Real-Time Continuous Monitoring of Cerebral Blood Flow Autoregulation Using Near-Infrared Spectroscopy in Patients Undergoing Cardiopulmonary Bypass

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Background and Purpose—Individualizing mean arterial blood pressure targets to a patient's cerebral blood flow autoregulatory range might prevent brain ischemia for patients undergoing cardiopulmonary bypass (CPB). This study compares the accuracy of real-time cerebral blood flow autoregulation monitoring using near-infrared spectroscopy with that of transcranial Doppler.

Methods—Sixty adult patients undergoing CPB had transcranial Doppler monitoring of middle cerebral artery blood flow velocity and near-infrared spectroscopy monitoring. The mean velocity index (Mx) was calculated as a moving, linear correlation coefficient between slow waves of middle cerebral artery blood flow velocity and mean arterial blood pressure. The cerebral oximetry index was calculated as a similar coefficient between slow waves of cerebral oximetry and mean arterial blood pressure. When cerebral blood flow is autoregulated, Mx and cerebral oximetry index vary around zero. Loss of autoregulation results in progressively more positive Mx and cerebral oximetry index.

Results—Mx and cerebral oximetry index showed significant correlation ($r=0.55$, $P<0.0001$) and good agreement (bias, 0.08 ± 0.18, 95% limits of agreement: -0.27 to 0.43) during CPB. Autoregulation was disturbed in this cohort during CPB (average Mx 0.38, 95% CI 0.34 to 0.43). The lower cerebral blood flow autoregulatory threshold (defined as incremental increase in Mx >0.45) during CPB ranged from 45 to 80 mm Hg.

Conclusions—Cerebral blood flow autoregulation can be monitored continuously with near-infrared spectroscopy in adult patients undergoing CPB. Real-time autoregulation monitoring may have a role in preventing injurious hypotension during CPB.

Clinical Trials Registration—at www.clinicaltrials.gov (NCT00769691). (*Stroke*. 2010;41:1951-1956.)

Key Words: cardiopulmonary bypass ■ cerebrovascular circulation ■ surgery

During cardiopulmonary bypass (CPB), mean arterial blood pressure (MAP) is empirically managed often to targets of 50 to 60 mm Hg and transiently even lower. These low MAPs are not believed to result in cerebral injury because they are within the putative range of normal cerebral blood flow (CBF) autoregulation.[1] This widespread view, however, fails to acknowledge that a growing proportion of surgical patients have cerebral vascular disease that may alter the limits of normal CBF autoregulation, predisposing them to cerebral ischemic injury.[2,3] Individualizing MAP targets during CPB to be within a patient's autoregulatory range might prevent cerebral hypoperfusion from low MAP and cerebral edema from high MAP.

Clinically, the linear regression correlation coefficient between cerebral perfusion pressure and transcranial Doppler (TCD)-measured CBF velocity has been calculated to assess autoregulation in patients with neurological conditions.[4–7]

This method provides a means to monitor CBF autoregulation continuously at the bedside and has been recommended as an option to define the optimal cerebral perfusion pressure targets for patients with traumatic brain injury.[5,8] The routine use of TCD, however, has limitations, including the need for frequent transducer repositioning and the inability to obtain a transcranial "window" in some patients.

Near-infrared spectroscopy (NIRS) is increasingly used during cardiac surgery to monitor cerebral O_2 supply and demand balance. Because changes in the main determinants of NIRS (eg, arterial oxygenation, cerebral metabolic O_2 demand) are relatively stable over short periods of time, NIRS provides a surrogate of fluctuations in CBF.[9–12] Our group has reported that the lower CBF autoregulatory limits can be detected reliably by measuring a moving linear correlation coefficient between cerebral perfusion pressure and cerebral oximeter waveforms in a piglet model.[11] Fur-
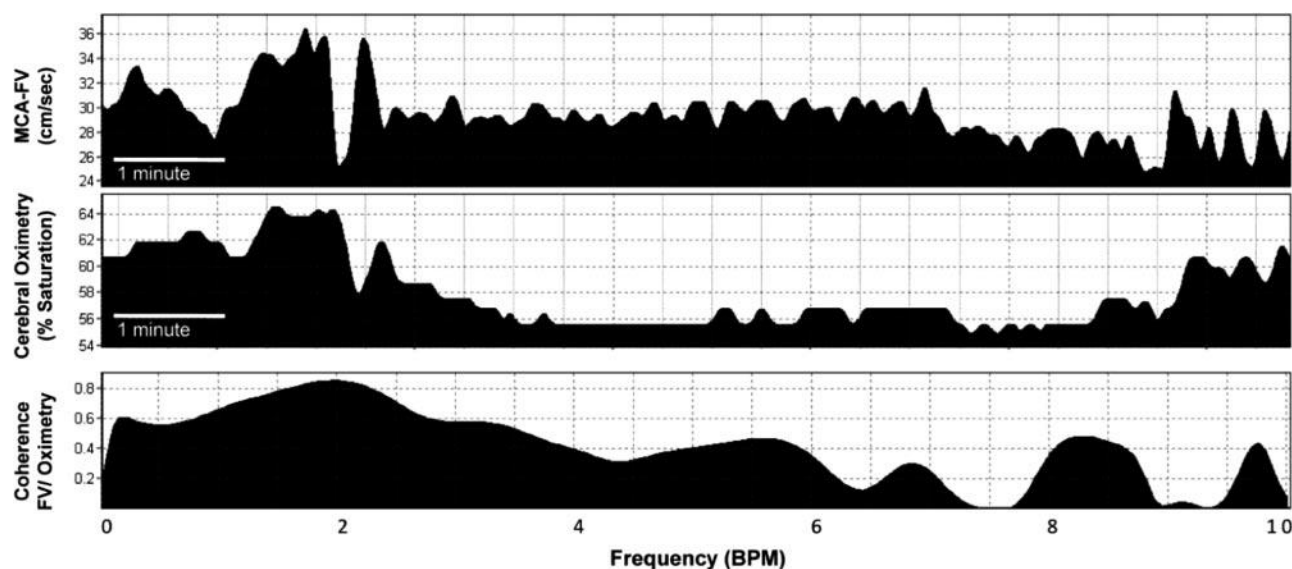
Figure 1. Coherence analysis between middle cerebral artery flow velocity (MCA-FV) and cerebral oximetry. The top panel shows low-pass-filtered MCA-FV across a 12-minute window. The middle panel shows cerebral oximetry across the same time window. The bottom panel shows coherence between MCA-FV and cerebral oximetry as a function of frequency from the 12-minute window shown. The maximum coherence at the frequency of slow waves (0.4 to 4 beats per minute) was averaged across the entire monitoring period to give the results reported.

thermore, good correlation was recently reported between NIRS and TCD assessments of CBF autoregulation in 23 patients with sepsis.[12] NIRS is noninvasive, continuous, and requires minimal caregiver manipulation compared with TCD and, thus, could be applied in a broad range of clinical settings to monitor CBF autoregulation. The purpose of this proof of concept study was to compare the accuracy of a NIRS-derived index of CBF autoregulation with that of a validated TCD-based method in adult patients undergoing CPB for cardiac surgery. We hypothesized that during CPB, the middle cerebral artery CBF velocity would be coherent with cerebral oximetry waveforms at frequencies relevant to autoregulation.

Materials and Methods

All procedures were approved by The Johns Hopkins Medical Institutions Investigational Review Board and were performed after receiving written informed consent. Subjects aged ≥45 years undergoing coronary artery bypass graft surgery and/or valvular surgery requiring CPB were eligible for enrollment in this prospective pilot study. Sixty patients were enrolled in the study, but 5 patients were subsequently excluded because of inability to obtain TCD monitoring.

Perioperative Care

Patients received standard perioperative monitoring, including direct radial artery blood pressure monitoring. Nasal temperature was recorded every 5 minutes. Anesthetic drugs included midazolam, fentanyl, and isoflurane. End-tidal isoflurane concentrations before and after CPB were between 0.2% and 1.2%. During CPB, isoflurane concentrations were kept between 0.5% and 1.0% on a vaporizer connected to the oxygenator inflow. CPB was performed using nonpulsatile flow between 2.0 and 2.4 L/min/m^2 and α-stat pH management. The CPB circuit included a membrane oxygenator and a 40-μm arterial line filter. MAP targets during surgery were based on usual clinical practice. Arterial blood gases and hemoglobin level were measured after tracheal intubation, 10 minutes after initiation of CPB, and then hourly. Mechanical ventilation and CPB gas flow were altered to maintain normocarbia based on arterial Paco$_2$ results

or continuous in-line arterial blood gas monitoring during CPB. There was no protocol for transfusion of packed red blood cells. The rate of rewarming was not standardized. Institutional policy is to maintain the temperature of the perfusate blood at ≤37°C.

CBF Autoregulation Monitoring

Patients were attached to either an INVOS (Somenetics, Inc, Troy, Mich) or Foresight (CAS Medical Systems, Branford, Conn) NIRS monitor, depending on availability. Electrodes for monitoring NIRS were placed on the right and left forehead using the respective manufacturer's recommendations and after first cleaning the skin with an alcohol swab. TCD monitoring (Doppler Box, DWL; Compumedics, USA, Charlotte, NC) of the middle cerebral arteries was with 2 2.5-MHz transducers fitted on a headband. The depth of insonation varied between 35 and 52 mm until representative spectral artery flow was identified.

Analog arterial pressure data from the operating room hemodynamic monitor, TCD, and NIRS 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). These 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. This operation was used to eliminate high-frequency noise from the respiratory and pulse frequencies at the same time as allowing detection of oscillations and transients that occur below 0.05 Hz. Doppler, oximetry, and arterial blood pressure waveforms were further high-pass-filtered with a DC cutoff set at 0.003 Hz. This step removed 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 TCD blood flow velocities and between MAP and NIRS data, rendering the variables Mx (mean velocity index) and COx (cerebral oximetry index), respectively. Of note, MAP is used in this calculation and not cerebral perfusion pressure because intracranial pressure data are not available and because central venous pressure is often negative as a result of suction-assisted venous drainage to the CPB reservoir. Consecutive, paired, 10-second averaged values from 300 seconds' duration were used for each calculation incorporating 30 data points for each index. Intact CBF autoregulation is indicated by an Mx value of approximately zero (CBF and MAP are not correlated), and CBF dysautoregulation is indicated by an Mx value

approaching +1 (CBF and MAP correlated). Similar findings occur experimentally with COx.[11]

Data Analysis

Blood pressure, TCD, and oximetry waveforms were all inspected for artifact, which was manually removed before analysis of the data. Causes of artifact included accessing the arterial line for blood samples, electrocautery interfering with TCD signal acquisition, movement of the TCD probes, which commonly occurred during sternal opening, and internal mammary artery dissection.

NIRS-TCD Coherence Analysis

Waveforms of TCD (sampled at 60 Hz) and cerebral oximetry obtained during CPB were analyzed for coherence by the Welsh method; TCD was used as the input and cerebral oximetry as the output. Periods of uninterrupted waveforms of TCD with a standard physiological appearance were analyzed within a spectral range from 0.4 to 4 beats per minute by using a moving 12-minute window composed of 8 segments that had 50% overlap (Figure 1). 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 during CPB.

Comparing Mx and COx

Right and left TCD recordings were combined for analysis. If only unilateral recordings were available, only NIRS data from the corresponding brain hemisphere were included in the analysis. Time-averaged values for Mx and COx obtained during CPB were evaluated with linear regression and Pearson correlation. Bland-Altman bias analysis was used to compare the differences in Mx and COx versus the average of these values.[13] Analysis was performed with GraphPad Prism software (GraphPad Software, Inc, La Jolla, Calif) or Stata software (Version 9.0; Stata Corp, College Station, Texas).

Quantifying the Effect of Hypotension

To show the effect of MAP on autoregulation, all values of COx and Mx were categorized and averaged in bins of MAP spanning 5 mm Hg for each patient. These individual histograms were then combined in a single histogram showing the autoregulatory indices as a function of MAP. Average values of COx and Mx were compared separately across the categorized MAP through a multiple linear regression model with generalized estimating equations and robust variance estimation (Stata Version 10). This approach was used to account for within-individual correlations.[14] Determining an absolute Mx cutoff indicating the lower autoregulatory threshold is difficult, but it is likely between 0.3 and 0.5.[11,15] Each individual's Mx data for each 5 mm Hg MAP was further evaluated to assess for the lower CBF autoregulatory threshold defined as the MAP (in 5-mm Hg increments) where Mx incrementally increased to >0.45. The average COx value at the lower CBF autoregulatory was determined and the number of individuals with an increase in COx ≥this value determined.

Results

TCD recordings with adequate stability (ie, >30 minutes) were available for analysis from 53 during CPB, whereas NIRS data were available from all patients. Demographic and medical data for the enrolled patients are listed in Table 1. Twenty-nine patients were monitored with INVOS and 31 patients with Foresight NIRS. Unilateral TCD monitoring was available from 7 patients; the remainder had bilateral monitoring. Monitoring was performed for 100.5±25.9 minutes during CPB. MAP was 72.2±11.1 mm Hg during CPB. Physiological data obtained during CPB are listed in Table 2.

Table 1.   Patient Demographic and Medical Data*

Parameter	No. of Patients (N=60)
Age, years (mean±SD)	64±13
Male/female	49/11
Prior stroke	10 (17%)
Prior transient ischemic attack	7 (12%)
Hypertension	43 (72%)
Diabetes (insulin- and noninsulin-dependent)	11 (18%)
Prior myocardial infarction	15 (25%)
Congestive heart failure	10 (17%)
Peripheral vascular disease	8 (13%)
Chronic obstructive lung disease	7 (12%)
Current smoker	7 (12%)
Prior cardiac surgery	2 (3%)
Preoperative echocardiogram function	
Left ventricular ejection fraction ≥50%	41 (69%)
Left ventricular ejection fraction <50%	14 (23%)
Left ventricular ejection fraction <30%	5 (8%)
Preoperative medication	
Statins	45 (75%)
Aspirin	39 (65%)
Beta-blockers	33 (55%)
ACE inhibitors	15 (25%)
Ca^{2+} channel blockers	9 (15%)
Surgical procedure	
CABG only	36 (60%)
CABG with aortic valve replacement	13 (22%)
CABG with mitral valve replacement/repair	6 (10%)
Aortic valve replacement	3 (5%)
Mitral valve replacement	2 (3%)

*Data listed as no. of patients with percentage in parenthesis.
ACE indicates angiotensin-converting enzyme; CABG, coronary artery bypass graft.

The temperature nadir and peak (mean±SD [95% confidence interval]) during CPB was 31.1±3.2°C (30.3°C to 32.0°C) and 37.1±0.8°C (36.9°C to 37.3°C), respectively.

A representative example of data used for coherence analysis is shown in Figure 1. Coherence between middle cerebral artery blood flow velocity and cerebral oximetry values averaged 0.72±0.11 during CPB. Linear regression and Bland-Altman analysis results are shown in Figure 2A–B. There was a correlation ($r=0.55$, $P<0.0001$) between COx and Mx for the time-averaged data. There was also good agreement with limited bias between Mx and COx (95% limits of agreement: −0.27 to 0.43, bias 0.08±0.18). The correlation between Mx and COx during CPB for the Foresight device was $r=0.49$ ($P<0.0001$) and the bias −0.034 (95% limits of agreement −0.404 to 0.34). The correlation between Mx and COx during CPB for the Somentics device was $r=0.57$ ($P<0.0001$) and the bias −0.05 (95% limits of agreement −0.34 to 0.25).

Values for Mx and COx at different MAP values are shown in Figure 3A–B. Both Mx and COx increased with decreasing MAP, indicating CBF autoregulation dysfunction ($P<0.0001$).

Table 2. Physiological Data During CPB

Variable	Result
pH	7.40±0.03
$Paco_2$, mm Hg	39.1±2.9
PaO_2, mm Hg	253.8±30.7
Hemoglobin, g/dL	9.5±1.4
MCA CBF velocity, cm/s	
Left	37.7±9.1
Right	36.5±9.9
Left frontal NIRS O_2 saturation	
$SctO_2$ % (n=31)	64.2±6.9
rSO_2 % (n=29)	50.9±10.6
Right frontal NIRS O_2 saturation	
$SctO_2$ % (n=31)	62.8±6.9
rSO_2 % (n=29)	48.1±15.8

Values are listed as mean±SD.

MCA CBF indicates middle cerebral artery CBF; $SctO_2$, regional cerebral tissue oxygen saturation measured with Foresight (CAS Medical Systems, Branford, Conn); rSO_2, regional cerebral oxygen saturation measured with Invos (Somenetics, Inc, Troy, Mich).

MAP changes recorded were those that occurred during the course of surgery and were not intentionally induced for the purpose of the study. Not all individuals experienced a MAP <50 mm Hg; 3 patients had a MAP as low as 30 mm Hg.
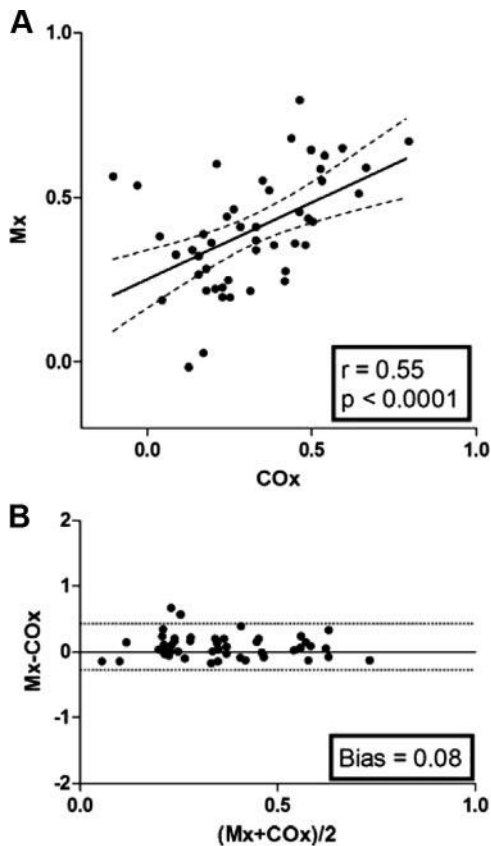

Figure 2. Average Mx and COx values obtained during CPB were compared by linear correlation (A) and the Bland-Altman method (B). The dashed lines represent the 95% confidence band of the regression line and the 95% limits of agreement (−0.27 to 0.43) for the bias analysis.
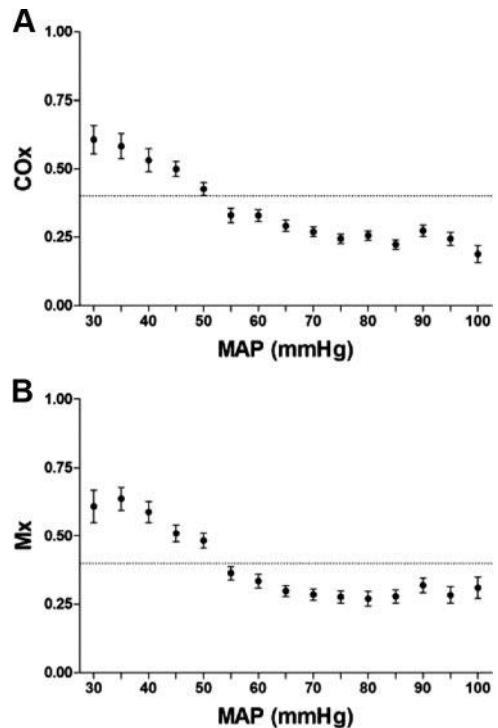

Figure 3. Distribution of COx and Mx over MAP during CPB for the study cohort. A, COx values (mean±SD) are binned to the corresponding MAP at the time of the measurement. B, Simultaneous reading of Mx (mean±SD) is also binned to the corresponding MAP. Note that a wide range of MAP is covered during CPB with a significant increase (impaired autoregulation) in both the COx and Mx at lower MAP.

Furthermore, the time spent at each MAP was not evenly distributed. Low MAPs were typically transient, particularly during initiation of CPB or during rewarming from hypothermia.

Autoregulation as measured by Mx was disturbed in multiple subjects during CPB. In this cohort, the average Mx observed during CPB was 0.38 (95% CI 0.34 to 0.43). Although the absolute threshold of Mx indicating disturbed autoregulation is not known, an average Mx >0.3 was also found in a cohort of patients with sepsis and delirium. By comparison, septic patients without delirium had an average Mx <0.2.[12]

Forty-six patients demonstrated an incremental increase in Mx >0.45 with declining MAP during CPB (Figure 4). The average COx at the MAP where Mx increased >0.45 was 0.38±0.27. A representative CBF autoregulation monitoring
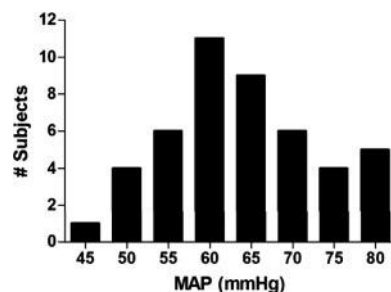

Figure 4. Histogram showing the number of subjects versus the MAP during cardiopulmonary bypass where the Mx increased to >0.45 indicating a putative lower CBF autoregulatory limit.
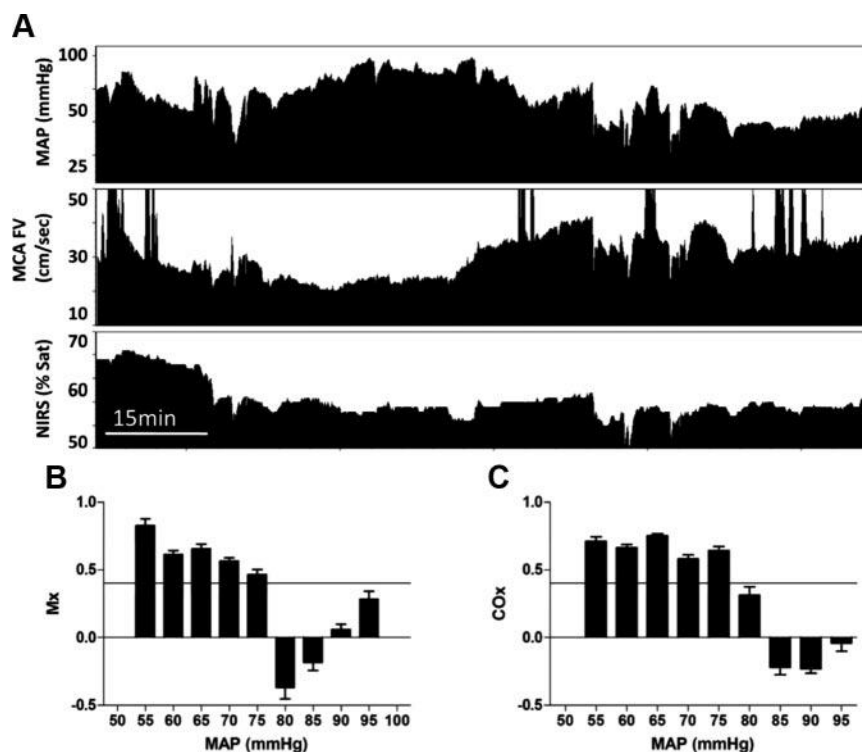
Figure 5. Representative graph of CBF autoregulation monitoring during CPB in a single patient. A, The top panel shows MAP, the middle panel shows the middle cerebral artery flow velocity (MCA-FV), and the lower panel shows the NIRS measurements of frontal lobe oximetry, all synchronously measured on the same time scale. B, Values of Mx and (C) values of COx obtained from the time window in A are sorted according to MAP and show a similar putative lower limit of autoregulation at 75 mm Hg, where Mx and COx values increase precipitously. A horizontal line at Mx and COx values of 0.4 is shown for reference. BPM indicates beats per minute.

study for a patient during CPB is shown in Figure 5. Forty-two (91%) patients had an increase in COx >0.38 within 10 mm Hg of the MAP where Mx increased to >0.45. All but 1 patient had an increase in COx to >0.30 at the MAP where Mx increased >0.45.

Discussion

Our results suggest that CBF autoregulation can be monitored reliably and continuously by NIRS in patients undergoing CPB. We document high Mx in patients undergoing CPB consistent with a state of impaired CBF autoregulation. These data suggest that for many individuals, CBF is pressure passive during CPB, placing patients at risk of delirium and neurological injury. Our data further suggest a wide range of MAP at the lower CBF autoregulatory limit (45 to 80 mm Hg).

Assessment of CBF autoregulation is increasingly used in neurosurgical intensive care unit patients for optimizing MAP.[8,16] Impaired autoregulation was associated with poor outcome after traumatic brain injury, whereas outcomes were better when MAP was optimized within the autoregulatory range.[5,17] Application of this technology to the CPB arena may be similarly informative. We evaluated the MAP where Mx increased to >0.45 as an indicator of the lower CBF autoregulatory threshold. The exact Mx where CBF becomes pressure-passive is not known and may occur at Mx values lower or higher than 0.45.[11,15] It is likely that the patient-specific autoregulatory curves for Mx and COx (Figure 5) provide more useful information regarding the MAP where CBF autoregulation is optimal. Regardless, our data showing a wide range of MAP at the lower CBF autoregulation range suggests that for many patients, CBF may be pressure-passive during portions of CPB using current MAP targets.

There is precedence for using NIRS to monitor CBF autoregulation. Tsuji et al[10] found high coherence between slow waves in NIRS and blood pressure in premature neonates, and this was associated with a high incidence of neurological injury. The frequency-domain technique used in that study is analogous to the time-domain method reported here (COx). Using cerebral oximetry, Steiner et al[12] recently reported that slow waves with periodicity of 20 seconds to 2 minutes were observed with NIRS that had high coherence with similar slow waves of TCD in patients with sepsis. The present study confirms this result and extends it to the clinical scenario of CPB. Our finding of high coherence between slow waves of CBF velocity and NIRS supports the assumption that slow changes in cerebral oximetry at this frequency are the result of changes in CBF. These slow fluctuations in CBF velocity and NIRS signals, which represent autoregulatory compensations for slow hemodynamic oscillations, have been previously observed.[9,12,17]

Monitoring COx in a vascular territory distinct from the middle cerebral artery where Mx was calculated might explain the lower correlation between these methods in our study compared with the results of Steiner et al[12] ($r=0.81$) and our experimental findings ($r=0.67$).[11] Error might be introduced conceivably in monitoring NIRS in the frontal lobe in an individual with significant stenosis of the middle cerebral artery. Maintaining MAP above the lower CBF autoregulatory threshold, even if estimated from vascular territories with functional autoregulation, would likely ensure an adequate cerebral perfusion to pressure-dependent brain regions.[18] The responsiveness of Mx and COx to declining MAP may vary during CPB compared with that observed in intensive care unit patients. Regardless, limitations associated with comparing 2 measurements with simple correlation are

well described.[13] We, therefore, performed bias analysis finding the mean difference on average between Mx and COx was 0.08 and the 95% CIs for the limits of agreement between −0.27 and 0.43. The correlation and agreement was significant for both NIRS devices used in our study. The small number of comparisons and the fact that both devices (INVOS and Foresight) were not used simultaneously in the same patient precludes drawing conclusions regarding the accuracy of 1 device versus the other.

Prior studies of CBF pressure autoregulation in patients undergoing CPB were derived by intermittently measuring CBF (eg, ^{133}Xe methodology).[1,19,20] These studies revealed a slightly positive slope to the CBF autoregulation plateau. This finding might explain, in part, the positive Mx and COx we observed during CPB. In combination, these data show that in most patients, CBF is pressure-passive during CPB. Thus, simply raising MAP targets during CPB to reduce the risk of cerebral hypoperfusion might inadvertently increase the risk for cerebral injury in some patients by increasing cerebral embolic load.[21] Furthermore, increased CBF that results from higher MAP could lead to cerebral edema if a patient is experiencing enhanced inflammation from CPB or possibly intracerebral hemorrhage.[22] The cause of increased pressure passivity of CBF during CPB is not known, but it might result simply from MAP below an individual's autoregulatory threshold or possibly endothelial dysfunction resulting from hypothermic CPB.[12,23]

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Disclosures

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