

Cerebral Autoregulation Monitoring with Ultrasound-Tagged Near-Infrared Spectroscopy in Cardiac Surgery Patients

Daijiro Hori, MD,* Charles W. Hogue, Jr., MD,† Ashish Shah, MD,* Charles Brown, MD,† Karin J. Neufeld, MD,‡ John V. Conte, MD,* Joel Price, MD, MPH,* Christopher Sciortino, MD, PhD,* Laura Max, BA,† Andrew Laflam, BSc,† Hideo Adachi, MD, PhD,§ Duke E. Cameron, MD,* and Kaushik Mandal, MD, MPH, FRCS (CTh)*

BACKGROUND: Individualizing mean arterial blood pressure (MAP) based on cerebral blood flow (CBF) autoregulation monitoring during cardiopulmonary bypass (CPB) holds promise as a strategy to optimize organ perfusion. The purpose of this study was to evaluate the accuracy of cerebral autoregulation monitoring using microcirculatory flow measured with innovative ultrasound-tagged near-infrared spectroscopy (UT-NIRS) noninvasive technology compared with transcranial Doppler (TCD).

METHODS: Sixty-four patients undergoing CPB were monitored with TCD and UT-NIRS (CerOx™). The mean velocity index (Mx) was calculated as a moving, linear correlation coefficient between slow waves of TCD-measured CBF velocity and MAP. The cerebral flow velocity index (CFVx) was calculated as a similar coefficient between slow waves of cerebral flow index measured using UT-NIRS and MAP. When MAP is outside the autoregulation range, Mx is progressively more positive. Optimal blood pressure was defined as the MAP with the lowest Mx and CFVx. The right- and left-sided optimal MAP values were averaged to define the individual optimal MAP and were the variables used for analysis.

RESULTS: The Mx for the left side was 0.31 ± 0.17 and for the right side was 0.32 ± 0.17 . The mean CFVx for the left side was 0.33 ± 0.19 and for the right side was 0.35 ± 0.19 . Time-averaged Mx and CFVx during CPB had a statistically significant “among-subject” correlation ($r = 0.39$; 95% confidence interval [CI], 0.22–0.53; $P < 0.001$) but had only a modest agreement within subjects (bias 0.03 ± 0.20 ; 95% prediction interval for the difference between Mx and CFVx, -0.37 to 0.42). The MAP with the lowest Mx and CFVx (“optimal blood pressure”) was correlated ($r = 0.71$; 95% CI, 0.56–0.81; $P < 0.0001$) and was in modest within-subject agreement (bias -2.85 ± 8.54 ; 95% limits of agreement for MAP predicted by Mx and CFVx, -19.60 to 13.89). Coherence between ipsilateral middle CBF velocity and cerebral flow index values averaged 0.61 ± 0.07 (95% CI, 0.59–0.63).

CONCLUSIONS: There was a statistically significant correlation and agreement between CBF autoregulation monitored by CerOx compared with TCD-based Mx. (Anesth Analg 2015;XXX:00–00)

Maintaining mean arterial blood pressure (MAP) between 50 and 60 mmHg is an accepted practice during cardiopulmonary bypass (CPB). This practice is believed to be adequate for maintaining brain perfusion because cerebral blood flow (CBF) autoregulation is functional, provided that pH management is performed with the α -stat method.¹ However, recent findings by our group challenge this view. We have found that there is a wide interindividual variability in the MAP at the lower

limit of CBF autoregulation during CPB ranging from 40 to 90 mmHg.^{2,3} Moreover, we have found that the duration and magnitude that MAP is below or above the limits of autoregulation are associated with the risk of major morbidity and operative mortality as well as delirium.^{4–6} These findings suggest that MAP management based on physiologic end points derived from CBF autoregulation monitoring would more likely ensure cerebral and other organ perfusion during CPB than the current standard of care.

CBF autoregulation can be measured by the continuous calculation of the linear regression correlation coefficient between low-frequency changes in MAP and transcranial Doppler (TCD)-measured CBF velocity.^{7–11} The use of TCD has limitations, including difficulty in finding a transcranial window and avoiding artifacts from operative procedures, that prevent its widespread routine clinical use. An ultrasound-tagged near-infrared spectroscopy (UT-NIRS) is a methodology that has been described recently for the noninvasive measurement of microcirculatory blood flow using sensors attached to the forehead.^{12,13} This approach is based on the acousto-optic effect, whereby focused, low-power ultrasound is used to modulate light in the near-infrared spectrum in tissue.^{12–14} The ultrasound-tagged photons that travel through the region of interest in the tissue undergo

From the *Division of Cardiac Surgery, Department of Surgery, †Department of Anesthesiology and Critical Care Medicine, and ‡Department of Psychiatry & Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland; and §Division of Cardiovascular Surgery, Saitama Medical Center, Jichi Medical University, Saitama, Japan.

Accepted for publication June 3, 2015.

Funding: Funded, in part, by grant from Ornim, Inc., Kfar Saba, Israel (Kaushik Mandal, Karin Neufeld) and Japan Heart Association/Bayer Yakuhin Grant for Abroad (Daijiro Hori). Dr Hogue is the principal investigator on a grant from the National Institutes of Health (RO1 095529).

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

Address correspondence to Kaushik Mandal, MD, MPH, MS, FESC, FRCS (CTh), Division of Cardiac Surgery, The Johns Hopkins Hospital, Sheikh Zayed Tower, Suite 7107, 1800 Orleans St., Baltimore, MD 21287. Address e-mail to kmandal2@jhmi.edu.

Copyright © 2015 International Anesthesia Research Society
DOI: 10.1213/ANE.0000000000000930

a Doppler effect that is filtered and measured at the skin surface. The noninvasive measurement of microcirculatory CBF with this method could overcome many of the limitations of TCD, providing a clinically feasible method for monitoring CBF autoregulation. The purpose of this proof-of-concept study was to compare the accuracy of CerOx™ (Ornim, Inc., Kfar Saba, Israel)-measured CBF with a validated TCD-based method for monitoring autoregulation in adult patients undergoing CPB.

METHODS

From July 2013 to October 2014, 69 patients undergoing cardiac surgery with CPB were enrolled in a prospective observational study (clinical trial registration no. NCT02084394). The study was approved by the IRB of The Johns Hopkins Medical Institutions, and all patients were required to sign an informed consent before participation.

Patient Care

Standard perioperative care provided to all patients included monitoring of direct radial artery blood pressure and anesthesia with midazolam, fentanyl, and isoflurane. Nonpulsatile CPB was performed with flow between 2.0 and 2.4 L/min/m² and α -stat pH management. Arterial blood gases were measured 10 minutes after initiation of CPB and then hourly. Normocarbia was maintained by adjusting CPB gas flow based on in-line blood gas monitoring.

Monitoring of CBF Autoregulation

TCD (Doppler Box, DWL; Compumedics, Charlotte, NC) was used for measuring CBF velocity of the middle cerebral arteries using two 2.5-MHz transducers fitted on a headband. The depth of insonation was varied between 35 and 52 mm to obtain stable representative spectral artery flow. UT-NIRS monitoring was performed using a CerOx monitor using methodology described previously.^{12–14} Adhesive pads were attached on the right and left sides of the forehead, leaving 20 to 25 mm of space from both supraorbital ridges. Probes were then attached to the adhesive pads after application of ultrasound gel. Sensor stability was ensured by tightening a circumferential elastic band placed around the head. Briefly, the CerOx monitor introduces laser light into tissue in 3 wavelengths in the near-infrared spectrum. Reflected light is measured via sensors placed 12-mm distance from the light source. Low-power ultrasound waves are emitted from the same probes on the forehead. The ultrasound waves cause localized modulation of the detected light intensity emanating for deep tissue of 1 cm³ in volume. The UT-NIRS signals result from the correlation of the detected light intensity with the ultrasound signals. The ultrasound signal is a series of phase-modulated waves at a midfrequency of 1 MHz, less than the 2 to 2.5 MHz used for TCD. The flowmeter measures the effect of Doppler shifts in the signal resulting from the movement of blood cells in a manner similar to laser Doppler flowmetry.¹⁴

Analog arterial pressure data from the operating room hemodynamic monitor, TCD, and CerOx signals were sampled with an analog-to-digital converter at 60 Hz and then processed with ICM+ software version 6.1 (University of Cambridge, Cambridge, UK) as described previously.^{15,16}

Arterial blood pressure, Doppler, and NIRS signals were filtered to limit analysis to the frequency of slow vasogenic waves (0.05–0.003 Hz), which are relevant to autoregulation. The signals were time-integrated as nonoverlapping 10-second mean values, which is equivalent to applying a moving average filter with a 10-second time window and resampling at 0.1 Hz. The latter was performed to eliminate high-frequency noise from the respiratory and pulse frequencies while allowing the detection of oscillations and transients that occur <0.05 Hz.^{15,16} The signals were further high-pass filtered with a DC cutoff set at 0.003 Hz to remove slow drifts associated with hemodilution at the onset of bypass, blood transfusions, cooling, and rewarming. A continuous, moving Pearson correlation coefficient was calculated between the MAP and the TCD blood flow velocities and between MAP and CerOx data generating the variables mean velocity index (Mx) and cerebral flow velocity index (CFVx), respectively. Consecutive, paired, 10-second averaged values from 300-second duration were used for each calculation, incorporating 30 data points for each index.^{15,16} When CBF autoregulation is functional, Mx approaches zero or is negative (CBF and MAP are not correlated), whereas MAP outside the autoregulation limits is indicated by an Mx value approaching +1 (CBF and MAP correlated).

Sample Size

The sample size of this study is based, in part, on our previous analysis, where autoregulation monitored with NIRS-based cerebral oximetry index (COx) was shown to be comparable with that measured with TCD-based Mx.¹⁵ In that study of 60 patients undergoing cardiac surgery, COx and Mx were correlated and had agreement. The sample size calculations are further based on a projected agreement among the subjects between optimal MAP measured by CFVx and Mx during CPB. We used data from previous studies involving 489 patients, where COx and Mx were monitored during CPB, as well as data from 109 patients, where hemoglobin volume index was compared with Mx.¹⁷ Using those data, we estimate that the standard deviation of the differences in optimal blood pressure determined by CFVx and Mx would be between 10 and 13 mmHg. We conservatively base our sample size determinations on the larger value of 13. Based on the projected standard error of the bias and limits of agreement, we calculated that a sample size of 60 would give us a 95% confidence interval (CI) for bias between –2.1 and 4.7. The same sample size will provide a 95% CI for the limits of agreement between –24.7 and –13.3 for the lower limit and between 16.3 and 27.7 for the upper CI.¹⁸ Indeed, the clinical significance of these value differences in optimal MAP measurement is not yet clear. However, the calculated interval of the limit of agreement of 11.4 mmHg is within 14.4 mmHg described by Bland and Altman,¹⁸ which was considered “reasonably narrow” for the differences in blood pressure when comparing 2 methods of measurement.

Data Analysis

CerOx-TCD Coherence Analysis

Both TCD and continuous microcirculatory flow waveforms (sampled at 60 Hz) during CPB were analyzed for coherence by the Welsh method; TCD was used as the input

and microcirculatory blood flow cerebral as the output. Uninterrupted waveforms of TCD with a standard physiologic appearance were analyzed within a spectral range from 0.4 to 4 beats per minute by using a moving 12-minute window composed of 3 segments that had 20% overlap. Because each patient has a different fundamental frequency of slow-wave activity, the maximum coherence (after interpolation with zero padding) within the spectral band of slow waves was averaged across the moving time window to give the coherence result for each patient, as described previously.¹⁵

Comparing Mx and CFVx

Time-averaged values for Mx and CFVx obtained from the entire CPB period were evaluated with the Pearson correlation. The CPB period was used for this analysis because it provided the most reliable TCD waveform recordings devoid of electrical interference from electrocautery and motion artifact, whereas continuous microcirculatory flow waveforms were not affected. The Bland–Altman bias analysis was used to compare the differences in Mx and CFVx versus the average of these values.¹⁸

Comparing Optimal Blood Pressure Defined by Mx and CFVx

The values of Mx and CFVx were categorized and averaged in 5 mmHg bins of MAP for each patient.¹⁵ Optimal blood pressure was defined as the MAP at the lowest Mx and CFVx where blood flow is least correlated with changes in blood pressure. The right- and left-sided optimal MAP values were averaged to define the individual optimal MAP and were the variables used for analysis. Optimal blood pressure from Mx and CFVx for each patient was plotted and was evaluated with linear regression and Pearson correlation. The Bland–Altman bias analysis was used to compare the differences in optimal blood pressure measured by Mx and CFVx versus the average of these values. All analyses were performed with STATA (version 13.1; StataCorp, College Station, TX) and Prism 5 (GraphPad Software Inc., La Jolla, CA).

RESULTS

Sixty-nine patients were enrolled, but TCD monitoring was not performed in 5 patients because of lack of a transtemporal insonating window. Demographic and medical data for the 64 patients included in the analysis are listed in Table 1. Monitoring was performed for a median of 111 (interquartile range, 75–148) minutes. MAP was 71 ± 8.2 mmHg during the CPB period. Intraoperative parameters are listed in Table 2.

Coherence between blood flow velocity in the ipsilateral middle cerebral artery and cerebral flow index values averaged 0.61 ± 0.07 (95% CI, 0.59–0.63). Although phase is not accounted for in the coherence analysis, given the low-frequency range of the analysis, phase delays of relevance are unlikely to occur. The Mx for the left side was 0.31 ± 0.17 and for the right side was 0.32 ± 0.17 . The mean CFVx for the left side was 0.33 ± 0.19 and for the right side was 0.35 ± 0.19 . The “among-subject” correlation between time-averaged Mx and CFVx was $r = 0.39$ (95% CI, 0.22–0.53; $P < 0.0001$), and paired within-subject bias was 0.03 ± 0.20

Table 1. Patient Demographic and Medical Data

| Variable | n = 64 |
|------------------------------------------------------|--------------|
| Age (y) ^a | 65 ± 8.8 |
| Sex (male:female) | 38:26 |
| Hypertension (%) | 43 (67.2) |
| Diabetes (%) | 19 (29.7) |
| CHF (%) | 12 (18.8) |
| Peripheral vascular disease (%) | 6 (9.4) |
| COPD (%) | 11 (17.2) |
| Prior cerebral vascular event (%) | 6 (9.4) |
| Prior carotid endarterectomy (%) | 2 (3.1) |
| Aspirin (%) | 44 (68.8) |
| Statin (%) | 35 (54.7) |
| Angiotensin-converting enzyme inhibitor (%) | 20 (31.3) |
| Angiotensin II receptor blocker (%) | 10 (15.6) |
| Ca-blocker (%) | 17 (26.6) |
| β-blocker (%) | 32 (50.0) |
| Diuretics (%) | 23 (35.9) |
| Current smoker (%) | 11 (17.2) |
| Previous smoker (%) | 34 (53.1) |
| Surgery (%) | |
| CABG | 32 (50.0) |
| CABG + AVR/MVR | 8 (12.5) |
| AVR/MVR | 2 (3.1) |
| Others (aortic root, ascending aneurysm) | 4 (6.2) |
| Duration of CPB (min) ^b | 111 (75–148) |
| Duration of aortic cross-clamping (min) ^b | 70 (54–90) |
| Duration of hospitalization (d) ^b | 6 (5–9) |

The data are listed as number of patients with percentage in parenthesis unless otherwise noted.

AVR = aortic valve replacement; CABG = coronary artery bypass graft; CHF = chronic heart failure; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; MVR = mitral valve replacement or repair; statins = HMG-CoA reductase inhibitors.

^aMean ± SD.

^bMedian with interquartile range in parentheses.

Table 2. Intraoperative Measurements and Transcranial Doppler and CerOx Data During CPB

| Variables measured during cardiopulmonary bypass | |
|----------------------------------------------------------------------------------------|------------------|
| pH ^a | 7.39 ± 0.03 |
| Paco ₂ (mm Hg) ^a | 41.1 ± 1.95 |
| PaO ₂ (mm Hg) ^a | 249.9 ± 28.08 |
| Hemoglobin (g/dL) ^a | 9.2 ± 1.07 |
| Average mean arterial pressure (mm Hg) ^a | 71 ± 8.2 |
| Maximum temperature (°C) ^b | 36.6 (36.0–37.0) |
| Minimum temperature (°C) ^b | 32.0 (28.8–33.6) |
| Average middle cerebral artery flow velocity measured with transcranial Doppler (cm/s) | |
| Left ^a | 40 ± 8.9 |
| Right ^a | 40 ± 10.8 |
| Mean velocity index | |
| Left ^a | 0.31 ± 0.17 |
| Right ^a | 0.32 ± 0.17 |
| Cerebral flow velocity index | |
| Left ^a | 21.5 ± 10.26 |
| Right ^a | 20.5 ± 9.53 |
| Cerebral flow velocity index | |
| Left ^a | 0.33 ± 0.19 |
| Right ^a | 0.35 ± 0.19 |

^aMean ± SD.

^bMedian (interquartile range).

(95% prediction interval for the difference between Mx and CFVx, –0.37 to 0.42; Fig. 1A).

A representative example of values for Mx and CFVx during declining and rising MAP during CPB is shown in

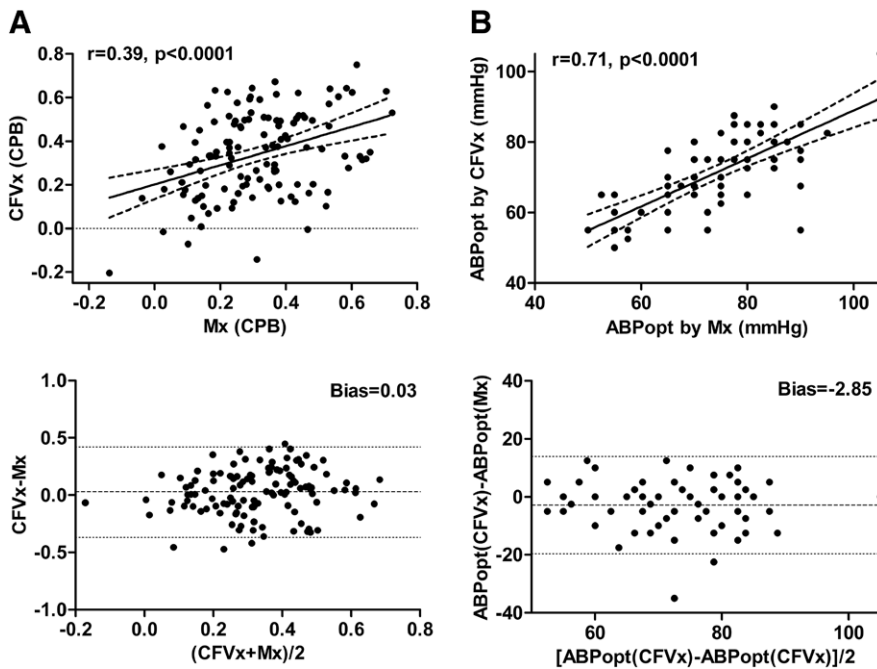


Figure 1. Linear correlation and Bland-Altman bias analysis results between time-averaged Mx and CFVx values obtained during CPB (A). Similar statistical analyses between optimal blood pressure (ABPopt) measured by CFVx and Mx, respectively, are shown (B). The dashed lines represent the 95% confidence interval of the regression line and the 95% limits of agreement for the bias analysis. Data that had the same value among patients are presented as one data point. Mx = mean velocity index; CFVx = cerebral flow velocity index; CPB = cardiopulmonary bypass.

Figure 2. Both Mx and CFVx changed in line with decreasing or increasing MAP, indicating correlation between CBF and MAP, especially when blood pressure was outside the limits of autoregulation. The mean optimal MAP based on Mx was 74 ± 12 mmHg and that based on CFVx was 71 ± 12 mmHg ($P = 0.0514$). The correlation between optimal MAP during CPB measured with Mx and CFVx was $r = 0.71$ (95% CI, 0.56–0.81; $P < 0.0001$) and bias -2.85 ± 8.54 mmHg (95% limits of within-subject agreement, -19.60 to 13.89 mmHg; Fig. 1B). Figure 3 demonstrates the number of patients versus the differences in optimal MAP during CPB based on Mx versus CFVx. Of the 64 patients, 25% of the patients had no difference in the optimal MAP between the methods, whereas this difference was between -5 and 5 mmHg in 62.5% of patients, -10 and 10 mmHg in 79.7% of patients, and >20 mmHg in only 3.1% of patients.

DISCUSSION

In this study, we found that CBF microcirculatory flow monitored with UT-NIRS (continuous flow index) was coherent with TCD. We further found that CBF autoregulation monitored with CFVx was correlated and had a modest agreement with that monitored with TCD-based Mx. The optimal MAP during CPB, as measured by these 2 methods, however, had a statistically strong correlation ($r = 0.71$; 95% CI, 0.56–0.81; $P < 0.0001$) among the subjects.

In a series of studies, we have found that there is wide variability of the MAP at the lower limit CBF autoregulation.^{15,19} Consequently, many patients spend varying portions of time during CPB with MAP below the lower limit of cerebral autoregulation. Previous laboratory experiments have demonstrated the physiologic preservation of CBF during CPB by shunting of blood flow primarily from visceral organs.^{20,21} Consequently, ensuring cerebral perfusion during CPB might provide a means to preserve more accurately other organ blood flow than the current method of patient management, where MAP targets are empirically

chosen. Indeed, we have found that blood pressure excursions below the limit of cerebral autoregulation are associated with acute kidney injury (AKI), as well as major morbidity and operative mortality after cardiac surgery.^{4,5} More recently, we have reported that the magnitude and duration that MAP are above the upper limit of autoregulation are associated with delirium.⁶ However, there were no differences in the average MAP during CPB between patients who developed AKI and those who did not (AKI, 75 ± 7 mmHg versus no AKI, 74 ± 8 mmHg; $P = 0.103$). Moreover, blood pressure excursions above empiric cutoffs of MAP were not associated with delirium. Together, these emerging data suggest that absolute MAP may not be as important for identifying risk for organ malperfusion, but that its relation to the individual's upper and lower limits of CBF autoregulation might be a more important determinant.

Thus, individualizing optimal MAP during CPB based on CBF autoregulation monitoring holds promise as an innovative approach to ensure organ perfusion and reduce the risk of complications from cardiac surgery. The use of TCD for this purpose is limited because of the need for frequent transducer repositioning, interference from electrocautery during surgery, and the inability to find a transcranial window for insonating cerebral arteries, as confirmed in this study. There is a clinical need for new methods of monitoring of CBF autoregulation during CPB that could easily be used in settings outside the clinical investigations. Unlike TCD, CerOx requires minimal operator intervention, and it is not affected by electrical interference from electrocautery. Our findings of coherence between slow waves of CBF velocity and microcirculatory flow measured with the CerOx suggest that slow changes in the latter at this frequency are the result of changes in CBF. As emphasized previously, these slow fluctuations in CBF velocity signals represent autoregulatory compensations for slow hemodynamic oscillations and have been observed by others as well.^{22–24} Our findings, that optimal MAP determined with

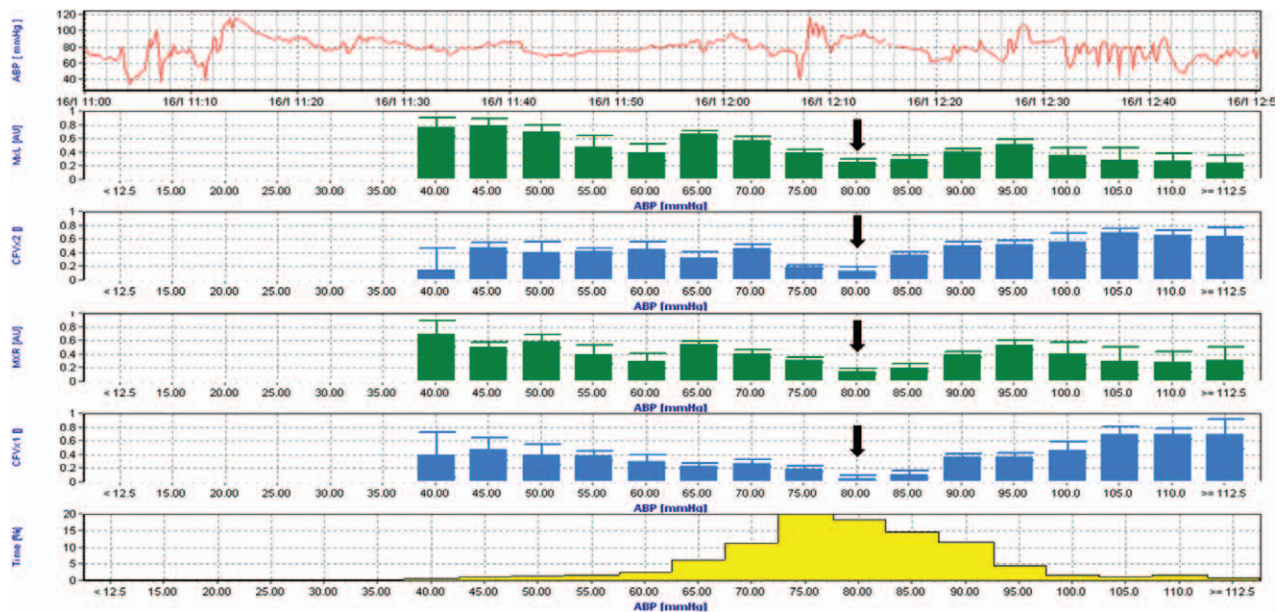


Figure 2. Average Mx and CFVx during cardiopulmonary bypass in 5 mmHg bins. Both Mx and CFVx show increase in their value as mean arterial pressure moves away from the optimal blood pressure, indicating trends toward pressure-dependent changes in cerebral blood flow. Mean arterial pressure at lowest Mx or CFVx was defined as the optimal blood pressure (black arrow). In this example, the optimal blood pressure based on MAP at which Mx is the lowest is 80 mmHg. Similarly, MAP at which CFVx is at the lowest is 80 mmHg. MxR = Mx right; CFVx1 = CFV x right; MxL = Mx left; CFVx2 = CFV x left; Mx = mean velocity index; CFVx = cerebral flow velocity index; MAP = mean arterial blood pressure; ABP = arterial blood pressure.

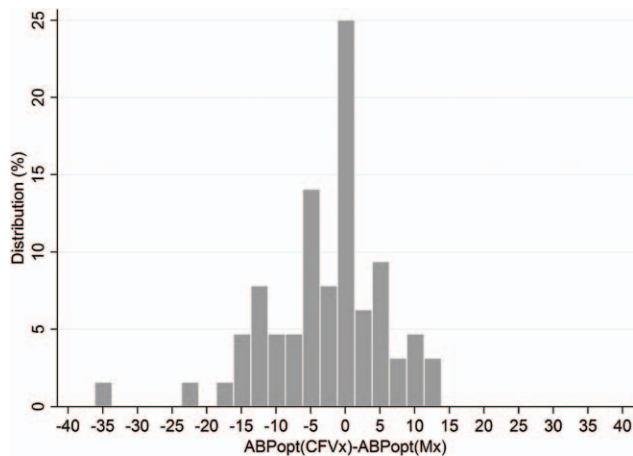


Figure 3. Histogram showing the percentage of patients versus the differences in optimal blood pressure (ABPopot) measured during cardiopulmonary bypass, as defined by Mx and CFVx, respectively. Mx = mean velocity index; CFVx = cerebral flow velocity index.

CFVx and Mx were correlated and in agreement, support the idea that monitoring of the former may provide information that could be used for individualizing MAP targets during CPB.

Rather than using admittedly arbitrary cutoffs for the Mx associated with the limits of autoregulation, in this study we report the MAP where autoregulation is optimal. Changes in cerebral vasoreactivity resulting from falling or rising MAP are not dichotomous but rather graded, making such arbitrary cutoffs to define the limits of autoregulation prone to bias. In contrast, targeting MAP to the pressure associated with the most robust autoregulation indicated by low Mx or CFVx is likely more clinically relevant and

less reliant on arbitrary cutoffs. This approach is more intuitive in situations where autoregulation is impaired because the MAP value at the lowest Mx or CFVx is still likely to be apparent.²⁵ Although the agreement between Mx and CFVx was modest for individual measurements, we found that CFVx identified optimal MAP with relatively good accuracy compared with that measured by Mx.

This is the first study to use UT-NIRS methods of monitoring CBF in patients undergoing CPB. Previous studies in human volunteers have found high correlation between acetazolamide-induced changes in continuous flow index measured with the CerOx monitor with CBF measured with ¹³³Xenon single photon emission computer tomography.¹³ In experiments in piglets, continuous flow index detected increases and decreases in cerebral and muscle blood flow induced pharmacologically and those induced by hyperventilation, hypoxia, and hypercarbia with high discriminatory power compared with laser Doppler flow.¹⁴

There are several limitations to this study. Although slow waves of CBF velocity and microcirculatory flow measured with the CerOx were coherent in the frequency range of responses of cerebral vasoreactivity mediating autoregulation, this relationship is moderate at best.²²⁻²⁴ This moderate coherence might be explained, in part, by the different frequencies used for the UT-NIRS method (1 MHz) compared with TCD (2.5 MHz). Furthermore, the UT-NIRS method measures microcirculatory flow in a small volume of superficial gray matter (1 cm³), whereas TCD measures flow in the large middle cerebral artery. This difference in vascular bed might explain the modest agreement we observed between the 2 methods. Furthermore, monitoring CBF velocity with TCD may be affected by the diameter of the middle cerebral artery, whereas UT-NIRS

cerebral flow index could be influenced by the varying concentrations of red blood cells during hemodilution associated with CPB. It is conceivable that the variability in the increase in tissue blood flow induced by hemodilution during CPB could disproportionately influence the latter parameters more than flow in the middle cerebral artery.²⁶ Despite the moderate coherence and modest within-subject correlation and agreement in Mx and CFVx, we had a strong statistical correlation for optimal MAP during CPB as measured by these 2 methods.

Sixty-three percent of patients had only a minimal difference (within 5 mm Hg) in the optimal MAP measured by the 2 methods; however, 23% patients had a difference >10 mm Hg. With future larger clinical studies, the range of this difference can be estimated with greater precision and also the clinical significance of range assessed.

In conclusion, in this pilot study, we found that monitoring of CBF autoregulation using a new noninvasive technology that measures cerebral microcirculation flow is feasible for patients undergoing CPB. The significant correlation between CFVx and Mx, particularly in determining the MAP where CBF autoregulation is optimal, suggests that the former might be a suitable clinical substitute for TCD in determining individual blood pressure targets during CPB. ■■

DISCLOSURES

Name: Daijiro Hori, MD.

Contribution: This author is the archival author and contributed to data collection, quality control, and analysis and preparation of manuscript.

Attestation: Daijiro Hori attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Charles W. Hogue, Jr., MD.

Contribution: This author helped with study design, IRB application, quality control, and analysis and preparation of manuscript.

Attestation: Charles W. Hogue, Jr., attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author serves as an advisor to Ornim Medical, Inc., and has stock-buying options.

Name: Ashish Shah, MD.

Contribution: This author contributed to quality control and analysis and preparation of the manuscript.

Attestation: Ashish Shah attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Charles Brown, MD.

Contribution: Charles Brown helped with study design, IRB application, quality control, and analysis and preparation of the manuscript.

Attestation: This author attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Karin J. Neufeld, MD.

Contribution: This author helped with study design, IRB application, and preparation of the manuscript.

Attestation: Karin J. Neufeld attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author was funded, in part, by grant from Ornim, Inc., Kfar Saba, Israel.

Name: John V. Conte, MD.

Contribution: This author contributed to data collection, quality control, and preparation of the manuscript.

Attestation: John V. Conte attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Joel Price, MD, MPH.

Contribution: This author contributed to data collection, quality control, and preparation of the manuscript.

Attestation: Joel Price attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Christopher Sciortino, MD, PhD.

Contribution: This author contributed to data collection, quality control, and preparation of the manuscript.

Attestation: Christopher Sciortino attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Laura Max, BA.

Contribution: This author is the second archival author and contributed to data collection, quality control, and preparation of the manuscript.

Attestation: Laura Max attests to the integrity of the original data in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Andrew Laflam, BSc.

Contribution: This author contributed to data collection, quality control, and preparation of the manuscript.

Attestation: Andrew Laflam attests to the integrity of the original data in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Hideo Adachi, MD, PhD.

Contribution: This author contributed to quality control and preparation of the manuscript.

Attestation: Hideo Adachi approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Duke E. Cameron, MD.

Contribution: This author contributed to data collection, quality control, and analysis and preparation of the manuscript.

Attestation: Duke E. Cameron attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author has no conflicts of interest to declare.

Name: Kaushik Mandal, MD, MPH, FRCS (CTh).

Contribution: This author helped with study design, IRB application, data collection, quality control, and analysis and preparation of the manuscript.

Attestation: Kaushik Mandal attests to the integrity of the original data and the analysis reported in this manuscript and approves the submitted manuscript.

Conflicts of Interest: This author is the principal investigator of the study and was funded, in part, by a grant from Ornim, Inc., Kfar Saba, Israel.

ACKNOWLEDGMENTS

Dr. Gayane Yenokyan, Assistant Scientist, Biostatistics Consulting Centre, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, provided statistical guidance and assistance with sample size calculation.

RECUSE NOTE

Dr. Charles W. Hogue, Jr., is the Associate Editor-in-Chief for Cardiovascular Anesthesiology of *Anesthesia & Analgesia*. This manuscript was handled by Maxime Cannesson, MD, PhD, Section Editor for Technology, Computing, and Simulation, and Dr. Hogue was not involved in any way with the editorial process or decision.

REFERENCES

- Schell RM, Kern FH, Greeley WJ, Schulman SR, Frasco PE, Croughwell ND, Newman M, Reves JG. Cerebral blood flow and metabolism during cardiopulmonary bypass. *Anesth Analg* 1993;76:849–65
- Joshi B, Brady K, Lee J, Easley B, Panigrahi R, Smielewski P, Czosnyka M, Hogue CW Jr. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. *Anesth Analg* 2010;110:321–8
- Ono M, Joshi B, Brady K, Easley RB, Kibler K, Conte J, Shah A, Russell SD, Hogue CW. Cerebral blood flow autoregulation is preserved after continuous-flow left ventricular assist device implantation. *J Cardiothorac Vasc Anesth* 2012;26:1022–8
- Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF, Hogue CW Jr. 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;147:483–9
- Ono M, Arnaoutakis GJ, Fine DM, Brady K, Easley RB, Zheng Y, Brown C, Katz NM, Grams ME, Hogue CW. Blood pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. *Crit Care Med* 2013;41:464–71
- Hori D, Brown C, Ono M, Rappold T, Sieber F, Gottschalk A, Neufeld KJ, Gottesman R, Adachi H, Hogue CW. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. *Br J Anaesth* 2014;113:1009–17
- Steiner LA, Coles JP, Johnston AJ, Chatfield DA, Smielewski P, Fryer TD, Aigbirhio FI, Clark JC, Pickard JD, Menon DK, Czosnyka M. Assessment of cerebrovascular autoregulation in head-injured patients: a validation study. *Stroke* 2003;34:2404–9
- Steiner LA, Czosnyka M, Piechnik SK, Smielewski P, Chatfield D, Menon DK, Pickard JD. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med* 2002;30:733–8
- Minhas PS, Smielewski P, Kirkpatrick PJ, Pickard JD, Czosnyka M. Pressure autoregulation and positron emission tomography-derived cerebral blood flow acetazolamide reactivity in patients with carotid artery stenosis. *Neurosurgery* 2004;55:63–7
- Reinhard M, Roth M, Guschlbauer B, Harloff A, Timmer J, Czosnyka M, Hetzel A. Dynamic cerebral autoregulation in acute ischemic stroke assessed from spontaneous blood pressure fluctuations. *Stroke* 2005;36:1684–9
- Bratton S, Chestnut R, Ghajar J, McConnell F, Harris O, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. *J Neurotrauma*. 2007;24(suppl 1):S59–64
- Mahan GD, Engler WE, Tiemann JJ, Uzgiris E. Ultrasonic tagging of light: theory. *Proc Natl Acad Sci U S A* 1998;95:14015–9
- Schytz HW, Guo S, Jensen LT, Kamar M, Nini A, Gress DR, Ashina M. A new technology for detecting cerebral blood flow: a comparative study of ultrasound tagged NIRS and ¹³³Xe-SPECT. *Neurocrit Care* 2012;17:139–45
- Ron A, Racheli N, Breskin I, Metzger Y, Silman Z, Kamar M, Nini A, Shechter R, Balberg M. Measuring tissue blood flow using ultrasound modulated diffused light. *Proc SPIE* 2012;8223:82232J
- Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB, Hogue CW Jr. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. *Stroke* 2010;41:1951–6
- Brady KM, Mytar JO, Lee JK, Cameron DE, Vricella LA, Thompson WR, Hogue CW, Easley RB. Monitoring cerebral blood flow pressure autoregulation in pediatric patients during cardiac surgery. *Stroke* 2010;41:1957–62
- Blaine Easley R, Kibler KK, Brady KM, Joshi B, Ono M, Brown C, Hogue CW. Continuous cerebrovascular reactivity monitoring and autoregulation monitoring identify similar lower limits of autoregulation in patients undergoing cardiopulmonary bypass. *Neurol Res* 2013;35:344–54
- Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;1:307–10
- Joshi B, Ono M, Brown C, Brady K, Easley RB, Yenokyan G, Gottesman RF, Hogue CW. Predicting the limits of cerebral autoregulation during cardiopulmonary bypass. *Anesth Analg* 2012;114:503–10
- Rhee CJ, Kibler KK, Easley RB, Andropoulos DB, Czosnyka M, Smielewski P, Brady KM. Renovascular reactivity measured by near-infrared spectroscopy. *J Appl Physiol* (1985) 2012;113:307–14
- Boston US, Slater JM, Orszulak TA, Cook DJ. Hierarchy of regional oxygen delivery during cardiopulmonary bypass. *Ann Thorac Surg* 2001;71:260–4
- Smielewski P, Kirkpatrick P, Minhas P, Pickard JD, Czosnyka M. Can cerebrovascular reactivity be measured with near-infrared spectroscopy? *Stroke* 1995;26:2285–92
- Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke* 1996;27:1829–34
- Steiner LA, Pfister D, Strelbel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. *Neurocrit Care* 2009;10:122–8
- Ono M, Joshi B, Brady K, Easley RB, Zheng Y, Brown C, Baumgartner W, Hogue CW. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. *Br J Anaesth* 2012;109:391–8
- Plöchl W, Liam BL, Cook DJ, Orszulak TA. Cerebral response to haemodilution during cardiopulmonary bypass in dogs: the role of nitric oxide synthase. *Br J Anaesth* 1999;82:237–43