.5 (110-115)
Mean Arterial Pressure (mmHg) [†]	
Baseline	92±12.3 (90-94)
CPB	75±6.5 (74-77)
ICU	74±7.3 (73-75)
Optimal BP (mmHg) [†]	78±12.8 (75-80)
Cardiopulmonary bypass duration (min) [‡]	98 (76-132)
Aortic cross-clamp duration (min) [‡]	61 (47-83)
Lowest hemoglobin (g/dl) [†]	7.9±1.14 (7.7-8.2)
Cooling (Cooling : Drift)	65:56
Minimum temperature (°C) [†]	31.3±2.74 (30.9-31.8)
Minimum temperature (Cooling) (°C) [†]	29.1±2.33 (28.5-29.7)
Minimum temperature (Drift) (°C) [†]	33.3±1.10 (33.0-33.5)
Plasma GFAP level (before incision) [‡]	0.023 (0.010-0.035)
Plasma GFAP level (conclusion of surgery) [‡]	0.034 (0.014-0.079)
Plasma GFAP level postoperativ day 1 [‡]	0.044 (0.029-0.080)

Data are listed as

[†] mean±SD (95% Confidence Interval) for continuous variables that were normally distributed and

[‡] median (interquartile range) for continuous variables that were non-normally distributed.

Table 3
Multivariate linear regression results for variables independently associated with plasma GFAP levels measured on postoperative day 1 (Logarithmically transformed). Values are presented as e^{β}

	Coefficient	Standard Error	95% Confidence Interval	P-value
Log plasma GFAP level at the conclusion of surgery	1.48	1.09	1.254-1.743	<0.001
ICU mean MAP below optimal MAP	1.77	1.18	1.266-2.479	0.001
Low cardiac output syndrome	2.08	1.26	1.309-3.267	0.002

Variables that had $p < 0.1$ in the univariate analysis were included in the model. The mean r^2 of this model was 0.32.