ORIGINAL CLINICAL RESEARCH REPORT

OPEN

Real-Time Intraoperative Determination and Reporting of Cerebral Autoregulation State Using Near-Infrared Spectroscopy

Dean Montgomery, PhD,* Charles Brown, MD,† Charles W. Hogue, MD,‡ Ken Brady, MD,‡§ Mitsunori Nakano, MD,† Yohei Nomura, MD,‖ Andre Antunes, PhD,* and Paul S. Addison, PhD*

BACKGROUND: Cerebral blood flow (CBF) is maintained over a range of blood pressures through cerebral autoregulation (CA). Blood pressure outside the range of CA, or impaired autoregulation, is associated with adverse patient outcomes. Regional oxygen saturation (rSo_2) derived from near-infrared spectroscopy (NIRS) can be used as a surrogate CBF for determining CA, but existing methods require a long period of time to calculate CA metrics. We have developed a novel method to determine CA using cotrending of mean arterial pressure (MAP) with rSo_2 that aims to provide an indication of CA state within 1 minute. We sought to determine the performance of the cotrending method by comparing its CA metrics to data derived from transcranial Doppler (TCD) methods.
METHODS: Retrospective data collected from 69 patients undergoing cardiac surgery with cardiopulmonary bypass were used to develop a reference lower limit of CA. TCD-MAP data were plotted to determine the reference lower limit of CA. The investigated method to evaluate CA state is based on the assessment of the instantaneous cotrending relationship between MAP and rSo_2 signals. The lower limit of autoregulation (LLA) from the cotrending method was compared to the manual reference derived from TCD. Reliability of the cotrending method was assessed as uptime (defined as the percentage of time that the state of autoregulation could be measured) and time to first post.
RESULTS: The proposed method demonstrated minimal mean bias (0.22 mmHg) when compared to the TCD reference. The corresponding limits of agreement were found to be 10.79 mmHg (95% confidence interval [CI], 10.09–11.49) and −10.35 mmHg (95% CI, −9.65 to −11.05). Mean uptime was 99.40% (95% CI, 99.34–99.46) and the mean time to first post was 63 seconds (95% CI, 58–71).
CONCLUSIONS: The reported cotrending method rapidly provides metrics associated with CA state for patients undergoing cardiac surgery. A major strength of the proposed method is its near real-time feedback on patient CA state, thus allowing for prompt corrective action to be taken by the clinician. (Anesth Analg 2020;131:1520–8)

KEY POINTS

- **Question:** Can the lower limit of autoregulation (LLA) be assessed in real time?
- **Findings:** A near-infrared spectroscopy (NIRS)–based LLA can be calculated to provide near real-time feedback to the clinician regarding the current state of a patient's cerebral autoregulation.
- **Meaning:** A real-time approach for the assessment of the LLA is feasible for the cardiovascular operating room (CVOR), but further work remains to explore its clinical utility.

GLOSSARY

ABP = arterial blood pressure; **CA** = cerebral autoregulation; **CBF** = cerebral blood flow; **CI** = confidence interval; **COPD** = chronic obstructive pulmonary disease; **COx** = correlation index; **CPB** = cardiopulmonary bypass; **CVOR** = cardiovascular operating room; **IQR** = interquartile range; **LLA** = lower limit of autoregulation; **LOA** = limit of agreement; **MAP** = mean arterial pressure; **Mx** = mean flow index; **NIRS** = near-infrared spectroscopy; **$Paco_2$** = partial pressure of carbon dioxide; **RMSD** =

From the *Medtronic Respiratory & Monitoring Solutions, Edinburgh, United Kingdom; †Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland; ‡Department of Anesthesiology, Northwestern University Feinberg, School of Medicine, Chicago, Illinois; §Cardiac Anesthesia, Ann & Robert Lurie Children's Hospital, Chicago, Illinois; and ‖Department of Cardiovascular Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan.

DOI: 10.1213/ANE.0000000000004614

Accepted for publication November 26, 2019.

Funding: Funded in part by a grant for the National Institutes of Health (NIH) to C.W.H. (RO1 HL092259) and in part by a grant to C.B. (NIA K76 AG057020).

Conflicts of Interest: See Disclosures at the end of the article.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.anesthesia-analgesia.org).

D. Montgomery's ORCID iD: http://orcid.org/0000-0001-5200-3439. A. Antunes's ORCID iD: https://orcid.org/0000-0002-9428-8759. P. S. Addison's ORCID iD: https://orcid.org/0000-0002-6925-0935.

Reprints will not be available from the authors.

Address correspondence to Andre Antunes, PhD, Medtronic Respiratory & Monitoring Solutions, Unit A, The Technopole Centre, Edinburgh EH26 0PJ, United Kingdom. Address e-mail to andre.antunes@medtronic.com.

root mean square deviation; **rSo_2** = regional oxygen saturation; **TCD** = transcranial Doppler; **TTFP** = time to first post

Cerebral autoregulation (CA) is the physiological mechanism that regulates cerebral blood flow (CBF) over a range of blood pressures, ensuring that cerebral blood supply meets metabolic demand. The CA operational range is defined by the limits of contractility and extensibility of the vasculature: at low blood pressures, the vessels maximally dilate while at high blood pressures, the vessels maximally constrict. Thus, when blood pressure is outside CA limits, CBF is directly related to blood pressure and the CA state is impaired. CA limits are patient-specific with marked interindividual variability.[1,2] Impaired CA is strongly associated with negative outcomes in a variety of neurological conditions (traumatic brain injury,[3–5] cerebral hemorrhage,[6,7] stroke,[8,9] cardiovascular disease,[10,11] and in premature infants,[12,13] patients undergoing cardiac and noncardiac surgery[14–16]). In patients undergoing cardiac surgery, blood pressure excursions outside the limits of autoregulation are associated with organ injury and brain dysfunction.[14,17–19] Individualized blood pressure management targeted to optimize CA thus might provide a more rational approach to patient care during surgery than standardized blood pressure management.

Continuous direct CBF assessment (eg, positron emission tomography, direct radioisotope measurement) is not clinically viable for continuous CA monitoring. As such, noninvasive surrogate methods for determining CBF have been developed, including those using transcranial Doppler (TCD) and regional oxygen saturation (rSo_2).[20] While TCD is considered the most accurate noninvasive assessment of CBF, its use clinically is limited by patient movement, electrical interference from electrocautery, and other limitations. Other studies have shown that rSo_2 is a clinically feasible method of inferring CBF, overcoming the limitations of TCD.[1,21,22]

A limitation of existing proposed CA monitoring methods is the relatively long time scales (ie, 30 minutes to several hours) to construct meaningful CA plots, and even then, an expert clinician is often needed to interpret the data. We have developed a novel method for the real-time, continuous monitoring of CA using noninvasive near-infrared spectroscopy (NIRS)–based technique. Using data from patients undergoing cardiac surgery with cardiopulmonary bypass (CPB), we hypothesize that a novel technique that compares the relationship between instantaneous rSo_2 and mean arterial pressure (MAP) will be able to determine the lower limit of autoregulation (LLA) when compared to a TCD reference.

METHODS

Data Collection

A data set obtained from 69 patients[a] that underwent cardiac surgery with CPB at The Johns Hopkins Hospital, Baltimore, MD, was used in this retrospective study. We did not prespecify a sample size because this was a pilot study and, therefore, we included all data that were available to us. The protocol was approved by The Johns Hopkins Medical Institute's research review board (jhmeirb@jhmi.edu), and the patients provided written informed consent to participate in the study. This was an observational study, so anesthetic care was not affected by study participation. However, routine clinical care included fentanyl and/or propofol for induction and/or pain control, midazolam for anxiolysis, isoflurane for maintenance, and a nondepolarizing paralytic for muscle relaxation.

Arterial blood pressure (ABP) was monitored with a direct radial catheter and the signal collected at a frequency of 100 Hz (GE Medical, Milwaukee, WI) using a laptop computer running ICM+ software (Cambridge Enterprises, Cambridge, UK). CPB was achieved after anticoagulation with heparin using a nonocclusive roller pump with flows of 2.0–2.4 $L{\cdot}minute^{-1}{\cdot}m^{-2}$ and a membrane oxygenator. CBF velocity of the middle cerebral arteries was monitored bilaterally with TCD (Doppler Box, DWL, Compumedics, Charlotte, NC) using two 2.5 MHz transducers held in place with brackets fitted on a headband as previously described.[10,23] The depth of insonation varied between 35 and 52 mm until representative spectral middle cerebral artery flow was identified. Bilateral rSo_2 was collected from sensors placed on the forehead (INVOS 5100C monitor, Medtronic, Boulder, CO) at a sampling rate of 0.2 Hz. All data analysis was performed retrospectively with tools implemented in MATLAB (MathWorks, Natick, MA).

LLA Determination by Cotrending

We determined the LLA from each patient by evaluating the cotrending behavior of the MAP and rSo_2 signals (Supplemental Digital Content, Figure 1, http://links.lww.com/AA/C992), in contrast with previous CA methods that use the Pearson correlation

[a]Fifty-three patients had missing or poor TCD signal. In addition, a further 29 patients were not used because the TCD reference did not exhibit an LLA. This left 69 cases for use in this study. (Note that it is not possible to determine whether the lack of identifiable LLA was due to signal issues or because the patient genuinely did not transit the LLA during signal acquisition.)

[b]The gradient of the signal is the trend of the signal with respect to time.

coefficient to build a correlation index (COx) plot.[1,11,14,21] The cotrending method uses windows of data with a duration of 50 seconds (in contrast with the 300 seconds used in COx), inside of which the gradients[b] of MAP and rSo_2 signals are computed and then compared. From this comparison of the trending behavior of the 2 signals, an instantaneous assessment of the CA state is made—the CA state can be intact (trending in the same direction), impaired (trending in opposite directions), or not determined (one or more signals too noisy or constant). The latter refers to the instant in time where limited information precludes assigning CA state. If there is a strong agreement in the values of the gradients of both MAP and rSo_2, the state is considered impaired; while if the values of the gradients differ, the CA state is considered intact. That is, the similarity between MAP and rSo_2 gradients is indicative of a pressure-passive CBF state, while dissimilarity indicates functional autoregulation.

To attain a visual representation of the CA state, it is necessary to integrate the instantaneous information over time and across MAP. The COx method achieves this by binning the COx values in 5 mmHg bins and plotting them as a function of MAP (thus collapsing the time dimension). The result is a CA plot that is not straightforward to interpret, takes significant time (up to several hours) to build up, and is very slow to reflect any changes in the CA state. Automated identification of the LLA in the COx plot is very difficult, with the thresholds used varying across studies.[7,11,21] In addition, existing

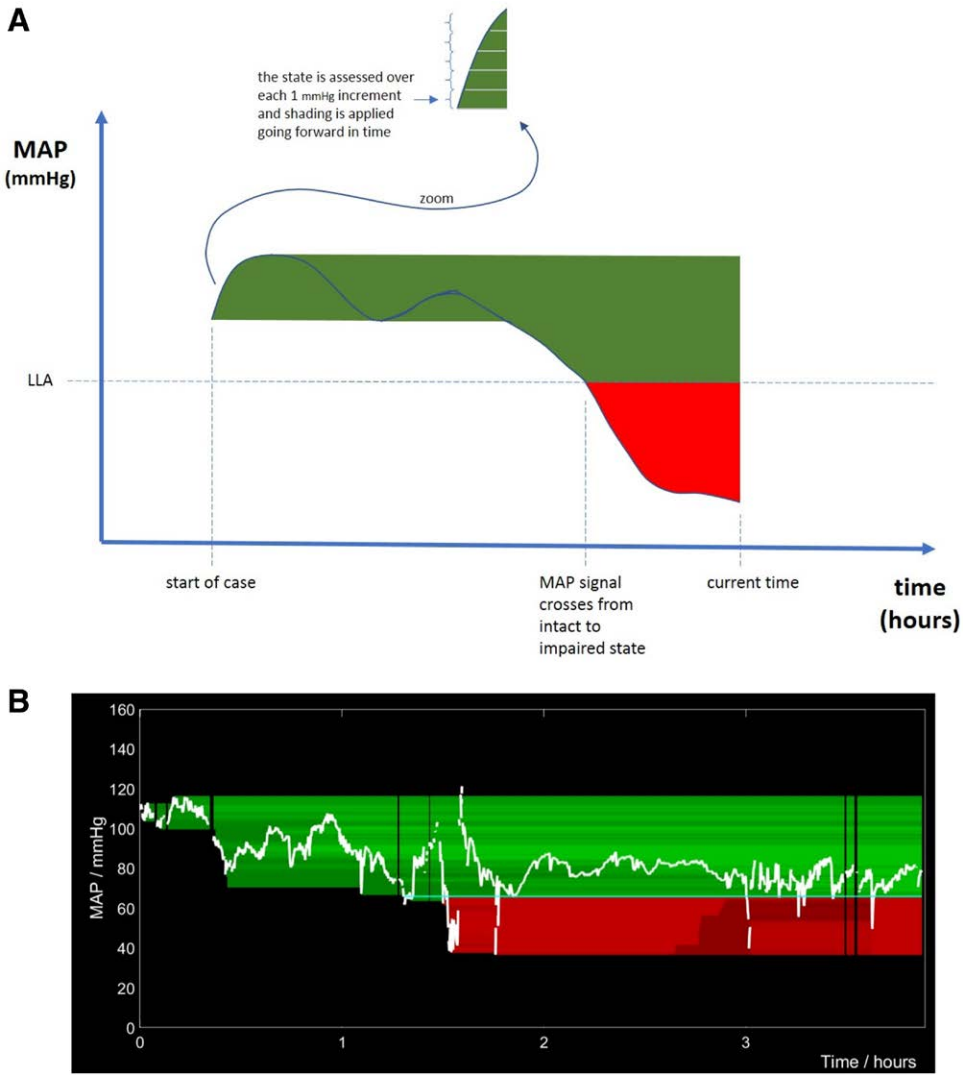

Figure 1. Cotrending algorithm schematic and example. A, Schematic showing the buildup of state indication (intact: green; impaired: red) over time for the MAP signal determined through comparison of the cotrending of MAP with the rSo_2 signal (not shown). The LLA is defined as the transition between the red and green sections. B, Display output showing MAP signal over time with state determination (green: intact; red: impaired) superimposed as MAP values are visited. The state has been determined from the cotrending of MAP and rSo_2 using our method. The cyan line is the reference LLA, determined from the TCD signal. Note that the proposed method does not post a result during periods when the MAP or rSo_2 are missing (indicated as the periods displayed as vertical black bands). LLA indicates lower limit of autoregulation; MAP, mean arterial pressure; rSo_2, regional oxygen saturation; TCD, transcranial Doppler.

studies require a fallback to manual interpretation of the COx plot when the automated thresholds fail to find an LLA. In the cotrending method, CA is displayed as a 2-dimensional color map: MAP on the y-axis and time on the x-axis as is seen in Figure 1A. By shading each distinct region of CA state, it becomes self-evident which MAP values are associated with intact CA or impaired CA. Instead of collapsing the time dimension as for COx, the state at the current time and MAP value are updated in real time in the display matrix.

Obtaining a Manual Reference LLA From TCD

Many studies[3,21,24] have asserted the measurement of autoregulation using a variety of correlation functions without validation against a standard. To obtain a reference, this study used plots of flow velocity against MAP, allowing for direct visualization of the transition between a state of intact and impaired autoregulation.[25] The LLA reference was assessed by generating and then manually inspecting the Lassen curve based on scatter plots of TCD CBF velocity versus MAP for each patient. The corresponding mean flow index (Mx) plot was inspected alongside the Lassen curve. The Mx plot was derived as a Pearson correlation between low-frequency changes in CBF velocity and MAP.[20] A custom tool was developed to display these plots and to allow the user to select time periods and assign an LLA for each selected period. An example of the usage of this tool can be seen in Figure 2. Data from the right and left sides from each individual case were randomly shuffled with all the other cases to minimize LLA evaluation bias, and the plots presented to 2 of the authors (D.M. and A.A.). Each author assigned LLAs to different time segments as they saw fit. These estimations of the LLA were then combined to generate a single reference LLA time series for each case.

Statistical Analysis

The statistical analysis consisted of the calculation of 4 measures of performance of the cotrending method compared with the TCD-determined CA: agreement, accuracy, reliability, and time to first post (TTFP).

Agreement was determined from the LLA time series output calculated by the cotrending method compared with the LLA manually assessed using the TCD reference. Agreement was measured using a Bland-Altman analysis of the data where bias and limits of agreement were reported. To account for multiple measurements within patients, confidence interval (CI) estimation for the limits of agreement was produced using the delta

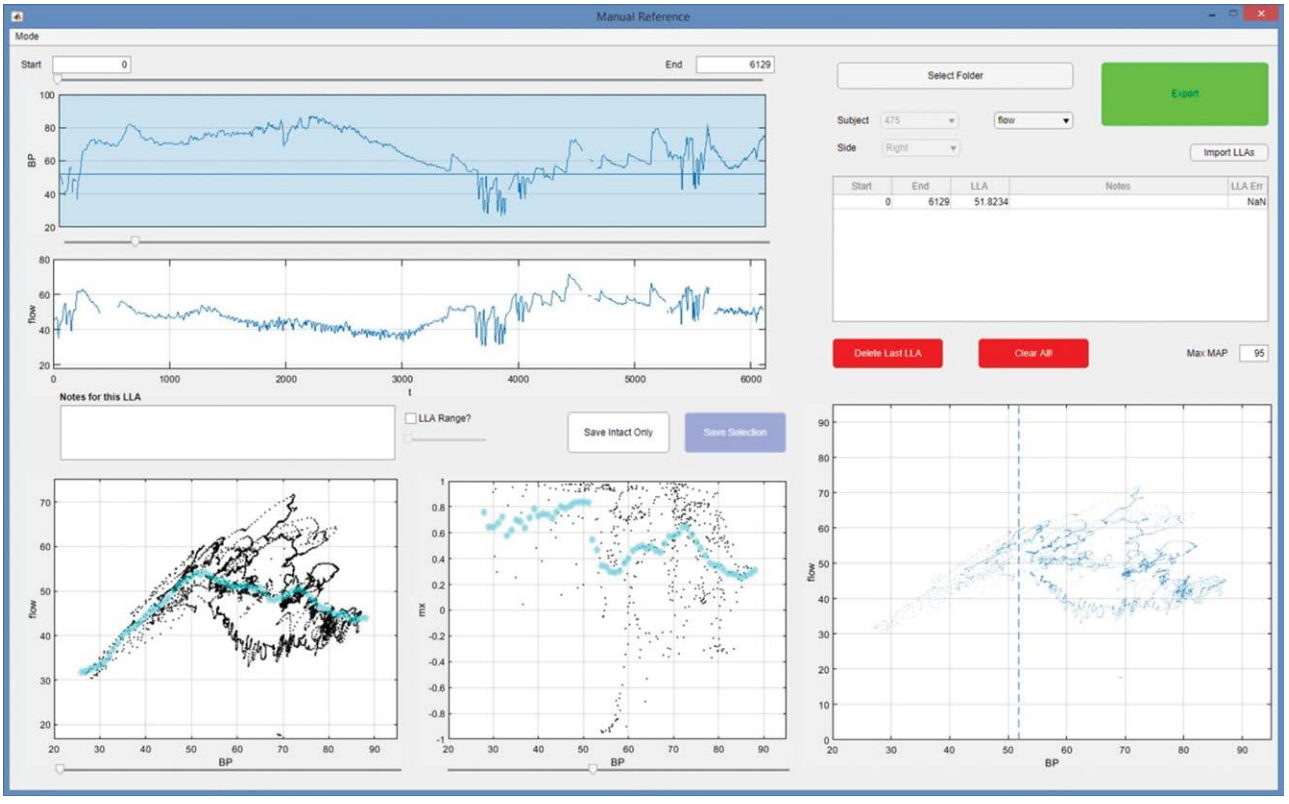

Figure 2. Manual LLA assessment tool. An example usage of the tool used to build the reference LLAs from the TCD signals—a single case has been loaded. Top 2 plots: MAP and TCD flow time series. Bottom left plot: TCD flow-MAP plot; bottom middle plot: Mx-MAP plot (the black dots are the raw points and the blue overlay the corresponding binned values). The user is able to interrogate the signals in different time windows and is able to integrate the information from all 4 plots to help set a reference value. In this example, the user has selected the whole case and assigned a single LLA at 52 mmHg. LLA indicates lower limit of autoregulation; MAP, mean arterial pressure; Mx, mean flow index; TCD, transcranial Doppler.

method described by Zou,[26] considering the case when the true value may vary.

Accuracy was also determined using the same data, defined as the mean per-case root mean square deviation (RMSD) and 95% bootstrapped (10,000 iterations, bias-corrected and accelerated percentile method) CIs. We included the computation of this metric, because it is common for this statistic to be specified within medical device standards,[27–29] where "in practice, the accepted reference (here TCD) is substituted for the true value." This practice is generally adopted by device manufacturers to gain acceptance in regulatory submissions.

Reliability in the form of an uptime was computed. This is a measure of the percentage of time the cotrending method produces a result during each case, and a fundamental technical requirement for the development of a medical device. To be acceptable for use in clinical practice, both accuracy and uptime must be sufficiently high. Note that accuracy may be improved at the expense of uptime by avoiding posting results when the signal quality is poor (eg, due to noise) or if the cotrending method is not confident on the result. The results presented in this study did not follow this practice, that is, the results are based on the full output of the cotrending method and no manual exclusion of poor data segments has been performed.

The TTFP, an output value, was also measured. This is the amount of time it takes before the method posts an indication of state after starting, and is another important parameter when considering use in clinical practice. Both the reliability and TTFP CIs were bootstrapped using the same method as the accuracy.

All statistical analyses were performed in MATLAB (Mathworks, Natick, MA).

RESULTS

A summary of patient characteristics is provided in the Table. The 69 cases were successfully evaluated by the cotrending method and compared with the LLA reference results. Figure 1B contains an example of the output from the cotrending method for one of the patient data sets used in this study. The MAP signal (white) can be seen over the whole procedure which lasted approximately 4 hours. The instantaneous CA state is reported after 52 seconds (indicated by the green band) and at approximately 1.5 hours, the lower limit (at which the signal begins to cotrend) is indicated by the appearance of the red band as the MAP drops. The LLA can now be easily identified as the boundary between the red region and the green region. Figure 3 contains the final display of the cotrending method output for each case for the whole procedure.

Table. Patient Characteristics

Parameter	
N	69
Age (y), mean (range)	66 (25–82)
Male sex, n (%)	57 (82.6)
Diabetes mellitus, n (%)	21 (30.4)
Hypertension, n (%)	53 (76.8)
COPD, n (%)	2 (2.9)
Coronary artery disease, n (%)	53 (76.8)
Congestive heart failure, n (%)	3 (4.3)
Preoperative systolic BP (mmHg), mean (SD)	141.1 (22.5)
CPB duration (min), median (IQR)	97 (75–135)
Cross clamp (min), median (IQR)	63 (50–87)

Abbreviations: COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; IQR, interquartile range.

The distribution of TCD reference LLAs is shown in Figure 4A. The distribution of the 69 LLAs in this study is consistent with those found in a recent study by Hori et al.[17] Half of the study patients exhibited an LLA >60 mmHg, while 95% had an LLA >50 mmHg. For comparison, the distribution of the LLAs from the cotrending method can be seen in Figure 4B.

The Bland-Altman plot of the data is provided in Figure 5A, demonstrating minimal mean bias (0.22 mmHg). The limits of agreement are 10.79 mmHg (95% CI, 10.09–11.49) and −10.35 mmHg (95% CI, −9.65 to −11.05). The associated scatterplot of the data is shown in Figure 5B, which depicts the measured LLA values (ie, the LLA calculated at each second by the cotrending method) plotted against the reference LLA values. The accuracy in terms of the per-patient RMSDs between LLAs assessed with TCD and the NIRS-based cotrending method has a mean equal to 4.52 mmHg (95% CI, 3.94–5.17). The mean uptime was 99.40% (95% CI, 99.34–99.46) and the mean TTFP was 63 seconds (95% CI, 58–71). Distributions of these metrics can be found in Supplemental Digital Content, Figure 2, http://links.lww.com/AA/C992.

The cotrending method was successful in generating an LLA for all patients in the cohort. Interestingly, the method determined a change in the location of the LLA on average 7.0 times per case, with the mean of the standard deviations around the per-case mean LLA being 3.4 mmHg.

DISCUSSION

The LLA determined with the new MAP and NIRS cotrending method exhibited limits of agreement around 10 mmHg from a near-zero mean bias compared with the TCD CA reference for determining the LLA. The corresponding mean RMSD was found to be within 5 mmHg. Furthermore, the CA state was rapidly available (TTFP = 63 seconds) and the algorithm posted a value for 99.4% of the data it encountered. This approach for CA monitoring is a substantial improvement compared to previous methods, because TCD monitoring is difficult and time-consuming and previous rSo_2-based approaches require a long period

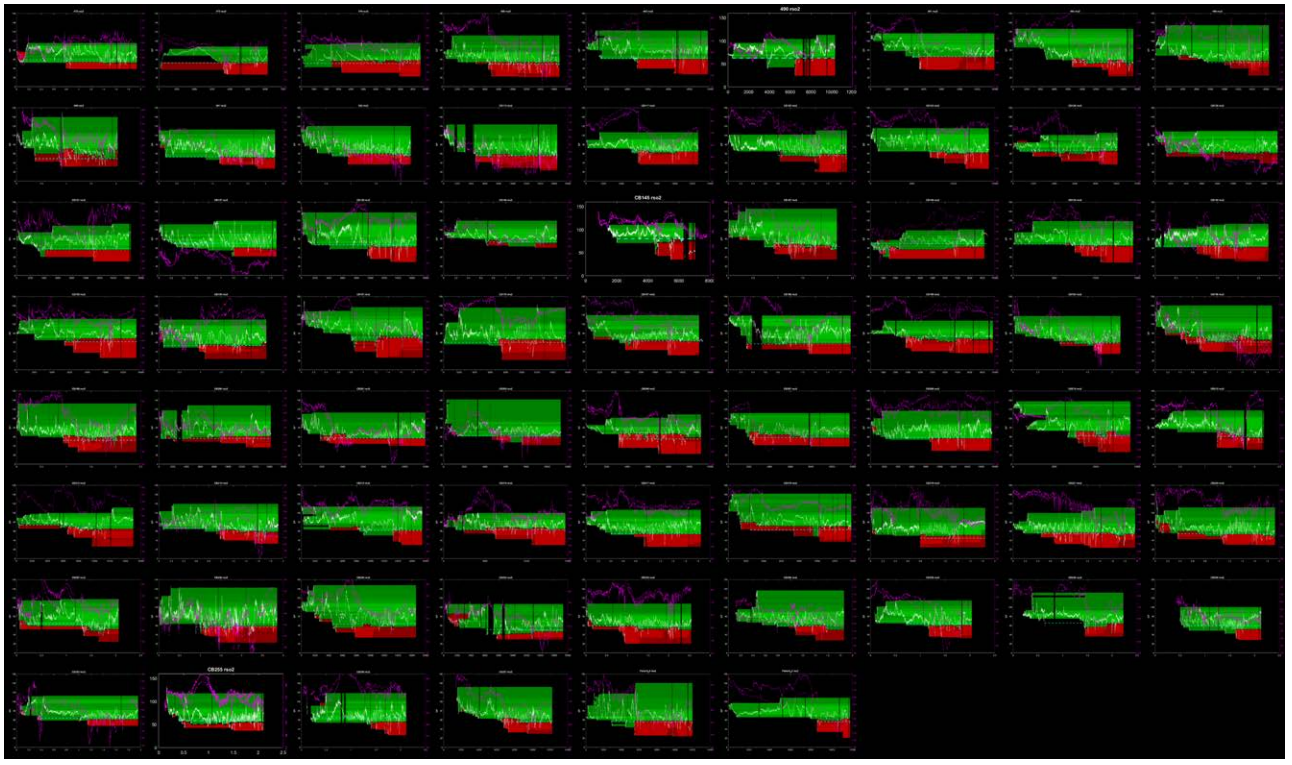

Figure 3. NIRS-based cotrending method output for all 69 cases showing the MAP signal (in white). The intact and impaired states are depicted in green and red, respectively. The rSo_2 signals are also included in magenta. The cyan line is the combined manual LLA assessment; the black dashed line is the LLA produced by the cotrending method. LLA indicates lower limit of autoregulation; MAP, mean arterial pressure; NIRS, near-infrared spectroscopy; rSo_2, regional oxygen saturation.

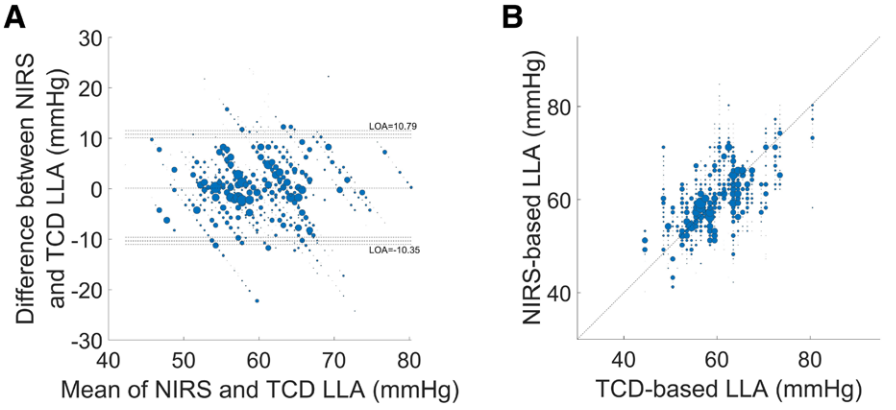

Figure 4. Cotrending algorithm performance versus TCD reference. A, Histogram of the LLA references taken from TCD signal for the 69 patients in this study. Many guidelines indicate a blood pressure management of 50 or 60 mmHg, but approximately 50% of patients have an LLA higher than 60 mmHg and 95% have an LLA >50 mmHg. B, Histogram of the LLAs calculated with our method. The distribution strongly resembles the reference LLA distribution. LLA indicates lower limit of autoregulation; NIRS, near-infrared spectroscopy; TCD, transcranial Doppler.

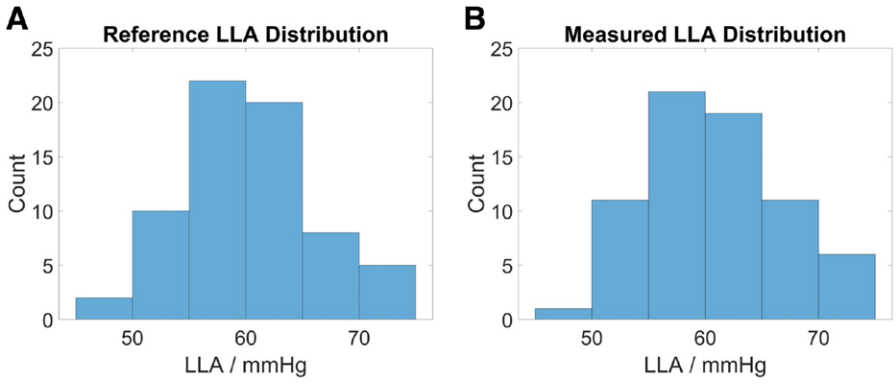

Figure 5. Distributions of LLAs–cotrending algorithm and TCD reference. A, Bland-Altman plot of the data displaying mean bias = 0.22 mmHg, an upper LOA = 10.79 mmHg (95% CI, 10.09–11.49) and a lower LOA = −10.35 mmHg (95% CI, −9.65 to −11.05). B, Scatter plot of individual LLAs over time over all cases (bubble sizes proportional to number of colocated data points). The dashed line in the middle represents the unity line, which indicates a perfect agreement between the method and the reference. CI indicates confidence interval; LLA, lower limit of autoregulation; LOA, limit of agreement.

of data capture (30 minutes to several hours) to generate clinically meaningful information.

There is strong evidence in associative studies for the link between adverse patient outcomes and the time spent in an impaired state and depth reached below the LLA.[14,17,18] In particular, managing patients during CPB using traditional practices that are arbitrary (eg, 50–60 mmHg) will result in some patients having their MAP below their LLA. This situation is associated with risk for acute kidney injury, the composite end point of major morbidity and mortality, stroke, and postoperative delirium. In a recent nested analysis of a prospectively randomized clinical trial, basing patient MAP targets on LLA information was shown to reduce the frequency of carefully assessed postoperative delirium compared with usual care.[30] Thus, a monitoring technology based on the proposed rSo_2 method would enable the clinician to rapidly respond intraoperatively to MAP below the LLA, possibly reducing adverse outcomes.

The cotrending method that we present is based on a direct interpretation of signal gradients to determine the degree of cotrending of contemporaneous rSo_2 and MAP signals. That is, above the LLA, no cotrending behavior is expected since rSo_2, as a surrogate of CBF, would remain independent despite fluctuations in systemic ABP. In contrast, when below the LLA, MAP would cotrend with rSo_2 because the autoregulatory mechanisms can no longer ensure constant CBF. The new method provides an indication of the state of autoregulation within a 1-minute timeframe, thus providing a near real-time feedback to the clinician on the status of the patient. Importantly, autoregulation state was reported with a high degree of reliability, demonstrated by the reporting uptime of 99.4%. This is a crucial performance parameter and, for less reliable methods, is often sacrificed to retain a high accuracy. In fact, we would advocate that accuracy and reliability should always be provided when reporting such data in the literature.

The fast, dynamic start-up time is an important, if often overlooked, property of a monitoring technology because the clinician wants to be informed of patient status as soon as possible. This is in stark contrast to the CA methods based on Pearson correlation between slow waves of MAP and CBF surrogates where it takes 5 minutes to obtain a single data point and a further 10 seconds to acquire each subsequent data point, which is then binned, taking several hours to accumulate enough data to delineate the LLA. Several engineering characteristics that allow fast start-up time (smaller window, disentanglement of time, and blood pressure) also allow characterization of changes in LLA intraoperatively. To be acceptable for use in clinical practice, a range of performance metrics must be met, including accuracy and uptime. Further study is needed to define exact targets for clinical acceptability. This is an emerging field with much yet to learn about the clinical use of CA technologies. Interestingly, the presented method identified a change in the LLA an average of 7 times per case. Further study is needed to understand the significance of this observation and the factors that may affect CA during surgery.

Because the CA state is determined by comparing rSo_2 and MAP trends, it is essential for any CA technology to have reliable and noise-free rSo_2 and MAP signals. We found the rSo_2 signal collected from the NIRS device to be adequate for our purposes. Indeed, the rSo_2 is usually much more reliable and easier to use than the TCD reference signal—the TCD signal acquisition requires constant vigilance and expert training to collect a reliable, continuous signal, whereas rSo_2 is collected simply by applying 2 sensors to the patient's forehead.

A major strength of the proposed method is in its continuous real-time feedback on patient CA status, thus allowing for prompt corrective action to be taken by the clinician. Clinically important information is presented in a simple red/green color scheme to allow easy identification of autoregulation state by a clinician in real time. In practice, the autoregulation management task is reduced to keeping the patient's MAP in the green zone.

Many have reported on the difficulties in obtaining good-quality TCD data.[31–34] We did remove much of the noisy TCD data to ensure as good a "gold standard" reference as possible, but it is possible that some noisy data may still have gotten through to the analysis; in which case, an error in the reference signal would propagate into the performance metric calculations, hence increasing their values. Another possible source of error stems from how well rSo_2 behaves as a proxy for flow. There may be circumstances in which rSo_2 does not behave in the same manner as flow in the brain (eg, during changes in arterial oxygen saturation). We suspect that these changes may be caused by partial pressure of carbon dioxide ($Paco_2$), depth of volatile anesthesia, interaction with other drugs, or the patient going on bypass; however, this is speculative, and considerably more research needs to be conducted to address this topic.

In summary, we have demonstrated a cotrending methodology that has promise for reliably differentiating impaired and intact patient CA. Because NIRS monitoring provides a simple, continuous output, these methods may allow for widespread patient-tailored blood pressure management and potentially improved patient outcomes by individualizing ABP during surgery to remain within the intact CA range.

DISCLOSURES

Name: Dean Montgomery, PhD.
Contribution: This author helped in the analysis of data including data preprocessing, method implementation and statistical analysis, preparation of the manuscript, and manuscript revisions.
Conflicts of Interest: D. Montgomery is an employee of Medtronic, a global healthcare company.
Name: Charles Brown, MD.
Contribution: This author helped in the study design, data acquisition, analysis and interpretation of data, preparation of the manuscript, and manuscript revisions.
Conflicts of Interest: C. Brown has provided data to Medtronic and has consulted for this study.
Name: Charles W. Hogue, MD.
Contribution: This author helped in the study design, data acquisition, analysis and interpretation of data, preparation of the manuscript, and manuscript revisions.
Conflicts of Interest: C. W. Hogue is a consultant to Medtronic and has provided data to Medtronic for this study.
Name: Ken Brady, MD.
Contribution: This author helped in the study design, data acquisition, analysis and interpretation of data, preparation of the manuscript, and manuscript revisions.
Conflicts of Interest: K. Brady is a consultant to Medtronic.
Name: Mitsunori Nakano, MD.
Contribution: This author helped in the data acquisition, critical revision of the manuscript, final approval of the manuscript.
Conflicts of Interest: None.
Name: Yohei Nomura, MD.
Contribution: This author helped in the data acquisition, critical revision of the manuscript, and final approval of the manuscript.
Conflicts of Interest: None.
Name: Andre Antunes, PhD.
Contribution: This author helped in the analysis of data including data preprocessing, method implementation and statistical analysis, preparation of the manuscript, and manuscript revisions.
Conflicts of Interest: A. Antunes is an employee of Medtronic, a global healthcare company.
Name: Paul S. Addison, PhD.
Contribution: This author helped in the analysis of data including data preprocessing, method implementation and statistical analysis, preparation of the manuscript, and manuscript revisions.
Conflicts of Interest: P. S. Addison is an employee of Medtronic, a global healthcare company.
This manuscript was handled by: Maxime Cannesson, MD, PhD.

REFERENCES

1. Brady K, Joshi B, Zweifel C, et al. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke*. 2010;41:1951–1956.
2. Joshi B, Ono M, Brown C, et al. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg*. 2012;114:503–510.
3. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke*. 1996;27:1829–1834.
4. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med*. 2002;30:733–738.
5. Aries MJ, Czosnyka M, Budohoski KP, et al. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. *Crit Care Med*. 2012;40:2456–2463.
6. Jaeger M, Schuhmann MU, Soehle M, Nagel C, Meixensberger J. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke*. 2007;38:981–986.
7. Budohoski KP, Czosnyka M, de Riva N, et al. The relationship between cerebral blood flow autoregulation and cerebrovascular pressure reactivity after traumatic brain injury. *Neurosurgery*. 2012;71:652–660.
8. Dohmen C, Bosche B, Graf R, et al. Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. *Stroke*. 2007;38:56–61.
9. Reinhard M, Rutsch S, Lambeck J. et al. Dynamic cerebral autoregulation associates with infarct size and outcome after ischemic stroke. *Acta Neurol Scand*. 2012;125:156–162.
10. Joshi B, Brady K, Lee J, et al. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. *Anesth Analg*. 2010;110:321–328.
11. Ono M, Joshi B, Brady K, et al. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. *Br J Anaesth*. 2012;109:391–398.
12. Tsuji M, Saul JP, du Plessis A, et al. Cerebral intravascular oxygenation correlates with mean arterial pressure in critically ill premature infants. *Pediatrics*. 2000;106:625–632.
13. Soul JS, Hammer PE, Tsuji M, et al. Fluctuating pressure-passivity is common in the cerebral circulation of sick premature infants. *Pediatr Res*. 2007;61:467–473.
14. Ono M, Arnaoutakis GJ, Fine DM, et al. Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit Care Med*. 2013;41:464–471.
15. Ono M, Brady K, Easley RB, et al. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. *J Thorac Cardiovasc Surg*. 2014;147:483–489.
16. Rappold T, Laflam A, Hori D, et al. Evidence of an association between brain cellular injury and cognitive decline after non-cardiac surgery. *Br J Anaesth*. 2016;116:83–89.
17. Hori D, Nomura Y, Ono M, et al. Optimal blood pressure during cardiopulmonary bypass defined by cerebral autoregulation monitoring. *J Thorac Cardiovasc Surg*. 2017;154:1590–1598.e2.
18. Hori D, Max L, Laflam A, et al. Blood pressure deviations from optimal mean arterial pressure during cardiac surgery measured with a novel monitor of cerebral blood flow and risk for perioperative delirium: a pilot study. *J Cardiothorac Vasc Anesth*. 2016;30:606–612.
19. Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. *Cerebrovasc Brain Metab Rev*. 1990;2:161–192.
20. Czosnyka M, Brady K, Reinhard M, Smielewski P, Steiner LA. Monitoring of cerebrovascular autoregulation: facts, myths, and missing links. *Neurocrit Care*. 2009;10:373–386.
21. Brady KM, Lee JK, Kibler KK, et al. Continuous time-domain analysis of cerebrovascular autoregulation using near-infrared spectroscopy. *Stroke*. 2007;38:2818–2825.
22. Zweifel C, Castellani G, Czosnyka M, et al. Continuous assessment of cerebral autoregulation with near-infrared spectroscopy in adults after subarachnoid hemorrhage. *Stroke*. 2010;41:1963–1968.

23. Brady KM, Lee JK, Kibler KK, Easley RB, Koehler RC, Shaffner DH. Continuous measurement of autoregulation by spontaneous fluctuations in cerebral perfusion pressure: comparison of 3 methods. *Stroke*. 2008;39:2531–2537.
24. Zweifel C, Dias C, Smielewski P, Czosnyka M. Continuous time-domain monitoring of cerebral autoregulation in neurocritical care. *Med Eng Phys*. 2014;36:638–645.
25. Lee JK, Kibler KK, Benni PB, et al. Cerebrovascular reactivity measured by near-infrared spectroscopy. *Stroke*. 2009;40:1820–1826.
26. Zou GY. Confidence interval estimation for the Bland-Altman limits of agreement with multiple observations per individual. *Stat Methods Med Res*. 2013;22:630–642.
27. ISO 80601-2-61:2017. Medical electrical equipment – Part 2-61: Particular requirements for basic safety and essential performance of pulse oximeter equipment. 2017.
28. ISO 3534-2:2006. Statistics - Vocabulary and symbols – Part 2: Applied statistics. 2006.
29. Bergese SD, Mestek ML, Kelley SD, et al. Multicenter study validating accuracy of a continuous respiratory rate measurement derived from pulse oximetry: a comparison with capnography. *Anesth Analg*. 2017;124:1153–1159.
30. Brown CH, Neufeld KJ, Tian J, et al. Effect of targeting mean arterial pressure during cardiopulmonary bypass by monitoring cerebral autoregulation on postsurgical delirium among older patients: a nested randomized clinical trial. *JAMA Surg*. 2019;154:819–26.
31. Willie CK, Colino FL, Bailey DM, et al. Utility of transcranial Doppler ultrasound for the integrative assessment of cerebrovascular function. *J Neurosci Methods*. 2011;196:221–237.
32. Tarumi T, Dunsky DI, Khan MA, et al. Dynamic cerebral autoregulation and tissue oxygenation in amnestic mild cognitive impairment. *J Alzheimers Dis*. 2014;41:765–778.
33. Panerai RB. Transcranial Doppler for evaluation of cerebral autoregulation. *Clin Auton Res*. 2009;19:197–211.
34. White H, Venkatesh B. Applications of transcranial Doppler in the ICU: a review. *Intensive Care Med*. 2006;32:981–994.