Optimal blood pressure during cardiopulmonary bypass defined by cerebral autoregulation monitoring

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ABSTRACT

Objectives: We sought to define the lower and upper limits of cerebral blood flow autoregulation and the optimal blood pressure during cardiopulmonary bypass. We further sought to identify variables predictive of these autoregulation end points.

Methods: Cerebral autoregulation was monitored continuously with transcranial Doppler in 614 patients during cardiopulmonary bypass enrolled in 3 investigations. A moving Pearson's correlation coefficient was calculated between cerebral blood flow velocity and mean arterial pressure to generate the variable mean velocity index. Optimal mean arterial pressure was defined as the mean arterial pressure with the lowest mean velocity index indicating the best autoregulation. The lower and upper limits of cerebral blood flow autoregulation were defined as the mean arterial pressure at which mean velocity index was increasingly pressure passive (ie, mean velocity index ≥ 0.4) with declining or increasing blood pressure, respectively.

Results: The mean ($\pm$ standard deviation) lower and upper limits of cerebral blood flow autoregulation, and optimal mean arterial pressure were 65 ± 12 mm Hg, 84 ± 11 mm Hg, and 78 ± 11 mm Hg, respectively, after adjusting for study enrollment. In 17% of patients, though, the lower limit of cerebral autoregulation was above this optimal mean arterial pressure, whereas in 29% of patients the upper limit of autoregulation was below the population optimal mean arterial pressure. Variables associated with optimal mean arterial pressure based on multivariate regression analysis were nonwhite race (increased 2.7 mm Hg; $P = .034$), diuretics use (decreased 1.9 mm Hg; $P = .049$), prior carotid endarterectomy (decreased 5.5 mm Hg; $P = .019$), and duration of cardiopulmonary bypass (decreased 1.28 per 60 minutes of cardiopulmonary bypass). The product of the duration and magnitude that mean arterial pressure during cardiopulmonary bypass was below the lower limit of cerebral autoregulation was associated with the risk for stroke ($P = .02$).

Conclusions: Real-time monitoring of autoregulation may improve individualizing mean arterial pressure during cardiopulmonary bypass and improving patient outcomes. (J Thorac Cardiovasc Surg 2017;154:1590-8)

Range of optimal MAPs.

Central Message

We provide evidence for optimal MAP during CPB based on cerebral autoregulation monitoring.

Perspective

There is no consensus on optimal MAP during CPB. Cerebral autoregulation monitoring in 614 patients during CPB showed that optimal MAP for patients was 78 ± 11 mm Hg. However, this target will not be accurate in 17% to 29% of patients. Real-time monitoring of autoregulation may better ensure perfusion during CPB.

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Abbreviations and Acronyms

ABP	= arterial blood pressure
CBF	= cerebral blood flow
CPB	= cardiopulmonary bypass
LLA	= lower limit of autoregulation
MAP	= mean arterial pressure
Mx	= mean velocity index
SD	= standard deviation
TCD	= transcranial Doppler
ULA	= upper limit of autoregulation

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Since its introduction on May 6, 1953, by J. H. Gibbons, Jr, cardiopulmonary bypass (CPB) has allowed surgical teams to improve survival and quality of life for patients with life-threatening cardiovascular disease.¹⁻³ Despite multiple technologic and patient management advances in the ensuing 60 years, controversy remains regarding the appropriate mean arterial pressure (MAP) for patients during CPB, with no definition of optimal MAP universally accepted.⁴ The guiding principle of blood pressure management during CPB is that cerebral blood flow (CBF) autoregulation must remain functional during CPB when α -stat pH management is used.⁴⁻⁶ Consequently, a MAP as low as 50 mm Hg, and even transiently lower, is often believed to be acceptable during CPB because CBF will not be compromised.^{5,7} However, cerebral autoregulation might be impaired by many conditions that are prevalent in patients with coronary artery disease.^{8,9} Indeed, neurologic complications, including stroke and acute cognitive disorders, affect 1% to 2% and up to 20% to 40% of patients, respectively, after cardiac surgery.^{4,10} Many such complications might be explained by cerebral hypoperfusion.¹¹⁻¹⁴

Cerebral autoregulation now can be monitored at the bedside by continuously calculating the correlation coefficient between slow-wave (ie, every 20 seconds to 3 minutes) changes in CBF velocity (measured with transcranial Doppler [TCD]) and MAP.¹⁵⁻¹⁷ By using these methods in patients undergoing CPB, our group has reported that MAP at the lower limit of autoregulation (LLA) is broad (40-90 mm Hg) and difficult to predict by patient demographics and other preoperative factors.¹⁶ We have further found that the magnitude and duration that MAP is

below the LLA during CPB is associated with major morbidity and mortality postoperatively.^{18,19} However, simply increasing MAP targets during CPB may be associated with other adverse postoperative outcomes, as we have found that blood pressure excursions above the upper limit of autoregulation (ULA) during CPB are associated with postoperative delirium.²⁰ Together, these studies suggest that guiding hemodynamics to ensure cerebral perfusion within the autoregulation range may be better for patient outcome than choosing these targets empirically. In our investigations, we have observed that as many as 20% of patients will not have a clear LLA because of a pattern of impaired autoregulation.²¹ In these situations, though, an optimal MAP usually is still observed at which autoregulation is best. Maintaining cerebral perfusion pressure in the optimal autoregulation range is associated with improved outcomes for patients with traumatic brain injury, supporting the potential clinical role of autoregulation monitoring.²² Our prior investigations did not have an adequate sample size to determine with high precision the range of optimal MAP for patients undergoing cardiac surgery with CPB, and we did not evaluate MAP with respect to ULA.

Despite growing data supporting a role for customized MAP targets based on autoregulation monitoring in patients undergoing cardiac surgery, the latter methods remain a research tool. The goal of this study was to expand on prior investigations of CBF autoregulation to provide guidance about optimal MAP to clinicians who care for patients undergoing cardiac surgery. We sought to define the LLA and ULA of CBF autoregulation and optimal blood pressure during CPB. We further sought to identify variables predictive of these autoregulation end points.

MATERIALS AND METHODS

From April 2008 to April 2015, 614 patients undergoing cardiac surgery at The Johns Hopkins Hospital were enrolled in 2 completed trials and 1 ongoing prospective trial that evaluated cerebral autoregulation monitoring with TCD (NCT00981474, NCT00769691).^{23,24} A flow diagram of the patients included in this study is shown in Figure 1. Enrollment in the largest of the 3 studies was limited to patients at high risk for neurologic complications as determined by the Johns Hopkins stroke and encephalopathy risk score.²⁵ Patients undergoing circulatory arrest were excluded. All procedures received the approval of the Institutional Review Board of The Johns Hopkins Medical Institutions, and all patients provided written informed consent. A total of 346 patients included in this analysis were enrolled in a study that included preoperative TCD examination by a trained vascular technologist. As part of that protocol, patients in whom a temporal window for TCD monitoring was not present were excluded from subsequent intraoperative monitoring.

Hemodynamic Management and Anesthesia

General anesthesia was induced and maintained with midazolam, fentanyl, and isoflurane, and pancuronium or vecuronium was administered for skeletal muscle relaxation. Before CPB, heparin was administered to achieve an activated clotting time greater than 480 seconds. The CPB flow was nonpulsatile and maintained with a target of 2.0 to 2.4 L/min/m². Arterial pressure was monitored via a radial artery

FIGURE 1. Flow diagram of the patients enrolled in the study and included in this analysis.

catheter and was controlled by adjusting CPB flow and the administration of vasoactive medications. The patients were managed with alpha-stat pH management. Normocarbia was ensured with a continuous in-line arterial blood gas monitor that was calibrated hourly. Protamine was administered to reverse the effects of heparin after separation from CPB.

Transcranial Doppler–Based Autoregulation Monitoring

After patients were anesthetized and intubated via the trachea, TCD monitoring (DWL, Compumedics DWL, El Paso, Tex) of the right and left middle cerebral arteries was initiated by positioning two 2.5-MHz transducers fitted on a headband over the temporal bone. Depth of insonation was varied between 35 and 52 mm until representative spectral CBF flow was identified. Analog arterial pressure and TCD signals from the operating room hemodynamic monitor were processed with a data-acquisition module (DT9800, Data Translation Inc, Marlboro, Mass) and then analyzed by

ICM+ software (University of Cambridge, Cambridge, United Kingdom) as described previously.^{15,26–28} 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 caused by 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 mean middle cerebral artery blood flow velocity was calculated to render the variable mean velocity index (Mx). Consecutive, average Mx values within a 10-second window were collected as 30 data points to monitor each Mx in a 300-second window. More details of these methods are provided in [Appendix E1](#). Mx approaches 1 when MAP is outside the limits of autoregulation, indicating pressure-passive CBF. In contrast, Mx approaches 0 or is negative when MAP is within the CBF autoregulation range. Average Mx values obtained during CPB were placed in 5 mm Hg MAP bins. The LLA was defined as the MAP at which Mx increased to a value 0.4 or greater with declining blood pressure. Optimal

FIGURE 2. Representative graph of cerebral autoregulation monitoring by Mx during CPB. The top graph represents the time-series of ABP, and the bottom bar-graph represents the percentage of the time of the recording spent at 5 mm Hg bin. Optimal MAP (ABP) for the left and right side of the brain was defined as that MAP with the lowest Mx. LLA and ULA were defined as the MAP at which Mx reached 0.4. In this example, the optimal MAP is 85 mm Hg (black arrow) and the LLA and ULA are 70 mm Hg and 95 mm Hg, respectively (black-outlined arrow). ABP, Arterial blood pressure.

TABLE 1. Demographics and intraoperative data for the entire cohort, based on enrolled study

Variable	Entire cohort N = 617	Study 1 ¹⁷ N = 183	Study 2 ²⁴ N = 105	Study 3 N = 326	P value
Age (y)*	67.2 ± 10.5	64.6 ± 11.3	61.2 ± 12.0	70.7 ± 8.0	<.001
Female gender	160 (26.1%)	34 (18.6%)	29 (27.6%)	97 (29.8%)	.021
White ethnicity†	520 (85.0%)	165 (90.2%)	90 (85.7%)	265 (81.8%)	.039
History of tobacco smoking	280 (45.6%)	72 (39.3%)	45 (42.9%)	163 (50.0%)	.056
COPD	65 (10.6%)	18 (9.8%)	10 (9.5%)	37 (11.3%)	.805
Diabetes	247 (40.2%)	53 (29.0%)	37 (35.2%)	157 (48.2%)	<.001
CHF	106 (17.3%)	29 (15.8%)	25 (23.8%)	52 (16.0%)	.15
Hypertension	490 (79.8%)	131 (71.6%)	76 (72.4%)	283 (86.8%)	<.001
Creatinine (g/dL)*	1.2 ± 1.0	1.2 ± 1.2	1.5 ± 1.6	1.1 ± 0.3	.001
Preoperative eGFR*	74.4 ± 24.7	77.3 ± 25.8	73.1 ± 28.9	73.2 ± 22.4	.156
Preoperative mean blood pressure (mm Hg)*	93.5 ± 13.3	93.7 ± 13.7	91.9 ± 14.0	93.9 ± 12.9	.39
Preoperative systolic blood pressure (mm Hg)*	136.2 ± 21.2	137.1 ± 20.5	132.9 ± 22.7	136.9 ± 21.0	.198
Preoperative hemoglobin (g/dL)*	12.5 ± 2.0	12.7 ± 2.0	12.2 ± 2.2	12.5 ± 2.0	.159
Angiotensin-converting enzyme inhibitors-I	226 (36.8%)	58 (31.7%)	37 (35.2%)	131 (40.2%)	.152
Statins	317 (51.7%)	116 (63.4%)	62 (59.0%)	139 (42.8%)	<.001
Aspirin	441 (71.8%)	119 (65.0%)	66 (62.9%)	256 (78.5%)	<.001
Beta-blocker	379 (61.7%)	107 (58.5%)	59 (56.2%)	213 (65.3%)	.137
Ca ⁺⁺ channel blocker	129 (21.0%)	26 (14.2%)	24 (22.9%)	79 (24.2%)	.025
Nitrates	107 (17.4%)	28 (15.3%)	12 (11.4%)	67 (20.6%)	.067
Diuretics	218 (35.5%)	42 (23.0%)	42 (40.0%)	134 (41.1%)	<.001
Prior carotid endarterectomy	23 (3.7%)	2 (1.1%)	5 (4.8%)	16 (4.9%)	.078
Prior CVA	57 (9.3%)	19 (10.4%)	5 (4.8%)	33 (10.1%)	.214
Prior TIA	33 (5.4%)	10 (5.5%)	1 (1.0%)	22 (6.7%)	.072
Peripheral vascular disease	89 (14.5%)	21 (11.5%)	10 (.5%)	58 (17.8%)	.043
Coronary artery disease	467 (76.1%)	143 (78.1%)	63 (60.0%)	261 (80.1%)	<.001
CPB duration (min)*	112.8 ± 48.0	116.58 ± 43.1	104.7 ± 44.5	113.4 ± 51.4	.129
Aortic crossclamp duration (min)*	69.2 ± 32.0	72.8 ± 33.6	57.1 ± 32.2	71.2 ± 30.0	<.001
Average MAP (mm Hg)*	73.7 ± 8.1	72.6 ± 8.5	72.0 ± 8.4	74.8 ± 7.6	.001
Lowest hemoglobin (g/L)*	8.2 ± 1.3	8.3 ± 1.3	8.3 ± 1.4	8.1 ± 1.3	.211

COPD, Chronic obstructive pulmonary disease; CHF, congestive heart failure; eGFR, estimated glomerular filtration rate; CVA, cerebral vascular accident; TIA, transient ischemic attack; CPB, cardiopulmonary bypass; MAP, mean arterial pressure. *Data are provided as mean ± SD for continuous variables that were normally distributed.

†Nonwhite race group is predominantly African-Americans, with only 16 patients in study 3 reporting other race.

MAP was defined as that MAP at the lowest Mx indicating the best autoregulation.²² The ULA was defined as the MAP at which Mx increased to 0.4 or greater with increasing blood pressure.²⁰ A representative autoregulation tracing obtained during CPB is shown in Figure 2. More details about the methods can be found in Appendix E1. We separately evaluated the LLA, ULA, and optimal MAP from the right and left Mx data. For the purpose of data analysis, we took the highest MAP to define the LLA and optimal MAP and the lowest MAP value for the ULA if there were discrepancies between cerebral hemispheres. We believe that this would be clinically the most applicable method when this type of monitoring becomes widespread. That is, the target MAP would be that which best ensures perfusion to the most compromised hemisphere while trying to avoid MAP greater than ULA.

Sample Size Calculation

The sample size was calculated with an estimation of optimal MAP that was based on CBF autoregulation end points collected previously from 225 patients undergoing cardiac surgery.¹⁶ In that study, average mean MAP at

the LLA was 66 mm Hg, and the standard deviation (SD) was 12 mm Hg. On the basis of those data, we estimated that a sample size of 553 patients would provide a 1 mm Hg margin of error in determining optimal MAP with a 95% confidence interval between 65 and 67 mm Hg.

Data Analysis

Complications after surgery were classified on the basis of definitions of the Society of Thoracic Surgery National Cardiac Surgery Database. Continuous variables are summarized as mean and SD. Normality assumption was checked, and non-normally distributed variables were log-transformed. Continuous variables were compared between groups using a *t* test or linear regression. Categorical variables were analyzed using the chi-square test or Fisher exact test if frequencies were low. Linear regression models were used to examine the effects of predictors on continuous outcomes (eg, LLA, MAP), adjusting for study. Multiple linear regression was used to identify baseline predictors of MAP; the final model was chosen using Akaike Information Criterion–based backward selection

TABLE 2. Optimal mean arterial blood pressure and mean arterial blood pressure at the lower limit of autoregulation and upper limit of autoregulation for the entire cohort and by study

	Entire cohort N = 617	Study 1 ¹⁷ N = 183	Study 2 ²⁴ N = 105	Study 3 N = 326	P value
Optimal MAP (mean $\pm$ SD, mm Hg)	78 $\pm$ 11	74 $\pm$ 12	75 $\pm$ 10	80 $\pm$ 11	<.001
LLA (mm Hg)	65 $\pm$ 12	63 $\pm$ 11	66 $\pm$ 13	66 $\pm$ 12	.024
ULA (mm Hg)	84 $\pm$ 11	81 $\pm$ 10	82 $\pm$ 9	86 $\pm$ 12	.002
Patients who crossed LLA	434 (71%)	141 (77%)	70 (67%)	223 (68%)	.074
Patients who crossed ULA	323 (52%)	102 (56%)	58 (55%)	163 (50%)	.387

The optimal MAP was defined as the MAP with the lowest Mx (see text). Data are listed as mean $\pm$ SD or number (%) of patients. MAP, Mean arterial pressure; SD, standard deviation; LLA, lower limit of autoregulation; ULA, upper limit of autoregulation.

from among baseline variables in Table 1, keeping demographics (age, gender, ethnicity, and smoking history) and study indicator in all models. Stability of the final model was checked using stepwise model selection strategies. Logistic regression models were used for binary outcomes (eg, CPB complications), adjusting for study. Analyses were performed using Stata version 14 (StataCorp LP, College Station, Tex).

RESULTS

Patient demographics and medical history are listed in Table 1. Predictably, demographic characteristics varied among the 3 studies. Table 2 presents the autoregulation data measured during CPB. An LLA during CPB was observed in 434 (71%) of 614 patients, and a ULA was observed in 323 patients (53%), whereas optimal MAP was observed in all patients. For these patients, the (mean $\pm$ SD) LLA was 65 $\pm$ 12 mm Hg and the ULA was 84 $\pm$ 11 mm Hg. The optimal MAP was 78 $\pm$ 12 mm Hg. The distribution of optimal MAP is shown in Figure 3. A pattern of impaired autoregulation (ie, Mx was >0.4 at all MAP) was observed in 98 patients (16%). In 82 patients (13%), an LLA was not observed, which may suggest that the normal fluctuations in MAP that occur during CPB never crossed the autoregulation threshold.

There was no relationship between patient age and the LLA, the optimal MAP, or the product of the magnitude

and duration for which MAP was below the LLA (ie, the “severity” of MAP below LLA) based on linear regression models. The distribution of optimal MAP is shown in Figure 3. In 17% of patients, the LLA was above this optimal MAP, whereas in 29% of patients the ULA was below the population optimal MAP. Patients with Mx greater than 0.4 at all MAPs (98 patients) were excluded from the latter analysis because we were unable to determine their LLA or ULA. An individual whose LLA MAP is above that of the group could experience cerebral hypoperfusion if the MAP during CPB is maintained at the group optimal MAP. Conversely, a ULA below the population median value could result in cerebral hyperperfusion if MAP is kept at the group median value. Strokes occurred in 5% of patients after surgery. The product of the magnitude and duration that MAP was less than LLA during CPB was associated with the risk of postoperative stroke ($P = .018$).

Predictors of optimal MAP based on multivariate linear regression adjusting for study are listed in Table 3. Nonwhite race, preoperative use of diuretic drugs, prior carotid endarterectomy, and duration of CPB were independently associated with optimal MAP during CPB. Optimal MAP was 2.73 mm Hg higher ($P = .034$) for nonwhite patients and 1.9 mm Hg lower ($P = .049$) for patients receiving diuretics. Optimal MAP was 5.5 mm Hg lower ($P = .019$) for patients with a prior carotid endarterectomy and 1.28 mm Hg lower per 60 minutes of CPB ($P = .22$). No other factors were significantly associated with optimal MAP in the linear regression model. The model explained little of optimal MAP variability ($R^2 = 0.1002$).

DISCUSSION

In this study, we found that the MAP (mean $\pm$ SD) at the LLA during CPB was 65 $\pm$ 12 mm Hg, the ULA was 84 $\pm$ 11 mm Hg, and the optimal MAP was 78 $\pm$ 11 mm Hg. An LLA during CPB was observed in 434 (71%) of 614 patients, and a ULA was observed in 323 patients (53%), whereas optimal MAP was observed in all patients. Patient age, history of hypertension, and diabetes were not

FIGURE 3. Distribution of optimal MAP for the entire cohort. MAP, Mean arterial pressure.

TABLE 3. Multiple regression model predicting optimal mean arterial pressure

Variable	Estimate	95% CI	P value
Study 1 vs 3	−6.03	(−8.6 to −3.9)	<.001
Study 2 vs 3	−4.95	(−7.5 to −2.4)	<.001
Age	−0.02	(−0.1 to 0.1)	.650
Female gender	0.52	(−1.5 to 2.6)	.618
White ethnicity	−2.73	(−5.3 to −0.21)	.034
History of tobacco smoking	−0.20	(−2 to 1.6)	.823
Hypertension	1.90	(−0.39 to 4.2)	.104
Ca ⁺⁺ channel blocker	1.84	(−0.34 to 4)	.098
Diuretics	−1.89	(−3.8 to −0.01)	.049
Prior carotid endarterectomy	−5.55	(−10 to −0.9)	.019
CPB duration (per 60 min)	−1.28	(−2.4 to −0.19)	.022

The final model was selected using backward selection based on Akaike Information Criterion from baseline predictors listed in Table 1. Demographic variables (age, gender, ethnicity, and smoking history) and study were kept in the model. Model $R^2 = 0.1002$. CI, Confidence interval; CPB, cardiopulmonary bypass.

related to the optimal MAP. Nonwhite race was predictive of a higher optimal MAP, whereas preoperative diuretic use, prior carotid endarterectomy, and duration of CPB predicted a slightly lower optimal MAP. Overall, the model for predicting optimal MAP explained only a small portion of the variance in this metric.

Blood flow to the brain is kept constant over a range of blood pressures to ensure a steady supply of substrates commensurate with cerebral metabolic demand. Current practices of patient blood pressure management during CPB are based on the concept that global cerebral perfusion should not be compromised as long as MAP is maintained above the LLA. Support for this practice is derived from studies, now more than 2 decades old, which showed that CBF is independent of MAP during CPB to a MAP of 20 to 55 mm Hg.^{4,5,7,29} In most of those studies, CBF was measured intermittently by ¹³³xenon clearance methods, and the analysis involved pooled or paired comparisons of CBF versus MAP. In contrast, our investigations used continuous measurements of CBF autoregulation throughout CPB and included a larger number of patients.

Monitoring of cerebral autoregulation may provide a more precise approach for determining individualized MAP targets during CPB, but this method requires specialized equipment and technical expertise. Our results suggest that the identified optimal MAP during CPB that we identified will reliably ensure perfusion within the autoregulation range for only 71% to 83% of patients. In others, the LLA will be above the identified population optimal MAP or the ULA will be below this value.

In our study, 16% of patients exhibited a pattern of impaired autoregulation in which Mx was greater than 0.4 at all MAPs. We have previously observed that this pattern is associated with risk for stroke.²¹ Even in this group, or for

those whose MAP does not cross the LLA, an optimal MAP can be identified. Many centers modify empiric MAP targets for CPB on the basis of patient age. In our analysis, however, we found no association between optimal MAP and patient age. In this study, we found a significant relationship between the product of the magnitude and the duration that MAP was below the LLA and risk for stroke. In a prior study, we found a relationship between MAP below the LLA in the intensive care unit after cardiac surgery and release of the brain-specific injury biomarker glial fibrillary acidic protein.³⁰ These data support a role of cerebral hypoperfusion in adverse neurologic complications after cardiac surgery. However, simply increasing MAP targets during CPB also could lead to adverse events. That is, we have found previously that the magnitude and duration that MAP is above the ULA during CPB is associated with postoperative delirium.²⁰ A plausible explanation for this outcome is that cerebral hyperperfusion in the context of heightened systemic inflammation related to cardiac surgery with CPB might result in adverse cerebral events.³¹⁻³³

Taken together, our data indicate the potential importance of maintaining MAP at a level that is neither below nor above the limits of autoregulation to optimize perfusion of the brain. In this study, we do not report on postoperative delirium or cognitive dysfunction. Moreover, our findings of a link between MAP below the LLA and stroke must be considered as an association. Whether targeting MAP on the basis of autoregulation metrics can lead to lower rates of stroke cannot be necessarily concluded from this study. We are currently conducting a prospectively randomized trial of autoregulation determined MAP versus the standard of care during CPB (National Institutes of Health R01HL092259). The primary end point of that ongoing study is a composite of adverse neurologic events, including stroke, brain magnetic resonance imaging–determined acute ischemic brain injury, and alterations in cognition from baseline.

Study Limitations

As with previous studies, we defined the limits of autoregulation as the MAP at which Mx increased to a value of 0.4 or greater. This value was associated with sepsis-associated delirium and mortality for patients with traumatic brain injury.^{22,34} Nonetheless, this cutoff is admittedly arbitrary and may not reflect the true lower limit, which could be an Mx greater than 0.3.³⁵ Regardless, any dichotomous definition of the LLA based on Mx fails to consider that vasoactive compensatory responses to blood pressure changes may persist even when MAP is outside the confines of autoregulation. In addition to its retrospective design, our study has several limitations. Cerebral blood vessel reactivity might be affected by body temperature. Body temperature was not included in

our analysis because we were unable to acquire this information in our data-acquisition scheme. Seven patients were excluded from analysis because of the lack of an identifiable TCD insonating window. However, because our sample size was above that required for identifying optimal MAP with precision, it seems unlikely that the exclusion of some patients for that reason led to an unintended bias in our results. Regardless, this finding underscores the limitations of TCD-based autoregulation monitoring that may preclude its routine adoption. Methods based on processing of near-infrared spectroscopy data hold promise as a clinically more feasible method for widespread cerebral autoregulation monitoring.¹⁷⁻²¹ Cerebral autoregulation measurements were based on CBF velocity in the middle cerebral arteries. Whether the LLA or optimal MAP thus identified applies to other major cerebral arterial systems is not known. Further, cerebral injury during cardiac surgery is primarily regional and may occur in vascular territories distal to an arterial stenosis or in the presence of small vessel disease.¹² Autoregulation distal to a flow-limiting stenosis would be expected to be impaired and the CBF pressure dependent. Determining optimal MAP for areas of the brain without stenosis may still provide adequate MAP for proximal vascular territories that provide the “driving pressure” across the stenosed vessel. Finally, the patients in this study were mostly those at high risk for brain injury. Whether our findings are applicable to lower-risk patients is not known.

CONCLUSIONS

These data suggest that optimal MAP during CPB is 78 ± 11 mm Hg, but in 17% and 29% of patients the LLA or ULA will be outside this range predisposing to unintentional cerebral hypoperfusion or hyperperfusion, respectively. Our finding of a relationship between MAP below the LLA during CPB and stroke supports a role of cerebral hypoperfusion and stroke. Development of clinical cerebral autoregulation monitors should be made a high priority to enable care providers the tools to individualize MAP during CPB.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: http://webcast.aats.org/2016/Video/Monday/05-16-16_Room_337_1645_Hori-800.mp4.

Conflict of Interest Statement

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Key Words: cardiopulmonary bypass, cerebral autoregulation, blood pressure

Discussion

K. Shann (*Boston, Mass*). Intensive intraoperative cerebral monitoring or brain monitoring in 614 patients is a significant achievement. This work complements a large series of work from the group at Hopkins now focused on the topic of cerebral autoregulation during CPB. This study highlights the differences in the autoregulation range between patients with coronary artery disease and patients without and gives us insight into optimal targets for blood pressure management during CPB.

Ten days ago we celebrated the 63rd anniversary of the heart-lung machine, and after all this time we still have limited data regarding the optimal blood pressure during CPB. So this work is also timely with the recent interest in creating strategies for goal-directed therapy for CPB.

I have 3 questions for you. You've identified optimal blood pressure targets of 80 and 75 mm Hg for patients

with and without coronary artery disease. In addition, your work identified an additional 14% of patients whose lower limit of autoregulation was higher than 75 mm Hg.

In some patients undergoing CPB, it is challenging to maintain empirical target arterial pressures from our protocols, and elevated flow rates, elevated levels of vasopressors, or perhaps even transfusion is considered if not required.

I noticed in your methods you maintain CPB flow rates at 2.0 to 2.4 L/min/m², which are consistent with common practice. I did not see any context in your article regarding the use of vasopressors to maintain a patient's pressure within their autoregulation range.

My first question is related to vasopressor use. We know from previous laboratory work that phenylephrine may redirect blood flow away from the bowel and muscle and direct it to the brain and the liver. In clinical practice, do we know whether strategies to maintain a patient's pressure within cerebral autoregulation range such as using increased pressors will ultimately improve outcome, or is it possible it causes other unwanted complications such as gut ischemia?

Dr Hori. We haven't looked at the other organ ischemia, but as I have shown in the previous slide, there is an association between the incidence of acute kidney injury (AKI) and the blood pressure management. In our institution, the majority of perfusionists change the pump flow first to control the blood pressure. Then, they will use phenylephrine to control the blood pressure.

Our previous studies have shown that blood pressures below the optimal MAP or below the low limit of autoregulation were associated with AKI, which means that if the blood pressure is too low, the incidence of AKI would increase. But we didn't look at the dosage of phenylephrine in association with AKI. That is something we need to look at.

The studies show that the blood pressures below the optimal MAP or below the low limit of autoregulation were associated with AKI, which means that if the blood pressure is too low, the incidence of AKI would go up. But we didn't look at the dosage of phenylephrine in association with an AKI, so that's something that we need to look at.

K. Shann. To follow with that question, in 1995 the Cornell group randomized 248 patients undergoing CPB to a blood pressure of 50 to 60 mm Hg or 80 to 100 mm Hg. They reported improved outcomes in the high pressure group; however, this work received scrutiny in part because of the high stroke rate in the low pressure group of 7.2%.

Other work your group has done, which was referenced your article, to study the association between autoregulation range, and outcome has been observational without measurement of interventions. Is it time to perform a randomized trial, kind of like the Cornell group did to

answer the question do interventions to maintain a patient's pressure within the autoregulation range during CPB improve outcome? In other words, do we need to do that randomized control trial now using your work as the basis?

Dr Hori. This is another good point, and we are doing a randomized trial at Hopkins right now. If the patient is randomized to treatment, we will tell the perfusionist and the anesthesiologist the optimal MAP. They will try to control the pressure at that optimal MAP, and we're going to look at the results.

K. Shann. Do you have an algorithm for the interventions?

Dr Hori. No. That's one of the limitations we have.

K. Shann. The optimal MAP targets you have identified will keep approximately 75% to 80% of patients within their autoregulation range, which leaves 20% to 25% of patients out of their autoregulation range.

In the current study, you used TCD combined with MAP put into a data housing unit that calculates an Mx and determines the upper and lower limits of autoregulation. For the majority of us in the room, that's not practical in routine clinical practice.

Your group also has published work using an investigational prototype device that you refer to as the near-infrared spectroscopy cerebral autoregulation monitor, which I don't believe has ever come to market. You more recently published material on the use of an ultrasound tag near-infrared spectroscopy autoregulation monitor that I believe is FDA approved. So my question is how close are we to having a user-friendly and clinically practical technology to monitor cerebral autoregulation during CPB?

Dr Hori. I think cerebral oximetry is easy to use. We just have to put the sensor stickers on the patient's forehead. If you use the ICM software, all we need to do is just plug in the near-infrared spectroscopy signals into the ICM computer, and it will calculate the cerebral oximetry index for

you. It's a very easy system to use. It's not that complicated, as I stated in the article. It's just 1 laptop and 1 INVOS (Medtronic/Covidien, Boulder, Colo), and you will have the data there.

K. Shann. So there is an application that...

Dr Hori. The ICM software calculates everything for you, right? The software is the most important thing.

Dr G. Pettersson (Cleveland, Ohio). This is an important topic. How do you distinguish between the global and local cerebral perfusion issues? Do we have any other ways of monitoring whether the brain is adequately perfused and at risk? What is the "reasonably safe underperfusion limit"?

Dr Hori. You mean for the monitoring?

Dr Pettersson. How far below the autoregulation limit can you go before you get damage to the brain?

Dr Hori. I'm not really sure about that. We are not sure if there is a cutoff value. But our studies have shown that the magnitude of blood pressure management outside the autoregulation range is positively correlated with the incidence of AKI and neurologic complications.

Dr Pettersson. Is there any way of studying it in advance so we could know?

Dr Hori. Know the limit you mean?

Dr Pettersson. So we could know the autoregulation in the individual patient before he/she goes to the operating room.

Dr Hori. It is difficult to predict autoregulation range without monitoring. To measure cerebral autoregulation using this system, you need data from a wide range of blood pressure levels to draw the cerebral autoregulation curve. But now, the ICM software can predict the optimal MAP by algorithm. So even if you only have few data, it will be able to draw that cerebral autoregulation curve by algorithm.

APPENDIX. SUPPLEMENTAL MATERIAL

More details can be found at: <http://www.neurosurg.cam.ac.uk/pages/ICM/about.php>.

AUTOREGULATION SIGNAL ACQUISITION AND PROCESSING METHODS

TCD monitoring (DWL, Compumedics DWL, El Paso, Tex) of the right and left middle cerebral arteries was performed with 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 was varied between 35 and 52 mm until representative spectral middle cerebral artery flow is identified, and then the transducers are locked in that position. Arterial pressure data (from an indwelling cannula placed for clinical purposes) were obtained from the operating room hemodynamic monitor via the analog output port. The arterial blood pressure data and the TCD signals were sampled at 58 Hz with an analog-to-digital converter and then imported into a laptop computer using ICM+ software (University of Cambridge, Cambridge, United Kingdom).^{E1-E7} This proprietary software collects and integrates high-resolution, multimodal data for real-time analysis of intracranial pressure, arterial pressure, brain oxygenation, blood flow, and other signals allowing for calculation of various physiologic indices, including autoregulation metrics (<https://www.enterprise.cam.ac.uk/opportunities/icm-software-for-brain-monitoring-in-neurological-intensive-care-research/>).

Blood pressure and TCD signals are time-integrated as nonoverlapping 10-second mean values, equivalent to applying a moving average filter with a 10-second time window and resampling 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's correlation coefficient is calculated between MAP and TCD cerebral blood flow velocity, rendering the variable Mx. Consecutive, paired, 10-second averaged values from 300-second duration are used for each calculation, incorporating 30 data points as we have reported.^{E8,E9} Mx values for each patient are placed into 5 mm Hg MAP bins and displayed on the laptop computer (Figure E1). When MAP is within the limits of CBF, autoregulation Mx approaches zero; when MAP is outside the limits of autoregulation, Mx approaches 1, indicating that CBF is blood pressure dependent.

On the basis of our prior studies, we designate the LLA as the highest blood pressure associated with Mx 0.4 or

greater. These values are within the range found to be associated with poor outcome after traumatic brain injury and adverse outcomes after cardiac surgery.^{E10-E13} In approximately 20% of patients, impaired autoregulation is observed when Mx is 0.4 or greater at all MAPs during CPB. An attenuated autoregulation plateau is usually observed. Thus, the "optimal" MAP, defined as the MAP with the lowest Mx, at this point is observed in patients with functional and impaired autoregulation. As blood pressure varies during the usual course of surgery, including during the initiation of CPB, no specific interventions are needed to establish autoregulation indices.

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FIGURE E1. Graph of autoregulation data obtained in the operating room during CPB. The top graph is the time series of blood pressure. The middle 2 bar graphs represent autoregulation data from the left and right sides, respectively, placed into 5 mm Hg ABP bins. The bottom histogram represents the percentage of the time of the recording spent at each ABP bin. The autoregulation variable is a dimensionless correlation coefficient between CBF velocity and ABP (Mx). An Mx approaching 1 represents impairment of autoregulation, and Mx close to zero represents functional autoregulation. The *red short arrow* represents the lower limit of autoregulation defined in this analysis as that ABP with Mx increases from less than 0.4 to 0.4 or greater. The *thick black arrow* indicates optimal ABP defined as that ABP with the lowest Mx. *ABP*, Arterial blood pressure.