Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality

Masahiro Ono, MD, PhD,[a] Kenneth Brady, MD,[b] R. Blaine Easley, MD,[b] Charles Brown, MD,[c] Michael Kraut, MD, PhD,[d] Rebecca F. Gottesman, MD, PhD,[e] and Charles W. Hogue, Jr, MD[c]

Objectives: Optimizing blood pressure using near-infrared spectroscopy monitoring has been suggested to ensure organ perfusion during cardiac surgery. Near-infrared spectroscopy is a reliable surrogate for cerebral blood flow in clinical cerebral autoregulation monitoring and might provide an earlier warning of malperfusion than indicators of cerebral ischemia. We hypothesized that blood pressure below the limits of cerebral autoregulation during cardiopulmonary bypass would be associated with major morbidity and operative mortality after cardiac surgery.

Methods: Autoregulation was monitored during cardiopulmonary bypass in 450 patients undergoing coronary artery bypass grafting and/or valve surgery. A continuous, moving Pearson's correlation coefficient was calculated between the arterial pressure and low-frequency near-infrared spectroscopy signals and displayed continuously during surgery using a laptop computer. The area under the curve of the product of the duration and magnitude of blood pressure below the limits of autoregulation was compared between patients with and without major morbidity (eg, stroke, renal failure, mechanical lung ventilation >48 hours, inotrope use >24 hours, or intra-aortic balloon pump insertion) or operative mortality.

Results: Of the 450 patients, 83 experienced major morbidity or operative mortality. The area under the curve of the product of the duration and magnitude of blood pressure below the limits of autoregulation was independently associated with major morbidity or operative mortality after cardiac surgery (odds ratio, 1.36; 95% confidence interval, 1.08-1.71; $P = .008$).

Conclusions: Blood pressure management during cardiopulmonary bypass using physiologic endpoints such as cerebral autoregulation monitoring might provide a method of optimizing organ perfusion and improving patient outcomes from cardiac surgery. (J Thorac Cardiovasc Surg 2014;147:483-9)

Currently, no consensus exists on the optimal mean arterial pressure (MAP) for patients during cardiopulmonary bypass (CPB). The current standard of care of empirically targeting MAP has been supported in part by findings that showed that cerebral blood flow (CBF)–blood pressure autoregulation remains functional during CPB when α-stat pH management is used.[1,2] Thus, a MAP as low as 50 mm Hg has traditionally been believed to be well tolerated, because the CBF has not been compromised.[1,3] Whether this approach is appropriate for the increasing number of elderly patients and for those with comorbidities that increase the risk of neurologic and other complications has been questioned. Our group has performed clinical studies of patients during CPB in which CBF autoregulation was monitored continuously in real time.[4-8] We have found in a contemporary cohort of patients that the lower limit of autoregulation varies widely (from 40 to 90 mm Hg) and is difficult to predict from the preoperative blood pressure and patient demographics.[4,7] Furthermore, as many as 20% of patients will have impaired autoregulation during CPB that results in pressure-passive CBF, particularly during patient rewarming after hypothermia.[6,8] This condition was associated with an elevated risk of stroke.[6,8]

Maneuvers aimed at optimizing cerebral perfusion will also influence systematic perfusion. This has led to the notion that the brain might serve as an index organ for ensuring other organ oxygenation during CPB.[9] Several

From the Division of Cardiac Surgery,[a] Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, Md; Department of Pediatrics and Anesthesiology,[b] Baylor College of Medicine, Texas Children's Hospital, Houston, Tex; and Departments of Anesthesiology and Critical Care Medicine,[c] Radiology,[d] and Neurology,[e] Johns Hopkins University School of Medicine, Baltimore, Md.

This study was funded in part by Grant-In-Aid 103363 from the Mid-Atlantic Affiliate of the American Heart Association; grant R01HL092259 from the National Institutes of Health (to Dr Hogue).

Disclosures: Dr Hogue has received research support from Somanetics, Inc, and its parent company, Covidien, Corp (Boulder, Colo). Ken Brady has consulted for Somanetics, Inc, in a relationship that was managed by the committee for outside interests at the Johns Hopkins University School of Medicine. All other authors have nothing to disclose with regard to commercial support.

Received for publication April 1, 2013; revisions received July 8, 2013; accepted for publication July 26, 2013; available ahead of print Sept 30, 2013.

Address for reprints: Charles W. Hogue, Jr, MD, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins Hospital, 1800 Orleans St, Zayed 6208, Baltimore, MD 21287 (E-mail: chogue2@jhmi.edu).

0022-5223/$36.00

http://dx.doi.org/10.1016/j.jtcvs.2013.07.069

PM

Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CBF = cerebral blood flow
CPB = cardiopulmonary bypass
MAP = mean arterial pressure
MMOM = major morbidity and operative mortality
NIRS = near-infrared spectroscopy
COx = cerebral oximetry index
$rScO_2$ = regional cerebral oxygen saturation

investigations have shown a relationship between decrements in regional cerebral oxygen saturation ($rScO_2$) measured using near-infrared spectroscopy (NIRS) and neurologic and non-neurologic complications after cardiac surgery, including the length of hospitalization.[10-12] Autoregulation can be clinically assessed at the bedside by evaluating the continuous correlation between the metrics of CBF and MAP.[13] In laboratory and clinical studies, we have shown that low-frequency changes in the relationship between the $rScO_2$, measured using NIRS, and MAP can serve as a surrogate for CBF in clinical autoregulation monitoring.[5,14] Because NIRS monitoring is noninvasive, requires little caregiver intervention, and is not associated with the limitations of other CBF monitoring modalities, our methods could be used in a wide variety of clinical settings. The finding that the limit of autoregulation varies widely among individuals suggests that empiric MAP management during CPB will invariably result in some patients having a MAP below the autoregulation threshold for at least a part of the surgery.[7] Knowing whether the MAP variations outside the autoregulatory range are associated with adverse patient outcomes after cardiac surgery could provide insights into potentially modifiable risk factors for adverse patient events. Major organ complications and mortality are common metrics for evaluating the quality of patient care after cardiac surgery.[15] In the present study, we hypothesized that the duration and magnitude of MAP outside the CBF autoregulatory range would be associated with major organ morbidity and mortality after cardiac surgery.

PM

METHODS

The institutional review board of Johns Hopkins Medical Institutions approved the present study (clinical trial registration no. NCT 00981474), which was performed after patients had provided written informed consent. Patients were eligible for the study if they were undergoing elective coronary artery bypass grafting (CABG) and/or valve surgery at Johns Hopkins Hospital and required CPB.

Patient Care

The patients received routine perioperative care that included invasive radial artery blood pressure monitoring and an anesthetic that consisted of midazolam, fentanyl, and isoflurane, along with a skeletal muscle relaxant, as previously described.[4,6,8,16] The patients received nonpulsatile CPB with a nonocclusive roller pump, a membrane oxygenator with flow of 2.0 to 2.4 L/min/m^2, and α-stat pH management. In-line arterial blood gas was monitored continuously, and the oxygen/air mixture to the oxygenator was varied to maintain normocarbia. Aspects of patient management such as the target MAP and the rate of patient rewarming were determined by standard practice and not dictated by the study protocol. The patients received standard postoperative care, including continuous electrocardiographic monitoring in the intensive care unit and on the postoperative ward.

NIRS-Based Autoregulation Monitoring

Before anesthesia was induced, the patients were connected to an NIRS monitor (INVOS, Somanetics, Inc, Boulder, Colo) using sensors placed on the right and left sides of the forehead. The acquisition and analysis methods for processing the NIRS signals and MAP have been previously described.[4,6] In brief, analog arterial blood pressure signals were digitized and then processed with the digital NIRS signals using a personal computer and ICM+ software (University of Cambridge, Cambridge, UK). The signals were filtered as nonoverlapping 10-second mean values that were time-integrated, a method equivalent to applying a moving average filter with a 10-second window and resampling at 0.1 Hz. The purpose of this process was to eliminate the high-frequency components (eg, respiration and pulse waveforms). Additional high-pass filtering was performed, with a dual channel cutoff set at 0.003 Hz to remove drifts, such as those resulting from hemodilution. A continuous, moving Pearson's correlation coefficient between the MAP and NIRS signals was then calculated to generate the variable cerebral oximetry index (COx). Each calculation was performed with consecutive, paired, 10-second averaged values from 300 seconds duration, incorporating 30 data points for each index.[4,6] When the MAP was within the limits of CBF autoregulation, the COx will approach 0; however, when the MAP is outside the limits of autoregulation, the COx will approach 1, indicating that the CBF is blood pressure passive.

Outcome Definitions

The primary endpoint of the present study was major morbidity and operative mortality (MMOM) using the Society of Thoracic Surgeons National Cardiac Surgery Database definitions. This endpoint consisted of operative death (ie, all deaths that occurred during the hospitalization in which the operation was performed, even if after 30 days, and deaths that occurred after discharge from the hospital but within 30 days of the procedure, unless the cause of death was clearly unrelated to the operation), stroke, renal failure (new requirement for dialysis postoperatively or increase in creatinine to >2 mg/dL and 2 times greater than baseline), mechanical lung ventilation >48 hours, or low cardiac output syndrome (inotrope use >24 hours or new requirement for intra-aortic balloon pump insertion).[17,18] We considered the baseline serum creatinine to be the last result before surgery, as measured in the Clinical Chemistry Laboratory of Johns Hopkins Hospital (Roche Diagnostics, Indianapolis, Ind). The lower sensitivity of this assay is 0.1 mg/dL. The estimated glomerular filtration rate was calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula.[19]

Statistical Analysis

The patients included in the present study were participants in several investigations.[4,7,8,16] No sample size calculations were performed for our retrospective database analysis. The autoregulation threshold was determined using previously described methods.[4,14,16] In brief, the COx values for each patient during CPB were placed into 5-mm Hg MAP bins. The exact COx denoting the limit of autoregulation threshold is not clear. The highest MAP associated with COx $\geq$0.3 was chosen as the lower limit of autoregulation on the basis of previous investigations.[4,14] Clinical COx recordings during CPB that illustrate the autoregulation thresholds are

shown in Figure 1. In some patients, the COx was ≥0.3 at all MAP values, indicating impairment of normal autoregulation.[8] In those instances, the MAP associated with the lowest COx was denoted as the optimal MAP according to similar methods used for patients with traumatic brain injury.[20] Periods of MAP below the limit of autoregulation were expressed in terms of magnitude (mm Hg) and duration (minutes). They are reported as the area under the curve of the product of MAP and time normalized for hours of CPB ($AUC_{MAP<LLA}$, where LLA is the lower limit of autoregulation) in units of mm Hg × min/h.[21]

The patients were categorized according to whether they had experienced the primary endpoint of MMOM. The continuous data between patients with and without this endpoint were compared using analysis of variance and with Bonferroni's correction when multiple comparisons were performed. Fisher's exact test was used for comparison of dichotomous data. Non-normally distributed data were log transformed before analysis. Multivariate logistic regression analysis was then performed for variables with $P < .1$ on univariate analysis. Statistical analysis was performed using Stata software, version 11 (StataCorp LP, College Station, Tex).

RESULTS

Autoregulation was monitored in 450 patients. The preoperative and operative patient characteristics are listed in Table 1. A dysregulated pattern (COx ≥0.3 at all MAPs) was observed in 83 patients (19%), similar to that reported previously.[8] Thirteen patients who required hemodialysis before surgery were excluded from the analysis. Of the remaining 437 patients, 83 (19.0%) developed the MMOM endpoint after surgery. A history of stroke, diabetes, congestive heart failure, impaired left ventricular function, previous cardiac surgery, and β-blocker use were more common in those with MMOM than in those without MMOM. Patients who developed MMOM had higher preoperative creatinine, a lower estimated glomerular filtration rate, a longer CPB duration, longer aortic crossclamping, and a longer hospitalization stay than did patients without major postoperative complications.

The $rScO_2$ and autoregulation results are listed in Table 2. The average MAP during CPB was similar between those who did and did not develop MMOM. Additionally, the lower limit of CBF autoregulation was similar between patients with and without MMOM. However, the area under the curve for MAP below the lower limit of autoregulation was larger for patients with MMOM than for those without MMOM (median, 6.5 mm Hg × min/h; interquartile range, 2.1-15.4; vs median, 2.4 mm Hg × min/h; interquartile range, 1.1-5.7; $P = .017$). The rate of each complication that constituted the MMOM endpoint is listed in Table 3. The area under the curve of the product of the duration and magnitude of MAP below the lower limit of autoregulation between patients with and without each specific

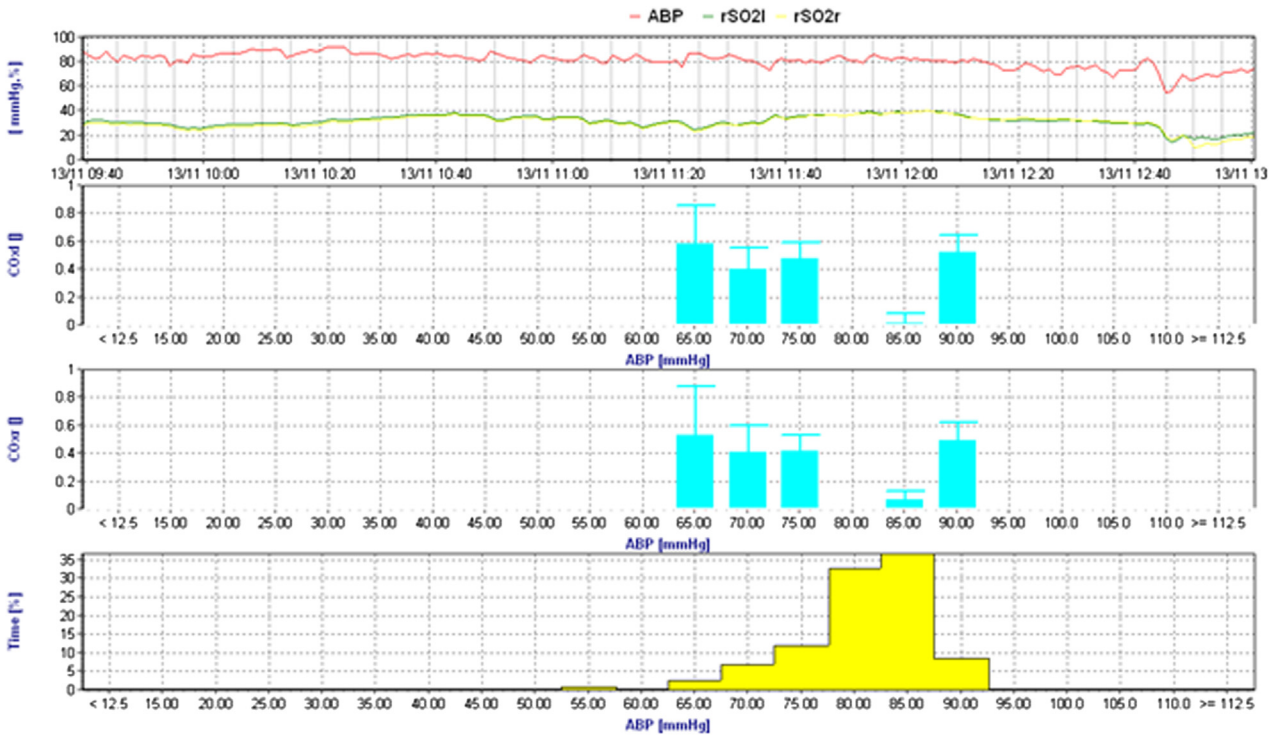

FIGURE 1. Cerebral oximetry index (*COx*) monitoring results during cardiopulmonary bypass. *Top channel*, Mean arterial blood pressure (*ABP*) and left *(l)* and right *(r)* regional cerebral oxygen saturation ($rScO_2$). *Middle 2 channels*, Right and left COx results are shown. *Bottom channel*, the percentage of time spent at each 5-mm Hg bin. COx represents the value for the Pearson's correlation coefficient between the low-frequency changes in $rScO_2$ and mean arterial pressure. In the example shown, the lower limit of autoregulation, defined as the mean arterial pressure at which COx increased from <0.3 to ≥0.3 was 75 mm Hg. Similar displays of COx shown continuously during surgery on a laptop computer enabled clinicians to assess the blood pressure associated with preserved cerebral autoregulation.

PM

TABLE 1. Patient characteristics stratified by major morbidity and operative mortality

Characteristic	No MMOM (n = 354)	MMOM (n = 83)	*P* value
Age (y)	66 ± 11	68 ± 11	.132
Male gender	264 (74.6)	61 (73.5)	.889
Baseline creatinine (mg/dL)	1.0 ± 0.3	1.2 ± 0.4	<.001
Baseline eGFR ($mL \times min^{-1} \times 1.73\ m^{-2}$)	81 ± 23	69 ± 24	<.001
Previous stroke	26 (7.3)	12 (14.5)	.050
COPD	35 (9.9)	10 (12.0)	.545
Current smoker	56 (15.8)	8 (9.6)	.171
PVD	40 (11.3)	13 (15.7)	.267
Hypertension	266 (75.1)	67 (80.7)	.505
Diabetes	125 (35.3)	41 (49.4)	.023
Congestive heart failure	45 (12.7)	23 (27.7)	.001
Prior myocardial infarction	90 (25.4)	22 (26.5)	.889
Preoperative LV ejection fraction	53 ± 12	47 ± 16	<.001
Previous cardiac surgery	21 (5.9)	11 (13.3)	.033
Aspirin	239 (67.7)	63 (76.8)	.112
β-Blockers	196 (55.5)	58 (70.7)	.013
ACEIs	122 (34.6)	30 (36.6)	.797
Statins*	216 (61.2)	53 (64.6)	.615
Baseline pulse pressure (mm Hg)	65 ± 19	64 ± 17	.818
Pulse pressure ≥60 mm Hg	204 (58.5)	49 (59.8)	.805
Type of surgery			.071
CABG	221 (62.4)	41 (49.4)	
CABG + AVR and/or MVR	46 (13.0)	16 (19.3)	
AVR and/or MVR	78 (22.0)	21 (25.3)	
Other	9 (2.5)	5 (6.0)	
Operative data			
CPB duration (min)	106 ± 38	133 ± 64	<.001
Crossclamp (min)	67 ± 27	77 ± 38	.008
Hospital stay (d)			<.001
Median	6.5	11	
Interquartile range	5-9	7-18	

Data presented as mean ± SD or n (%), unless otherwise noted. *MMOM,* Major morbidity and operative mortality; *eGFR,* estimated glomerular filtration rate; *CVA,* cerebral vascular accident; *COPD,* chronic obstructive pulmonary disease; *PVD,* peripheral vascular disease; *LV,* left ventricular; *ACEIs,* angiotensin-converting enzyme inhibitors; *CABG,* coronary artery bypass grafting; *AVR,* aortic valve replacement; *MVR,* mitral valve replacement or repair; *CPB,* cardiopulmonary bypass. *Statins included HMG-coenzyme A reductase inhibitors.

complication is also listed. Patients who developed stroke ($P = .056$), renal failure ($P = .03$), and prolonged mechanical ventilation ($P < .001$) had a greater $AUC_{MAP<LLA}$ than did patients without these complications.

The factors independently associated with MMOM are listed in Table 4. The area under the curve of the product of the duration and magnitude of MAP less than the lower limit of CBF autoregulation was an independent risk factor for MMOM after cardiac surgery (odds ratio, 1.36; 95% confidence interval, 1.08-1.71; $P = .008$).

DISCUSSION

Blood flow to the brain is normally autoregulated to ensure a steady supply of oxygenated blood to meet the metabolic demands. The lower limit of autoregulation can be affected by many conditions that result from vascular disease, including hypertension and previous stroke.[22] Because these conditions have widespread pathophysiologic consequences, it is logical that other organs, in addition to the brain, might require higher blood pressure to ensure organ perfusion during CPB in affected patients. In the present study, we found a relationship between the product of the duration and magnitude of MAP below the limits of cerebral autoregulation and MMOM. Our findings suggest that maintaining MAP within the autoregulatory range for the brain will ensure perfusion to other organs, particularly the kidney, whose blood flow is also autoregulated.[23]

Our results are consistent with those of others who found improved outcomes after cardiac surgery for patients whose treatment during CPB included manipulating MAP according to the $rScO_2$ monitoring results. In a prospectively randomized study of 200 patients undergoing CABG, Murkin and colleagues[11] found that patients receiving an intervention for $rScO_2$ decrements during CPB had a lower frequency of the composite outcome of operative death, lung ventilation >48 hours after surgery, stroke, myocardial infarction, or mediastinal re-exploration compared with control patients when clinicians were unaware of the NIRS results ($P = .048$). In a randomized study of 122 patients aged >65 years undergoing abdominal surgery, Casati and colleauges[12] found that control patients receiving blinded NIRS monitoring with intraoperative desaturation had a longer time until postanesthesia care unit discharge and longer hospitalization than did patients who had received active intervention for $rScO_2$ decrements. In those studies, renal injury endpoints were not included in the composite outcomes. Furthermore, our methods of monitoring COx might indicate insufficient organ perfusion earlier than $rScO_2$ desaturation, which would indicate the presence of conditions of inadequate cerebral oxygen supply in relation to demand. This earlier warning might explain why we found a stronger relationship between hypotension defined by COx monitoring and MMOM than did previous studies that evaluated only $rScO_2$.

Because CBF autoregulation is functional during CPB when α-stat pH management is used, clinicians have traditionally believed a MAP of 50 mm Hg or even lower to be adequate, because the blood to the brain is relatively constant.[1,3,24,25] Other data from Gold and colleagues[26] have suggested that MAP targets during CPB of 80 to 100 mm Hg might lower the combined frequency of stroke and myocardial outcomes compared with MAP targeted to 50 to 60 mm Hg. However, those data have been questioned because of the high stroke rate in the control group (7.2%) and the failure to ensure compliance with MAP management.[27] The limits of autoregulation during CPB vary widely; thus, empirically targeting higher MAP

TABLE 2. Blood pressure, regional cerebral oxygen saturation, and cerebral oximetry index autoregulation data stratified by major morbidity or mortality

Variable	No MMOM (n = 354)	MMOM (n = 83)	*P* value
Average MAP during CPB (mm Hg)	74 ± 8 (73-75)	75 ± 9 (72-76)	.203
Average $rScO_2$	54 ± 11 (52-55)	55 ± 7 (53-56)	.388
Average COx	0.27 ± 0.18 (0.25-0.29)	0.26 ± 0.17 (0.21-0.29)	.749
LLA (mm Hg)	69 ± 14 (67-70)	71 ± 12 (67-72)	.136
$AUC_{MAP<LLA}$ (mm Hg × min/h)	2.4 (1.1-5.7)	6.5 (2.1-15.4)	.017

Data reported as mean ± SD (95% confidence intervals), except for $AUC_{MAP<LLA}$, which is reported as the median (25%-75% interquartile range). *MMOM,* Major morbidity and operative mortality; *MAP,* mean arterial pressure; *CPB,* cardiopulmonary bypass; *$rScO_2$,* regional cerebral oxygen saturation; *COx,* cerebral oximetry index; *LLA,* lower limit of autoregulation; *$AUC_{MAP<LLA}$,* area under the curve of MAP less than the LLA during CPB.

thresholds might not necessarily be recommended, because such a strategy could result in MAPs greater than the upper autoregulation threshold in some patients.[28] In this situation, a higher MAP will result in an unnecessarily high CBF that could increase the cerebral embolic load and promote cerebral edema if CPB-associated systemic inflammation is present.[24,29] Defining the optimal MAP during CPB might be more precise when physiologic endpoints are used than when empiric MAP management is used, particularly for the increasing proportion of patients with cerebral vascular disease.[30,31]

Given the low rate of operative mortality as an endpoint, major complications have been increasingly included as a metric for evaluating the quality of care for patients undergoing cardiac surgery.[15] Our rate of MMOM (19%) was greater than that previously reported by the Society of Thoracic Surgeons National Cardiac Surgery Database (13.4%).[15] We focused on the complications likely to be influenced at least in part by organ perfusion but did not include other complication metrics such as sternal wound infection. Our findings can be contrasted with the more recent updates of these outcomes after CABG-only surgery, for which the rates of operative mortality, stroke, and prolonged mechanical lung ventilation have been reported to have declined to 1.9%, 1.2%, and 5.9%, respectively, from 2000 to 2009.[32] Our higher rates of MMOM can likely be explained by the higher risk cohort and the inclusion of procedures in addition to CABG-only surgery. Nonetheless, the factors we found associated with MMOM are consistent with those of previous investigations. One such factor is preoperative renal dysfunction, which has been found to be associated with the risk of death, subsequent myocardial infarction, and revascularization even up to 2 years after CABG.[33] The frequency of renal failure in our study (3.6%) was similar to that reported by Shroyer and colleagues[15] from the Society of Thoracic Surgeons database (3.53%).

In a report by El Bardissi and colleagues[32] that documented improvements in the national trends of operative mortality and complications, the frequency of renal failure after CABG actually increased by 5.5% from 2000 to 2009. Thus, modifying the risk of this complication would be highly clinically relevant. The present results complement our previous analysis in which we found a relationship between excursions of MAP below the autoregulatory limits and acute kidney injury using the sensitive RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria.[16,34,35] In that study, acute kidney injury occurred within 7 days of surgery in 34.8% of 348 patients. Using a similar approach, we found that the duration and magnitude by which MAP was below the lower limit of autoregulation (mm Hg × min/h of CPB) were independently associated with the risk of acute kidney injury (relative risk, 1.02; 95% confidence interval, 1.01-1.03; $P < .0001$). Most of the episodes of acute kidney injury (84%) were of the ''risk'' category, defined as an increase in plasma creatinine × 1.5 or a decrease in the estimated glomerular filtration rate by >25% from baseline. The present study has extended those findings to a clinically monitored endpoint of MMOM that used a more strict definition of renal failure (new requirement for dialysis postoperatively or increase in creatinine to >2 mg/dL and

PM

TABLE 3. Specific complication rates for patients with major morbidity and mortality after surgery and relationship to duration and magnitude of mean arterial pressure below the lower limit of cerebral blood flow autoregulation measured with the cerebral oximetry index

Complication	Patients (n)	$AUC_{MAP<LLA}$ (mm Hg × min/h)		*P* value
		With complication	Without complication	
Stroke	18 (4.1)	20.2 ± 26.5	9.5 ± 9.3	.056
Renal failure	16 (3.6)	15.5 ± 12.7	9.7 ± 10.6	.030
Mechanical ventilation >48 h	31 (7.1)	16.5 ± 15.1	9.4 ± 10.2	<.001
Inotrope use >24 h or new IABP insertion	47 (10.8)	11.7 ± 13.1	9.7 ± 10.4	.108
Operative death	15 (3.4)	15.1 ± 19.1	9.8 ± 10.3	.081

Data presented as n (%) or mean ± standard deviation. *$AUC_{MAP<LLA}$,* Area under the curve of mean arterial pressure less than the lower limit of autoregulation during cardiopulmonary bypass; *IABP,* intra-aortic balloon pump.

TABLE 4. Variables independently associated with major organ morbidity and mortality on multivariate logistic regression analysis*

Variable	OR	*P* value	95% CI
Baseline eGFR	0.98	<.001	0.97-0.99
Previous stroke	2.42	.035	1.07-5.51
Diabetes	1.64	.087	0.93-2.89
Preoperative LV ejection fraction	0.96	<.001	0.95-0.98
β Blockers	2.31	.006	1.27-4.21
Type of surgery	1.63	.001	1.22-2.19
$AUC_{MAP<LLA}$ (mmHg × min/h)	1.36	0.008	1.08-1.71

OR, Odds ratio; *CI,* confidence interval; *eGFR,* estimated glomerular filtration rate; *LV,* left ventricular; $AUC_{MAP<LLA}$, area under the curve of mean arterial pressure less than the lower limit of autoregulation during cardiopulmonary bypass. *The area under receiver operating characteristic curve, 0.7601.

2 × baseline) and other indicators of multiorgan dysfunction.

Although we found a relationship between the product of the duration and magnitude of MAP below the autoregulation threshold during CPB and the risk of MMOM, we were not able to infer a direct causal relationship between MAP and the included outcomes. Our methods of autoregulation monitoring might merely have identified patients at greater risk of organ injury that might or might not be modified by individualized MAP management. Nonetheless, in the present study, the lower limit of autoregulation was not different between patients with and without MMOM. Furthermore, the association between the duration and magnitude of MAP below the autoregulation threshold and the risk for MMOM persisted after adjusting for other important covariates. The etiology of renal injury after cardiac surgery is likely multifactorial and could include exposure to nephrotoxins, emboli, inflammation, and other causes. Similarly, the etiology of stroke is multifactorial and can result from macro- or microembolism and can be exacerbated by inflammation from CPB.[2] Hypoperfusion, however, might contribute to injury of both organs. Experiments in piglets, for example, have shown that renal blood flow is nearly 25% of baseline during hemorrhagic shock before the limits of CBF autoregulation have been reached.[23] Thus, preemptive MAP management using COx monitoring might have a plausible mechanistic basis for modifying these risks.

In conclusion, we found a relationship between the duration and magnitude of MAP below the limits of cerebral autoregulation during CPB and the risk of MMOM. This finding suggests that blood pressure management during CPB using physiologic endpoints such as cerebral autoregulation monitoring might provide a method for optimizing organ perfusion and potentially improving patient outcomes after cardiac surgery.

PM

References

1. Schell R, Kern F, Greeley W, Schulman S, Frasco P, Croughwell N, et al. Cerebral blood flow and metabolism during cardiopulmonary bypass. *Anesth Analg*. 1993; 76:849-65.
2. Hogue CW Jr, Palin CA, Arrowsmith JE. Cardiopulmonary bypass management and neurologic outcomes: an evidence-based appraisal of current practices. *Anesth Analg*. 2006;103:21-37.
3. Taylor K. The hemodynamics of cardiopulmonary bypass. *Semin Thorac Cardiovasc Surg*. 1990;2:300-12.
4. Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley B, et al. Real time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke*. 2010;41:1951-6.
5. Brady KM, Mytar JO, Lee JK, Cameron DE, Vricella LA, Thompson WR, et al. Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. *Stroke*. 2010;41:1957-62.
6. Joshi B, Brady K, Lee J, Easley B, Panigrahi R, Smielewski P, et al. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. *Anesth Analg*. 2010;110:321-8.
7. Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, et al. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg*. 2012;114:503-10.
8. Ono M, Joshi B, Brady K, Easley RB, Zheng Y, Brown C, et al. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. *Br J Anaesth*. 2012;109:391-8.
9. Murkin J, Arango M. Near-infrared spectroscopy as an index of brain and tissue oxygenation. *Br J Anaesth*. 2009;103(suppl 1):i3-13.
10. Zheng F, Sheinberg R, Yee MS, Ono M, Zheng Y, Hogue CW. Cerebral near-infrared spectroscopy monitoring and neurologic outcomes in adult cardiac surgery patients: a systematic review. *Anesth Analg*. 2013;116:663-76.
11. Murkin JM, Adams SJ, Novick RJ, Quantz M, Bainbridge D, Iglesias I, et al. Monitoring brain oxygen saturation during coronary artery bypass surgery: a randomized, prospective study. *Anesth Analg*. 2007;104:51-8.
12. Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Danelli G, et al. Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. *Anesth Analg*. 2005;101:740-7.
13. Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA. Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. *Neurocrit Care*. 2009;10:373-86.
14. Brady KM, Lee JK, Kibler KK, Smielewski P, Czosnyka M, Easley RB, et al. Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. *Stroke*. 2007;38:2818-25.
15. Shroyer AL, Coombs LP, Peterson ED, Eiken MC, DeLong ER, Chen A, et al. The Society of Thoracic Surgeons 30-day operative mortality and morbidity risk models. *Ann Thorac Surg*. 2003;75:1856-64; discussion 64-5.
16. Ono M, Arnaoutakis GJ, Fine DM, Brady KM, Easley RB, Zheng Y, et al. Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit Care Med*. 2013; 41:464-71.
17. Maganti MD, Rao V, Borger MA, Ivanov J, David TE. Predictors of low cardiac output syndrome after isolated aortic valve surgery. *Circulation*. 2005; 112(9 suppl):I448-52.
18. Algarni KD, Maganti M, Yau TM. Predictors of low cardiac output syndrome after isolated coronary artery bypass surgery: trends over 20 years. *Ann Thorac Surg*. 2011;92:1678-84.
19. Levey AS, Coresh J, Greene T, Marsh J, Stevens LA, Kusek JW, et al. Expressing the Modification of Diet in Renal Disease Study equation for estimating glomerular filtration rate with standardized serum creatinine values. *Clin Chem*. 2007;53:766-72.
20. Aries MJ, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. *Crit Care Med*. 2012;40:2456-63.
21. Aries MJ, Elting JW, De Keyser J, Kremer BP, Vroomen PC. Cerebral autoregulation in stroke: a review of transcranial Doppler studies. *Stroke*. 2010;41:2697-704.
22. Yamamoto M, Meyer J, Sakai F, Yamaguchi F. Aging and cerebral vasodilator responses to hypercarbia: responses in normal aging and in persons with risk factors for stroke. *Arch Neurol*. 1980;37:489-96.
23. Rhee CJ, Kibler KK, Easley RB, Andropoulos DB, Czosnyka M, Smielewski P, et al. Renovascular reactivity measured by near-infrared spectroscopy. *J Appl Physiol*. 2012;113:307-14.
24. Henriksen L, Hjelms E, Lindeburgh T. Brain hyperperfusion during cardiac operations: cerebral blood flow measured in man by intra-arterial injection of

xenon 133: evidence suggestive of intraoperative microembolism. *J Thorac Cardiovasc Surg*. 1983;86:202-8.
25. Murkin JM, Farrar J, Tweed W, McKenzie F, Guiraudon G. Cerebral autoregulation and flow/metabolism coupling during cardiopulmonary bypass: the influence of $PaCO_2$. *Anesth Analg*. 1987;66:825-32.
26. Gold JP, Charlson ME, Williams-Russo P, Szatrowski TP, Peterson JC, Pirraglia PA, et al. Improvement of outcomes after coronary artery bypass: a randomized trial comparing intraoperative high versus low mean arterial pressure. *J Thorac Cardiovasc Surg*. 1995;110:1302-11.
27. Reves JG, White WD, Amory DW. Improvement of outcomes after coronary artery bypass. *J Thorac Cardiovasc Surg*. 1997;113:1118-20.
28. Barodka VM, Joshi BL, Berkowitz DE, Hogue CW Jr, Nyhan D. Implications of vascular aging. *Anesth Analg*. 2011;112:1048-60.
29. Harris D, Bailey S, Smith P, Taylor K, Oatridge A, Bydder G. Brain swelling in first hour after coronary artery bypass surgery. *Lancet*. 1993;342:586-7.
30. Moraca R, Lin E, Holmes JHIV, Fordyce D, Campbell W, Ditkoff M, et al. Impaired baseline regional cerebral perfusion in patients referred for coronary artery bypass. *J Thorac Cardiovasc Surg*. 2006;131:540-6.
31. Gottesman RF, Sherman PM, Grega MA, Yousem DM, Borowicz LM Jr, Selnes OA, et al. Watershed strokes after cardiac surgery: diagnosis, etiology, and outcome. *Stroke*. 2006;37:2306-11.
32. El Bardissi AW, Aranki SF, Sheng S, O'Brien SM, Greenberg CC, Gammie JS. Trends in isolated coronary artery bypass grafting: an analysis of the Society of Thoracic Surgeons adult cardiac surgery database. *J Thorac Cardiovasc Surg*. 2012;143:273-81.
33. Mehta RH, Hafley GE, Gibson CM, Harrington RA, Peterson ED, Mack MJ, et al. Influence of preoperative renal dysfunction on one-year bypass graft patency and two-year outcomes in patients undergoing coronary artery bypass surgery. *J Thorac Cardiovasc Surg*. 2008;136:1149-55.
34. Kuitunen A, Vento A, Suojaranta-Ylinen R, Pettilä V. Acute renal failure after cardiac surgery: evaluation of the RIFLE classification. *Ann Thorac Surg*. 2006;81:542-6.
35. Lassnigg A, Schmid ER, Hiesmayr M, Falk C, Druml W, Bauer P, et al. Impact of minimal increases in serum creatinine on outcome in patients after cardiothoracic surgery: do we have to revise current definitions of acute renal failure? *Crit Care Med*. 2008;36:1129-37.