

Determining thresholds for three indices of autoregulation to identify the lower limit of autoregulation during cardiac surgery

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Conflicts of Interest

Dr. Brown reported receiving grants from the National Institutes of Health (NIH) during the conduct of the study, and consulting for and participating in a data share with Medtronic. Dr. Hogue reported receiving grants and personal fees for being a consultant and providing lectures for Medtronic/Covidien, Inc., being a consultant to Merck, Inc., and receiving grants from the NIH outside of the submitted work. Dr. Lee has received support from and been a paid consultant for Medtronic, and she received research support from Edwards Life Sciences. Dr. Lee's arrangements have been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. Some methods used to measure and monitor autoregulation as described in this manuscript were patented by The Johns Hopkins University, listing Dr. Brady as a co-inventor. These patents are exclusively licensed to Medtronic Inc., and Dr. Brady received a portion of the licensing fee. Dr. Venkataraman reported consulting activities with Vixiar Medical outside the scope of this work.

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Abstract

Objectives: Monitoring cerebral autoregulation (CA) may help identify the lower limit of autoregulation (LLA) in individual patients. Mean arterial blood pressure (MAP) below LLA appears to be a risk factor for postoperative acute kidney injury (AKI). CA can be monitored in real-time using correlation approaches. However, the precise thresholds for different CA indexes that identify the LLA are unknown. We identified thresholds for intact autoregulation in patients during cardiopulmonary bypass surgery and examined the relevance of these thresholds to postoperative AKI.

Design: A single-center retrospective analysis

Setting: Tertiary academic medical center

Patients. Data from 59 patients was used to determine precise CA thresholds for identification of the LLA. These thresholds were validated in a larger cohort of 226 patients.

Methods and Main Results: Invasive MAP, cerebral blood flow velocities (CBFV), regional cortical oxygen saturation and total hemoglobin were recorded simultaneously. Three CA indices were calculated, including mean flow index (Mx), cerebral oximetry index (COx), and hemoglobin volume index (HVx). CA curves for the three indices were plotted, and thresholds for each index were used to generate threshold- and index-specific LLAs. A reference LLA could be identified in 59 patients by plotting CBFV against MAP to generate gold standard Lassen curves. The LLAs defined at each threshold were compared with the gold standard LLA determined from Lassen curves. The results identified the following thresholds: Mx (0.45), COx (0.35), and HVx (0.3). We then calculated the product of magnitude and duration of MAP < LLA in a larger cohort of 226 patients. When using the LLAs identified by the optimal thresholds above, MAP < LLA was greater in patients with AKI than in those without AKI.

Conclusions: This study identified thresholds of intact and impaired CA for three indices and showed that MAP below LLA is a risk factor for AKI after cardiac surgery.

Key Words

Cerebral Autoregulation; Near Infrared Spectroscopy; Lower Limit of Autoregulation; Acute Kidney Injury; Cardiopulmonary Bypass Surgery; Mean Flow Index; Cerebral Oximetry Index; Hemoglobin Volume Index

BACKGROUND

Cerebral autoregulation (CA) refers to the ability of the brain to maintain relatively constant cerebral blood flow (CBF) over wide changes in mean arterial blood pressure (MAP) (1–4). However, when MAP decreases below the lower limit of autoregulation (LLA), compensatory mechanisms become inadequate, and CBF decreases monotonically with MAP. Understanding the CA status and individual LLA of a patient is highly relevant in many clinical scenarios to avoid cerebral hypoperfusion. In the neurocritical care unit, targeting MAP at the correct range in patients with neurological emergencies is critical, as both over- and under-correction of blood pressure are associated with increased morbidity and mortality (5–9). During cardiopulmonary bypass (CPB) surgery, MAP targets are often lowered to reduce bleeding from collateral circulation, but a reduction in cerebral perfusion may cause unrecognized cerebral ischemia (10). Maintaining MAP above LLA may be especially important during CPB surgery, as studies have suggested that the extent of MAP below the LLA is associated with major morbidity and mortality, acute kidney injury (AKI), and delirium (1, 10–12).

The CA of critically ill patients can be assessed in real time by comparing spontaneous CBF changes in response to changes in MAP (6, 13–15). Using multimodal monitoring, a moving correlation coefficient is calculated between changes in CBF and changes in MAP. This correlation coefficient is termed the “index of autoregulation” and can vary between -1 (intact autoregulation) and 1 (impaired autoregulation) (6, 15–17). Based on the surrogate of CBF that is monitored, several indices of autoregulation have been described, including the mean flow index (Mx, derived from transcranial Doppler [TCD] flow), cerebral oximetry index (COx, derived from regional cortical oxygen saturation [rSO₂]), and hemoglobin volume index (HVx, derived from regional total hemoglobin [rTHb]) (16, 18–21).

However, the exact threshold for each index of autoregulation that denotes the precise LLA is unknown. Current estimates are based on balloon inflation experiments in neonatal pigs or data from traumatic brain injury patients, which suggest a threshold of 0.3–0.4, depending on

the index (17, 19, 20, 22–24). It is unclear whether these thresholds derived from neonatal pigs are similar in older adults (who often have hypertension and cerebrovascular disease) or in patients undergoing CPB. Therefore, we conducted this study to identify precise thresholds for Mx, COx, and HVx that could identify the LLA during CPB. We hypothesized that by comparing thresholds for each index of autoregulation to a gold standard LLA (25, 26) derived from classic Lassen curves, we could identify the optimal index-specific thresholds that would identify the LLA in real time. We then examined the significance of these thresholds in a larger cohort of patients to determine clinical relevance with respect to AKI.

MATERIALS AND METHODS

The Johns Hopkins Institutional Review Board reviewed and approved the study (jhmeirb@jhmi.edu; Baltimore, MD, IRB00128524). Written informed consent was obtained from each patient.

Patients

Patients undergoing CPB surgery at Johns Hopkins Hospital (Baltimore, Maryland, USA) were enrolled between January 4, 2017, and August 23, 2019. Patients were included if they were >18 years old and undergoing isolated or combined cardiac artery bypass graft, valve, aortic, or myectomy surgery. Exclusion criteria were lung or heart transplant, insertion of a ventricular assist device, or pre-existing kidney disease. Patients without windows for transcranial Doppler analysis were excluded.

Of the 226 patients enrolled, a subset of these patients (n=59) had Lassen curves and their data was used in the primary analysis to derive thresholds of autoregulation for identification of the LLA. The full cohort of 226 patients was then used to validate these thresholds in relation to AKI.

Signal Acquisition

Cerebral blood flow velocity (CBFV) was monitored through bilateral TCD of the middle cerebral arteries, MCA (Doppler Box, DWL; Singen, Germany) using 2.5-MHz probes. Two near-infrared spectroscopy (NIRS) probes (Covidien, Boulder, CO) were placed on the patient's forehead to monitor rTHb and rSO₂. The data were recorded continuously in the operating room. MAP was monitored invasively through the radial or femoral artery. All signals were sampled at 128 Hz and recorded synchronously using ICM+ software (University of Cambridge, Cambridge Enterprise, Cambridge, UK, <https://icmplus.neurosurg.cam.ac.uk>) through an A/D converter (DT9801, Data Translation, Marlboro, MA) or digitally, directly from GE Solar monitors. Artifacts introduced by tracheal suctioning, arterial line flushing, or transducer malfunction were removed manually.

Perioperative Care

Perioperative care was provided according to usual clinical practice. General anesthesia was induced and maintained with fentanyl (5-20 µg kg⁻¹), propofol (0.5-2.0 mg kg⁻¹), muscle relaxant, and isoflurane. Dexmedetomidine and/or ketamine infusions were used at the discretion of the attending anesthesiologist. CPB was carried out with a nonocclusive roller pump, a membrane oxygenator, and an arterial line filter of 40 µm or less. Nonpulsatile flow was maintained between 2.0 and 2.4 L/min·m², with α-stat pH management. Partial pressure of carbon dioxide was maintained between 35 and 45 mmHg. Rewarming was based on institutional standards, with a goal pharyngeal temperature <37°C. MAP targets in the intensive care unit were generally 65-90 mm Hg, and inotropes were weaned based on estimates of adequate perfusion. Sedation after surgery was maintained with dexmedetomidine or propofol until patients were ready for extubation.

Defining the LLA With the Gold Standard “Lassen Curve”

We defined the Lassen curve as a TCD CBFV (y-axis) –MAP(x-axis) graph with an apparent autoregulatory plateau, LLA, and pressure-passivity below LLA, as shown in Fig. 1A (4). The left turning point of the plateau indicates the LLA_Lassen (27), which was used as the

gold standard by which to distinguish intact and impaired CA. To generate the Lassen curves, we grouped 1-min-average MAPs of the whole recording into separate bins that ranged from 40 mmHg to 100 mmHg at 2 mmHg interval. The average TCD CBFV was calculated in each MAP bin, and then a curve fitting method (polyfit, 5-order) was applied to show the data trend. The MAP that demarcated the first ascending line and the plateau regression line was defined as the LLA_Lassen (Fig 1A). Four researchers (XYL, CHB, BB, and KA) who were blinded to patient outcome defined LLA_Lassen for each patient based on the following principles in a consensus conference: (1) The curve should have at least two parts, an initial ascending part followed by a flat or descending part; (2) The ascending line must have at least two data points and the flat line at least 4 data points. An upper limit of autoregulation was not required to define a patient's LLA. For small discrepancies, the four LLAs were averaged. If more than two authors thought there was no Lassen curve or the discrepancy between the researchers was judged to be sufficiently large, then the LLA was not included. All the Lassen curves used in this article were described into Supplementary 3.

Defining the LLA Using Three Different Indices of Autoregulation

Three different indices of autoregulation were calculated: Mx, HVx, and COx. Mx was calculated as a moving Pearson correlation coefficient between 10-second averages of MAP and TCD CBFV, using a 300-second data window (13, 21). Similarly, COx was calculated as a moving Pearson correlation coefficient between 10-second averages of MAP and NIRS rSO₂ (18), and HVx was calculated as the correlation between 10-second averages of MAP and NIRS rTHb. Functional autoregulation is indicated by negative or near-zero Mx, COx, or HVx values because MAP and CBF are negatively or not correlated. Impaired CA is indicated by high Mx, COx, or HVx (CBF and MAP are correlated) (19).

To define the LLA using CA correlation-based parameters, we plotted Mx (or COx or HVx) against MAP in 5-mm Hg bins and applied a “U-shape” curve fitting algorithm (17). We used different cutoffs to identify LLAs at different CA thresholds (ranging from 0.1 to 0.9 at

intervals of 0.05) by drawing a straight horizontal line at the cutoff value using ICM+ software(17) as shown in Fig. 1B. The x coordinate of the point at which the straight line meets the U-shaped curve was defined as the LLA (10, 28) (Fig 1B) or treated as missing in the absence of an intersection.

Area Under the Curve of MAP Below LLA

To quantify the relationship between LLA and patient outcome, we expressed the extent of MAP < LLA during the cardiac surgery procedure in terms of magnitude (mm Hg) and duration (hours) by calculating the area of MAP below the LLA area under the curve (AUC):

$\sum_{i=0}^N (Magnitude_i \times \Delta Time)$ [mmHg*min/h], where $\Delta Time$ is the time, and $Magnitude_i$ is the individual sample values for the magnitude of MAP deviation below the LLA (29, 30). (We refer to this product of magnitude-time dose of MAP < LLA as the extent of MAP below LLA).

Acute Kidney Injury

AKI was defined by comparing the maximal change in serum creatinine (SCr) in the first 2 postoperative days with baseline values measured before surgery using the AKIN criteria (increase in the ratio of SCr > 1.5 or acute rise in SCr > 0.3 mg/dL within 48 hours (31)).

Statistical Analysis

Statistical analyses were calculated with Matlab software (ver. R2019B, MathWorks, Inc., Natick, MA, USA) and SPSS (version 25.0, IBM, Armonk, NY, USA). Patient and perioperative characteristics were compared by Fisher's exact tests, Student t-tests, and Mann-Whitney tests. To analyze the relationship between LLA_Lassen and LLA defined by CA parameters, we calculated Bland Altman plots and root mean square (RMS) of the difference

between the two types of LLA. The RMS was calculated as $\sqrt{\frac{1}{N} \sum (LLA_Lassen - LLA_Mx)^2}$.

The mean difference in Bland-Altman indicates the "center" of the difference (the actual values are to be found on either side of the mean) and is only sensitive to location, while the

RMS is the square root of the arithmetic mean of the squares of the difference, and it is sensitive to both location and scale.

To validate the cutoffs obtained for the three CA parameters (Mx, HVx, and COx), we categorized the patients into groups with/without AKI after the surgery. The mean extent of MAP < LLA at different cutoffs was calculated for each patient with an LLA; otherwise, the extent was treated as missing. Then the mean extent of MAP < LLA of patients with and without AKI was compared by the non-parametric Mann-Whitney test. Unadjusted logistic regression and multivariable logistic regression adjusted by age, operation duration, and logistic EuroSCORE, diabetes, congestive heart failure, current smoker, aspirin use and hypertension history and pre-operative pulse pressure (potentially confounding variables based on prior literature (11)) were used to examine the association of mean extent of ABP < LLA with AKI. For all analyses, $p < 0.05$ was considered to be statistically significant.

RESULTS

Patient Characteristics

Characteristics of the 226 patients included in the study are listed in Table 1. A patient flow diagram is shown in Supplementary Figure 1. An LLA was identified in 59 patients who had an adequate reference Lassen curve (i.e., TCD-derived CBFV vs. MAP), as depicted in Figure 1A (All the Lassen curves can be found in Supplementary 3). The other 168 patients did not show clear Lassen curves, likely because of poor signal recordings, a limited scale of MAP changes not sufficient to create Lassen curves, or intraoperative physiologic changes.

Identification of Precise Thresholds for CA indexes Using a Reference Curve

Of the 59 patients with a reference LLA, an adequate curve based on a graph of the autoregulation index vs. MAP (see Fig. 1B for an example) was identified in 47 patients using Mx, in 46 patients using COx, and in 45 patients using HVx. For each of these patients, a “comparison” LLA was calculated at 17 different thresholds from 0.1 to 0.9.

Table 2 shows the agreement as measured by RMS deviation (RMSD) between the reference LLA (derived from the Lassen curve) and the comparison LLAs at each threshold. The lowest RMSDs were at the following thresholds: Mx = 0.45 (RMSD 8.77); COx = 0.35 (RMSD 5.81), HVx = 0.3 (RMSD 6.01). Figure 2 shows the Bland Altman plots at each of these thresholds for Mx, COx, and HVx.

Clinical Relevance of Optimal Thresholds for Each Index of Autoregulation

To validate the thresholds calculated in the prior section, we examined the clinical relevance with respect to the development of post-cardiac surgery AKI in the full cohort of 226 patients. Patient characteristics by AKI status are listed in Supplementary Table 1. For each index (Mx, COx, HVx) and for each threshold (0.1–0.9), we calculated an LLA and examined the extent of MAP < LLA during the cardiac surgery procedure. Supplementary Table 2 shows the extent of MAP below the LLA (as identified by each of the 17 thresholds) for patients with and without AKI. The largest differences in extent of MAP below the LLA and the most robust unadjusted and adjusted odds ratios for AKI were seen using the thresholds identified in the previous section: Mx threshold of 0.45; COx threshold of 0.35, and HVx threshold of 0.3. The extent of MAP below the LLA at each of these thresholds is illustrated in Figure 3, which shows significant differences by AKI status.

DISCUSSION

In this study, we identified optimal thresholds for distinguishing intact and impaired CA for three CA indices (Mx, COx, and HVx) in patients undergoing cardiac surgery. Classic Lassen curves were created by plotting CBFV vs. MAP to calculate a reference gold standard LLA for each patient. The results showed that different thresholds should be applied for different indices. We validated the clinical relevance of these thresholds by comparing the magnitude-duration dose of MAP below LLA using different thresholds in patients with and without AKI. The results reveal the strength of the association between the extent of MAP < LLA and the

incidence of AKI. This association was highest when the LLA was defined using the thresholds identified by comparison with Lassen curves. At these thresholds, patients with AKI experienced higher magnitude-duration dose with $MAP < LLA$ than did patients without AKI.

Clinical Significance of Renovascular autoregulation and Cerebral Autoregulation

Renovascular autoregulation and CA are two vital, protective mechanisms that maintain blood flow to support metabolism of kidney and brain (32). Rhee et al. reported that renovascular autoregulation was impaired before cerebrovascular autoregulation during hemorrhagic shock in a piglet model(32). A possible reason is that when MAP is decreased, cerebral blood flow is preserved by cerebral vascular constriction at the expense of splanchnic and renal perfusion, as the brain has priority to other organs. In the current study, we demonstrated that the larger the extent of $MAP < LLA$, the higher possibility of AKI after cardiac surgery. This may be due to the fact that once MAP is below the brain LLA, the kidney may already be in a state of hypoperfusion.

Defining the LLA Using CBFV-MAP Lassen Curves and CA-MAP Curves

In routine clinical care, most patients do not experience large changes in MAP, making it difficult to create a Lassen curve to define an individual LLA. There are several other reasons that Lassen curves may not be identifiable, including impaired or robust autoregulation, noise in TCD data, physiologic changes, and a highly effective baroreflex function(33). Indeed, in the first part of this study, we were able to identify LLA in only 59 patients by Lassen curve. Additionally, Lassen curves can be created only retrospectively; thus, they are not useful in real-time clinical management. We chose to study patients undergoing cardiac surgery because they often do experience large swings in MAP. Moreover, indices of autoregulation are updated in real time, providing potentially actionable information (17).

A key finding of this study is that optimal selection of a threshold to identify the LLA is important. For example, by using an Mx threshold of 0.45, we were able to show a significant difference in the extent of $MAP < LLA$ between patients with and without AKI ($p = 0.03$);

however, when the threshold was set at 0.5 or 0.7, the extent of MAP below LLA did not differ by AKI status. Moreover, different thresholds were identified for different indices of CA, and they are similar to those derived from piglet models, lending validity to our findings (34). Therefore, our results provide index-specific thresholds to identify the LLA that are clinically relevant with regard to AKI.

The invasive and non-invasive methods for CA assessment

The calculations of COx and HVx are based on the assumption that changes in rSO₂ in short time are a surrogate for changes in CBF in the frontal cortex. Thus, these methods are limited by spatial resolution and assumptions that other factors that influence rSO₂, such as hemoglobin concentration or cerebral metabolic rate, are constant in short time window. Although there are limitations to the use of NIRS in calculating the index of autoregulation, several studies in piglets using reference measurements of both PRx and laser Doppler measurement of cerebral blood flux support the hypothesis that COx can be used to identify the LLA (14, 20, 35). There also appears to be clinical relevance of the LLA derived from COx values, based on our prior studies in cardiac surgery patients(10–12). Moreover, due to its advantage of non-invasiveness, NIRS might have wider application in clinical world, especially in cardiac surgery.

Strengths and Limitations

Strengths of this study include the large patient cohort that underwent multimodal monitoring and LLA identification using a gold standard reference. However, several important limitations must be considered. A reference LLA could be identified in only 27% of patients. Although characteristics of patients with and without a reference LLA were similar, it is not certain that the thresholds we identified can be applied to all patients. However, the clinical relevance of the thresholds in the full cohort does support their generalizability. Additionally, we used only AKI outcome to validate the thresholds for the three indices; other outcomes should be considered in future studies.

Although previous studies showed close relationship between changes in CBF and changes in CBFV(36, 37), the correlation may vary with intracranial pathology(38). For CA assessment, TCD based CBFV can only be used as a surrogate of CBF under the assumption that the diameter of large vessels (e.g. MCA) do not change, and this relationship may vary based upon numerous variables (including cerebral vascular resistance, high PaCO₂ or hypoxia etc). However, in our cohort of patients, the CO₂ level was kept relatively stable and we had minimal hypoxia. Moreover, the combined characteristics of non-invasiveness and excellent temporal resolution make TCD an ideal tool to study the temporal course of CA in clinical practice(39). Although the correlation methods in this manuscript measure dynamic CA, they also give insight into static CA parameters and have been widely used in other cohort of patients for CA assessment.

Moreover, the LLA in this manuscript is determined using both NIRS based COx and TCD based Mx. The CBFV measured by TCD was measured in MCA while NIRS rSO₂ was obtained from the frontal cortex, which receives blood supply from the anterior cerebral artery (ACA) and the MCA(40, 41). In this case, we assume that the changes of CBF in MCA would be similar to that in ACA in response to ABP changes and the supplying anterior cerebral artery would likely react in a similar manner to MCA. However, given the anatomical differences and the patient age, intracranial atherosclerotic disease may play a role in CA and should be taken into consideration in the future.

Conclusion

In this study, we identified the thresholds at which three indices of autoregulation distinguished intact and impaired CA. These thresholds are clinically relevant and suggest that MAP below the LLA is a risk factor for AKI after cardiac surgery.

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Figure Legends

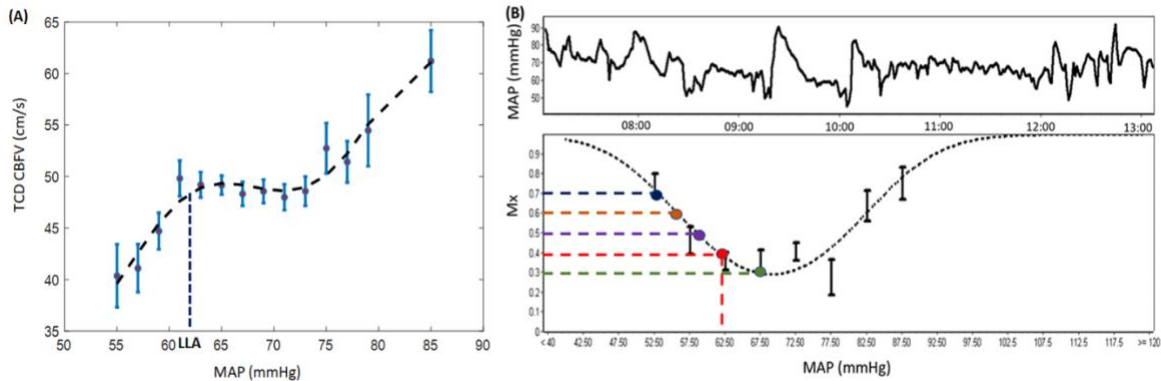


Figure 1. (A) Example cerebral autoregulation Lassen curve created by plotting transcranial Doppler (TCD) cerebral blood flow velocity (CBFV) vs. mean arterial blood pressure (MAP). The point in the regression line at which the first ascending line met the plateau was identified as the lower limit of autoregulation (LLA). This patient's LLA was 61 mmHg. (B) LLA defined using mean flow index (Mx) at different Mx thresholds of the same patient. A U-shaped curve was created by plotting Mx against MAP, and a straight horizontal line at the cutoff value was drawn to locate the x coordinate of the cross point where the straight line met the curve. In this example, an Mx threshold of 0.45 would identify an LLA of 61 mmHg.

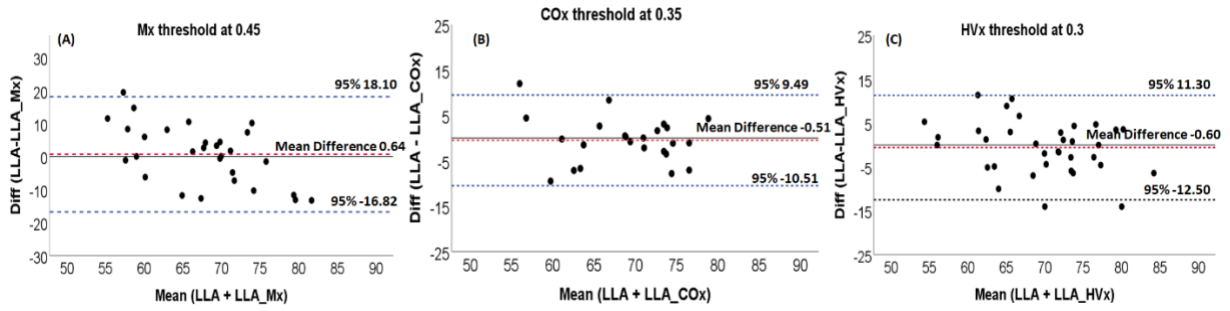


Figure 2. Bland-Altman plot between the lower limit of autoregulation (LLA) defined by the Lassen curve and by the mean flow index (Mx) at a threshold of 0.45 (A), by the cerebral oximetry index (Cox) at a threshold of 0.35 (B), and by the hemoglobin volume index (HVx) at a threshold of 0.3 (C).

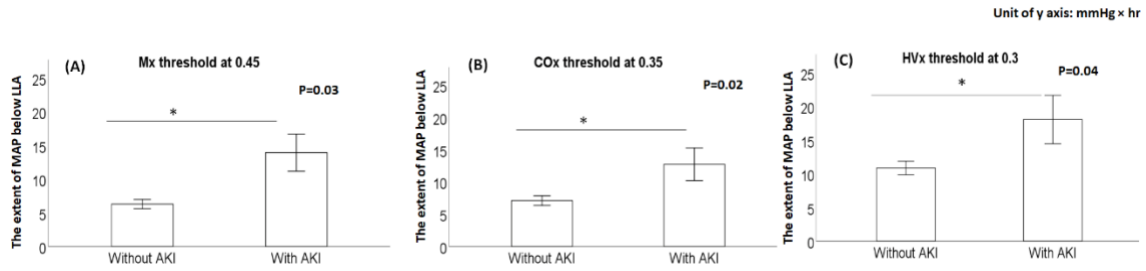


Figure 3. The extent of mean arterial blood pressure (MAP) below the lower limit of autoregulation (LLA; defined by Mx, Cox, and HVx) in patients with and without acute kidney injury (AKI) using Mann-Whitney tests. The bar is expressed as mean ± SEM; n=176 for (A), n=200 for (B) and n=192 for (C). More details can be found in Supplementary Table 2. * $p < 0.05$. Mx = mean flow index; COx = cerebral oximetry index; HVx = hemoglobin volume index.

Table 1. Patient Demographics

Characteristic	Patients with Lassen Curve (n=59)	Patients Without Lassen Curve (n=167)	<i>p</i> Value
Age, yr, mean ± SD	65.31 ± 9.40	63.63 ± 10.92	0.30
Male sex, n (%)	51 (86.4)	124 (74.3)	0.07
Height, cm, mean ± SD	173.37 ± 9.36	173.20 ± 10.29	0.91
Weight, kg, mean ± SD	85.55 ± 16.95	87.97 ± 23.22	0.46
Race, n (%)			0.40
Caucasian	48 (81.4)	137 (82.0)	
African American	7 (11.9)	20 (12.0)	
Asian	2 (3.4)	1 (0.6)	
Other	2 (3.4)	9 (5.4)	
Baseline creatinine, mg/dL, mean ± SD	1.20 ± 0.47	1.15 ± 0.49	0.50
Previous stroke, n (%)	1 (1.7)	6 (3.6)	0.68
Diabetes, n(%)	28 (47.5)	60 (35.9)	0.26
Congestive heart failure, (%)	18 (30.5)	56 (33.4)	0.75
Current Smoker, n(%)	6 (10.2)	28 (16.8)	0.28
Aspirin user, n(%)	50 (84.7)	120 (71.9)	0.12
Hypertension history, n(%)	51 (86.4)	132 (79.0)	0.33
Pre-operative pulse pressure, mmHg, mean ± SD	70.90 ± 11.55	71.85 ± 13.64	0.22
MAP, mmHg, mean ± SD	74.63 ± 6.32	74.95 ± 6.64	0.75
Mean CBFV, cm/s, mean ± SD	47.56 ± 13.56	45.38 ± 17.04	0.39
CPB duration, min, mean ± SD	102.59± 41.40	113.41 ± 43.95	0.18

Mx, mean \pm SD	0.58 \pm 0.11	0.55 \pm 0.12	0.07
HVx, mean \pm SD	0.25 \pm 0.11	0.26 \pm 0.12	0.73
COx, mean \pm SD	0.33 \pm 0.14	0.28 \pm 0.15	0.03

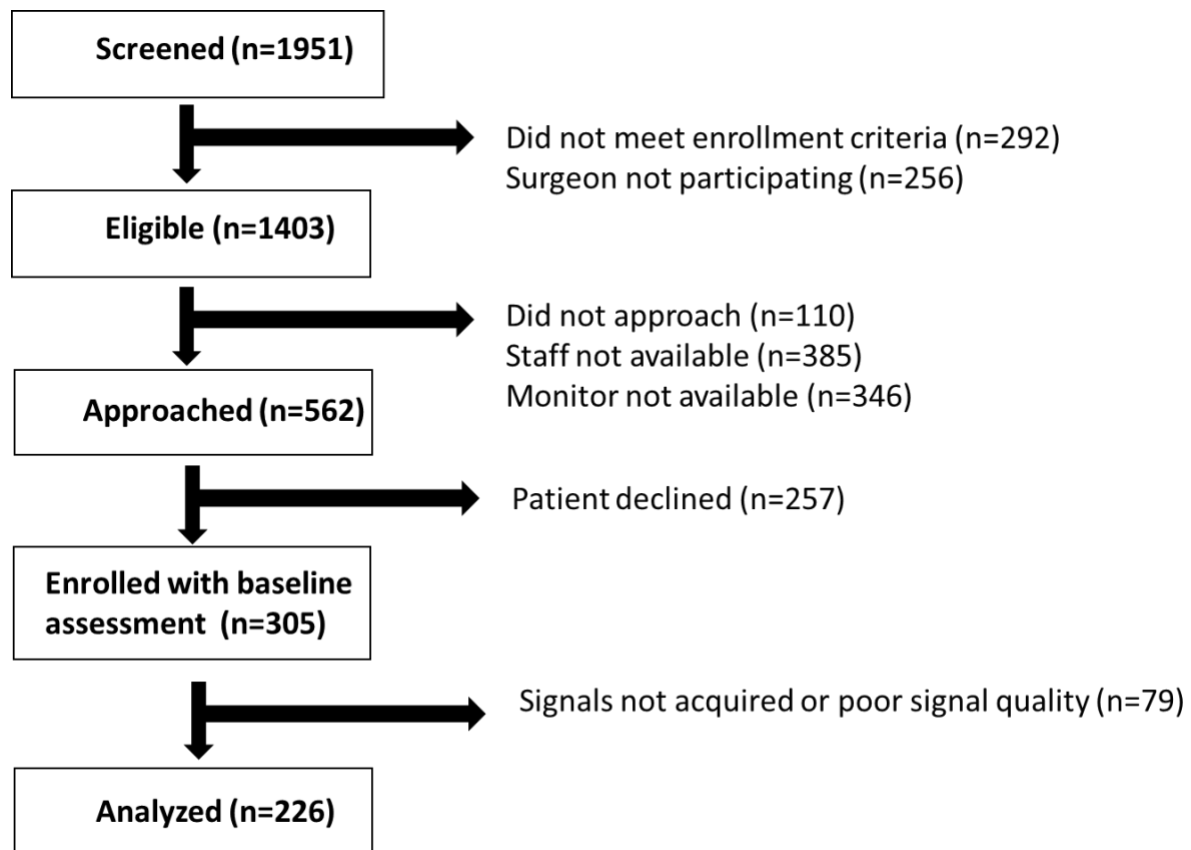
CBFV = cerebral blood flow velocity; COx = cerebral oximetry index; CPB = cardiopulmonary bypass; HVx = hemoglobin volume index; LLA = lower limit of autoregulation; MAP = mean arterial blood pressure; Mx = mean flow index.

Table 2. Root-mean squared and mean value of difference between lower limit of autoregulation defined by Lassen curves and different cerebral autoregulation thresholds.

CA threshold	Mx (n=47)		COx (n=46)		HVx (n=45)	
	RMS of difference	Mean \pm SD of difference	RMS of difference	Mean \pm SD of difference	RMS of difference	Mean \pm SD of difference
0.1	12.91	-7.20 \pm 11.30	11.56	-9.25 \pm 9.52	9.97	-7.06 \pm 7.22
0.15	13.73	-6.38 \pm 12.76	8.63	-6.60 \pm 6.18	8.02	-4.68 \pm 6.65
0.2	13.81	-6.16 \pm 12.82	7.17	-4.70 \pm 5.42	6.84	-2.87 \pm 6.33
0.25	12.05	-2.72 \pm 12.15	8.28	-2.66 \pm 5.43	7.05	-2.51 \pm 6.69
0.3	12.88	-2.49 \pm 13.00	6.46	-1.93 \pm 6.31	6.01	-0.60 \pm 6.07
0.35	10.33	-2.28 \pm 10.31	5.81	-0.51 \pm 5.10	6.30	0.34 \pm 6.38
0.4	9.06	-1.15 \pm 9.18	8.50	-1.45 \pm 8.04	6.28	2.21 \pm 5.95
0.45	8.77	0.64 \pm 8.91	8.37	-0.72 \pm 7.95	7.15	3.97 \pm 6.02
0.5	9.29	1.06 \pm 9.36	8.16	1.49 \pm 7.50	8.36	5.22 \pm 6.61
0.55	8.83	1.99 \pm 8.72	9.02	3.42 \pm 7.79	9.72	6.51 \pm 7.30
0.6	9.47	3.73 \pm 8.81	10.01	5.10 \pm 7.96	11.43	8.26 \pm 7.99
0.65	9.85	4.74 \pm 8.74	11.41	7.51 \pm 8.69	13.37	10.02 \pm 8.95
0.7	11.89	5.86 \pm 10.47	11.01	8.41 \pm 7.18	11.67	9.60 \pm 6.73
0.75	12.24	7.42 \pm 9.86	11.89	9.90 \pm 6.67	12.03	10.17 \pm 6.52
0.8	12.53	8.48 \pm 9.34	13.32	11.59 \pm 6.64	13.43	11.58 \pm 6.91
0.85	15.74	11.72 \pm 10.66	14.87	13.19 \pm 6.96	15.15	13.25 \pm 7.45
0.9	15.38	12.22 \pm 9.48	16.49	15.02 \pm 6.90	17.31	15.54 \pm 7.75

CA = cerebral autoregulation; COx = cerebral oximetry index; HVx = hemoglobin volume index;

Mx = mean flow index; RMS = root mean square (unit: mmHg).



Supplementary Fig 1. Patient flow chart.

Supplementary Table 1. Demographics of Patients With and Without Acute Kidney Injury

Characteristic	Patients With AKI (n=56)	Patients Without AKI (n=170)	<i>p</i> Value
Age, yr, mean \pm SD	64.75 \pm 10.48	63.85 \pm 10.59	0.58
Male sex, n (%)	46 (82.1)	129 (75.9)	0.46
Height, cm, mean \pm SD	173.43 \pm 10.53	173.18 \pm 9.90	0.88
Weight, kg, mean \pm SD	94.82 \pm 25.59	84.86 \pm 19.78	0.009
Race, n (%)			
Caucasian	43 (76.8)	142 (83.5)	0.46
African American	10 (17.9)	17 (10.0)	
Asian	1 (1.8)	2 (1.2)	
Other	2 (3.6)	9 (5.3)	
Baseline creatinine, mg/dL, mean \pm SD	1.31 \pm 0.66	1.11 \pm 0.40	0.042
Previous stroke, n (%)	3 (5.4)	4 (2.4)	0.37
MAP, mmHg, mean \pm SD	74.68 \pm 7.84	74.92 \pm 6.08	0.81
Mean CBFV, cm/s, mean \pm SD	48.83 \pm 19.61	45.23 \pm 14.72	0.19
CPB duration, min, mean \pm SD	119.09 \pm 46.45	107.72 \pm 42.20	0.09
Mx, mean \pm SD	0.57 \pm 0.12	0.56 \pm 0.12	0.56
HVx, mean \pm SD	0.26 \pm 0.11	0.26 \pm 0.12	0.85
COx, mean \pm S D	0.31 \pm 0.15	0.28 \pm 0.15	0.27

AKI = acute kidney injury; CBFV = cerebral blood flow velocity; COx = cerebral oximetry index; CPB = cardiopulmonary bypass; HVx = hemoglobin volume index; LLA = lower limit of autoregulation; MAP = mean arterial blood pressure; Mx = mean flow index.

Supplementary Table 2. Comparison of the extent of MAP below the LLA (mmHg × hr) in patients with and without AKI at different thresholds for three indices of autoregulation (Mx, COx, HVx)

CA Threshold	Mx (n=176)							Cox (n=200)					HVx (n=192)												
	Without AKI	With AKI	MW test	Unadjusted		Adjusted ^a			Without AKI	With AKI	MW test	Unadjusted		Adjusted ^a			Without AKI	With AKI	MW test	Unadjusted		Adjusted ^a			
				p	OR	p	OR	p				p	OR	p	OR	p				p	OR	p	p	OR	p
0.1	19.20 ±18.22	20.46 ±18.67	0.95	1.002	0.84	1.073	0.289	19.01 ±22.34	16.80 ±14.46	0.94	0.994	0.77	0.975	0.477	27.46 ±25.23	37.82 ±34.96	0.43	1.013	0.25	1.012	0.520				
0.15	17.99 ±20.35	21.89 ±25.51	0.62	1.008	0.58	1.028	0.487	14.51 ±16.17	11.97 ±10.73	0.82	0.987	0.63	0.961	0.304	20.07 ±19.60	26.82 ±26.10	0.26	1.014	0.26	1.008	0.675				
0.2	14.47 ±14.95	22.07 ±26.41	0.39	1.020	0.17	1.064	0.048	11.83 ±13.19	11.09 ±8.87	0.80	0.995	0.83	0.995	0.873	17.25 ±17.47	24.94 ±25.30	0.17	1.018	0.12	1.020	0.283				
0.25	11.21 ±13.01	18.61 ±22.46	0.19	1.025	0.10	1.035	0.152	11.42 ±12.97	18.25 ±20.61	0.24	1.027	0.09	1.012	0.608	13.88 ±13.99	21.89 ±21.28	0.05	1.028	0.03	1.019	0.313				
0.3	9.53 ±10.29	18.88 ±24.65	0.23	1.035	0.04	1.065	0.014	8.84 ±9.57	14.80 ±14.76	0.12	1.044	0.03	1.036	0.199	10.88 ±10.85	18.09 ±19.70	0.04	1.035	0.01	1.020	0.408				
0.35	10.42 ±13.79	21.61 ±29.69	0.22	1.026	0.03	1.054	0.040	7.11 ±7.48	12.74 ±12.94	0.02	1.061	0.01	1.063	0.046	8.54 ±8.29	11.96 ±12.34	0.12	1.035	0.07	1.020	0.516				
0.4	8.63 ±9.45	16.32 ±21.08	0.16	1.038	0.02	1.058	0.045	6.72 ±8.90	9.06 ±9.60	0.13	1.024	0.29	1.014	0.559	6.64 ±6.43	9.00 ±9.42	0.14	1.041	0.09	1.030	0.446				
0.45	6.30 ±6.32	13.95 ±15.62	0.03	1.071	0.002	1.100	0.007	5.62 ±7.30	8.12 ±8.22	0.06	1.040	0.10	1.034	0.244	5.67 ±6.55	6.86 ±7.39	0.27	1.024	0.34	1.027	0.534				
0.5	5.07 ±5.31	9.61 ±10.84	0.02	1.079	0.01	1.145	0.007	5.29 ±7.25	5.60 ±5.14	0.22	1.007	0.81	1.014	0.725	4.99 ±6.27	4.98 ±5.81	0.69	1.000	0.99	1.026	0.649				
0.55	6.01 ±12.21	7.58 ±8.68	0.06	1.011	0.47	1.064	0.124	4.46 ±6.43	5.92 ±6.18	0.05	1.012	0.54	0.992	0.780	4.41 ±6.06	4.35 ±6.06	0.68	0.998	0.95	0.984	0.712				
0.6	5.38 ±8.71	5.29 ±6.48	0.43	0.998	0.95	1.009	0.795	3.43 ±4.64	4.04 ±3.88	0.10	1.007	0.81	0.987	0.735	3.94 ±5.05	3.11 ±3.68	0.48	0.959	0.32	0.971	0.656				
0.65	4.65 ±6.45	4.02 ±5.11	0.92	0.981	0.57	0.992	0.881	2.85 ±4.37	2.86 ±2.93	0.39	0.987	0.75	0.958	0.367	3.26 ±3.95	2.32 ±2.82	0.09	0.919	0.16	0.952	0.572				
0.7	4.04 ±6.75	2.84 ±3.97	0.32	0.953	0.29	0.967	0.666	2.29 ±3.21	2.16 ±2.33	0.90	0.969	0.60	0.935	0.330	2.66 ±3.16	1.92 ±2.34	0.09	0.903	0.20	1.005	0.966				
0.75	3.05 ±5.20	2.03 ±2.96	0.14	0.924	0.24	0.912	0.413	1.78 ±2.43	1.75 ±2.03	0.77	0.970	0.69	0.920	0.342	2.10 ±2.55	1.54 ±2.01	0.12	0.891	0.24	1.045	0.723				
0.8	2.29 ±3.78	1.60 ±2.14	0.33	0.913	0.31	0.980	0.898	1.42 ±1.91	1.28 ±1.69	0.45	0.936	0.52	0.906	0.411	1.72 ±2.09	1.21 ±1.77	0.12	0.854	0.22	1.061	0.692				
0.85	1.45 ±2.50	0.90 ±1.31	0.12	0.834	0.27	0.920	0.766	1.08 ±1.53	1.02 ±1.41	0.54	0.941	0.65	0.906	0.558	1.31 ±1.74	1.06 ±1.57	0.09	0.900	0.49	1.063	0.715				
0.9	1.04 ±1.22	0.73 ±0.86	0.19	0.737	0.22	1.105	0.774	0.85 ±1.28	1.19 ±1.95	0.56	1.108	0.46	1.100	0.604	1.00 ±1.46	1.06 ±1.43	0.84	1.025	0.88	1.162	0.444				

AKI = acute kidney injury; CA = cerebral autoregulation; COx = cerebral oximetry index; HVx = hemoglobin volume index; MAP = mean arterial blood pressure; Mx = mean flow index; OR, odds ratio; MW test: Mann-Whitney tests.

^aAdjusted for age, operation duration, and logistic EuroSCORE, diabetes, congestive heart failure, current smoker, aspirin use and hypertension history and pulse pressure.

