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

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Abstract

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™, Israel). 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 was the variable used for analysis

Results—The mean velocity index (Mx) for the left side was 0.31±0.17 and for the right side 0.32±0.17. The mean cerebral flow velocity index (CFVx) for the left side was 0.33 ± 0.19 and for the right side 0.35 ± 0.19. Time averaged Mx and CFVx during CPB had a statistically significant "among subject" correlation (r=0.39, 95% CI 0.22 to 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 & CFVx, −0.37 to 0.42). The MAP with the lowest Mx and CFVx ("optimal blood pressure") were correlated (r=0.71, 95% CI, 0.56 to 0.81, p< 0.0001) and were in modest within-subject agreement (bias −2.85±8.54, 95% limits of agreement for MAP predicted by Mx & 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.

Introduction

Maintaining mean arterial pressure (MAP) between 50 to 60mmHg is an accepted practice during cardiopulmonary bypass (CPB). This practice is felt to be adequate for maintaining brain perfusion, since cerebral blood flow (CBF) autoregulation is functional provided that pH management is performed with the α-stat method.[1] Recent findings by our group, however, challenge this view. We have found that there is wide inter-individual 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 is associated with risk for 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.

Cerebral blood flow 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) methodology has recently been described for the non-invasive measurement of microcirculatory blood flow using sensors attached to the forehead.[12, 13] This approach is based on the acoustic-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 a Doppler effect that is filtered and measured at the skin surface. The non-invasive 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™-measured CBF with a validated TCD-based method for monitoring autoregulation in adult patients undergoing CPB.

Materials and 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. Non-pulsatile CPB was performed with flow between 2.0 and 2.4 L/min/m^2 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

Transcranial Doppler (Doppler Box, DWL, Compumedics, USA, Charlotte, NC) was used for measuring cerebral blood flow 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. Ultrasound-tagged NIRS monitoring was performed using a CerOx™ (Ornim, Inc, Kfar Saba, Israel) monitor using methodology previously described.[12-14] Adhesive pads were attached on the right and left side of the forehead, leaving 20-25mm 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 three 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 cm^3 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 mid-frequency 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 previously described.[15, 16] Arterial blood pressure, Doppler, and NIRS signals were filtered to limit analysis to the frequency of slow vasogenic waves (0.05 Hz to 0.003 Hz), which are relevant to autoregulation The signals were time-integrated as non-overlapping 10-second mean values, which is equivalent to applying a moving average filter with a 10-second time window and re-sampling at 0.1 Hz. The latter was performed to eliminate high-frequency noise from the respiratory and pulse frequencies, while allowing detection of oscillations and transients that occur below 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's correlation coefficient was calculated between the MAP and 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 seconds 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), while 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 prior analysis, where autoregulation monitored with near infrared spectroscopy based cerebral oximetry index (COx) was shown to be comparable to 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 prior 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 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 to 4.7. The same sample size will provide a 95% CI for the limits of agreement between −24.7 to −13.3 for the lower limit and 16.3 to 27.7 for the upper CI[18]. Admittedly, 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 11.4mmHg are within 14.4mmHg described by Bland and Altman[18] that was considered “reasonably narrow” for the differences in blood pressure when comparing two 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. As 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 previously described.[15]

Comparing Mx and CFVx—Time-averaged values for Mx and CFVx obtained from the entire CPB period were evaluated with Pearson correlation. The CPB period was used for this analysis because it provided the most reliable TCD waveform recordings devoid electrical interference from electrocautery and motion artifact, whereas continuous microcirculatory flow waveforms were not affected. Bland-Altman bias analysis was used to compare the differences in Mx and CFVx versus the average of these value.[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 was the variable used for analysis. Optimal blood pressure from Mx and CFVx for each patient were plotted and were evaluated with linear regression and Pearson correlation. 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 analysis was performed with STATA (Version 13.1; Stata Corp, College Station, TX, USA) and Prism 5 (GraphPad Software Inc., La Jolla, CA, USA)

Results

Sixty-nine patients were enrolled, but TCD monitoring was not performed in 5 patients due to 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 median of 111 (interquartile range:75-148) minutes. Mean arterial blood pressure was 71±8.2 mmHg during the CPB period. Intraoperative parameters are listed in Table 2.

Coherence between ipsilateral middle cerebral artery blood flow velocity 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 mean velocity index (Mx) for the left side was 0.31±0.17 and for the right side was 0.32±0.17. The mean cerebral flow velocity index (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 to 0.53, P<0.0001) and paired within subject bias was 0.03±0.20 (95% prediction interval for the difference between Mx & CFVx, −0.37 to 0.42) (Figures 1A).

Representative example of values for Mx and CFVx during declining and rising MAP during CPB are shown in 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 based on CFVx was 71±12 mmHg (p=0.0514). The correlation between optimal MAP during CPB measured with Mx versus CFVx was r=0.71, (95% CI, 0.56 to 0.81, p< 0.0001) and bias −2.85±8.54 mmHg (95% limits of within subject agreement −19.60 to 13.89 mmHg) (Figure 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% patients had no difference in the optimal MAP between the methods, while this difference was between −5mmHg to 5mmHg in 62.5% of patients, −10 mmHg to 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 two methods, however had a statistically strong correlation (r=0.71, 95% CI, 0.56 to 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. Prior laboratory experiments have demonstrated the physiologic preservation of CBF during CPB by

shunting of blood flow from primarily visceral organs.[20,21] Consequently, ensuring cerebral perfusion during CPB might provide a means to more accurately preserve 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 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 is above the upper limit of autoregulation is 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±7mmHg vs. No AKI, 74±8mmHg, p=0.103). Moreover, blood pressure excursions above empiric cut-offs 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, due to 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 of clinical investigations. Unlike TCD, CerOxTM requires minimal operator intervention, and it is not affected by electrical interference from electrocauotery. Our findings of coherence between slow waves of CBF velocity and microcirculatory flow measured with the CerOx™ suggests that slow changes in the latter at this frequency are the result of changes in CBF. As previously emphasized, 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 CFVx and Mx were correlated and in agreement, supports 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 cut-offs for the Mx associated with the limits of autoregulation, in this study we report the MAP where autoregulation is optimal. Cerebral vasoreactive changes resulting from falling or rising MAP are not dichotomous, but rather graded, making such arbitrary cut-offs 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 cut-offs. This approach is more intuitive in situations where autoregulation is impaired, since 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. Prior 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 ^{133}Xe-SPECT.[13] In experiments in piglets, continuous flow index detected increases and decreases in cerebral and muscle blood flow induced pharmacologically as well as those induced by hyperventilation, hypoxia, and hypercarbia, with high discriminatory power compared with laser Doppler flow.[14]

There are several limitations to this study. While slow waves of CBF velocity and microcirculatory flow measured with the CerOx™ were coherent in the frequency range of cerebral vasoreactive responses 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). Further, the UT-NIRS method measures microcirculatory flow in a small volume of superficial gray matter (1 cm^3) while TCD measures flow in the large middle cerebral artery. This difference in vascular bed might explain the modest agreement we observed between the two methods. Further, 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 two methods.

Sixty three percent patients had only minimal difference (within 5mmHg) in the optimal MAP measured by the two methods; however 23% patients had a difference greater than 10mmHg. 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 non-invasive 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 suitable clinical substitute for TCD for determining individual blood pressure targets during CPB.

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Disclosures

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

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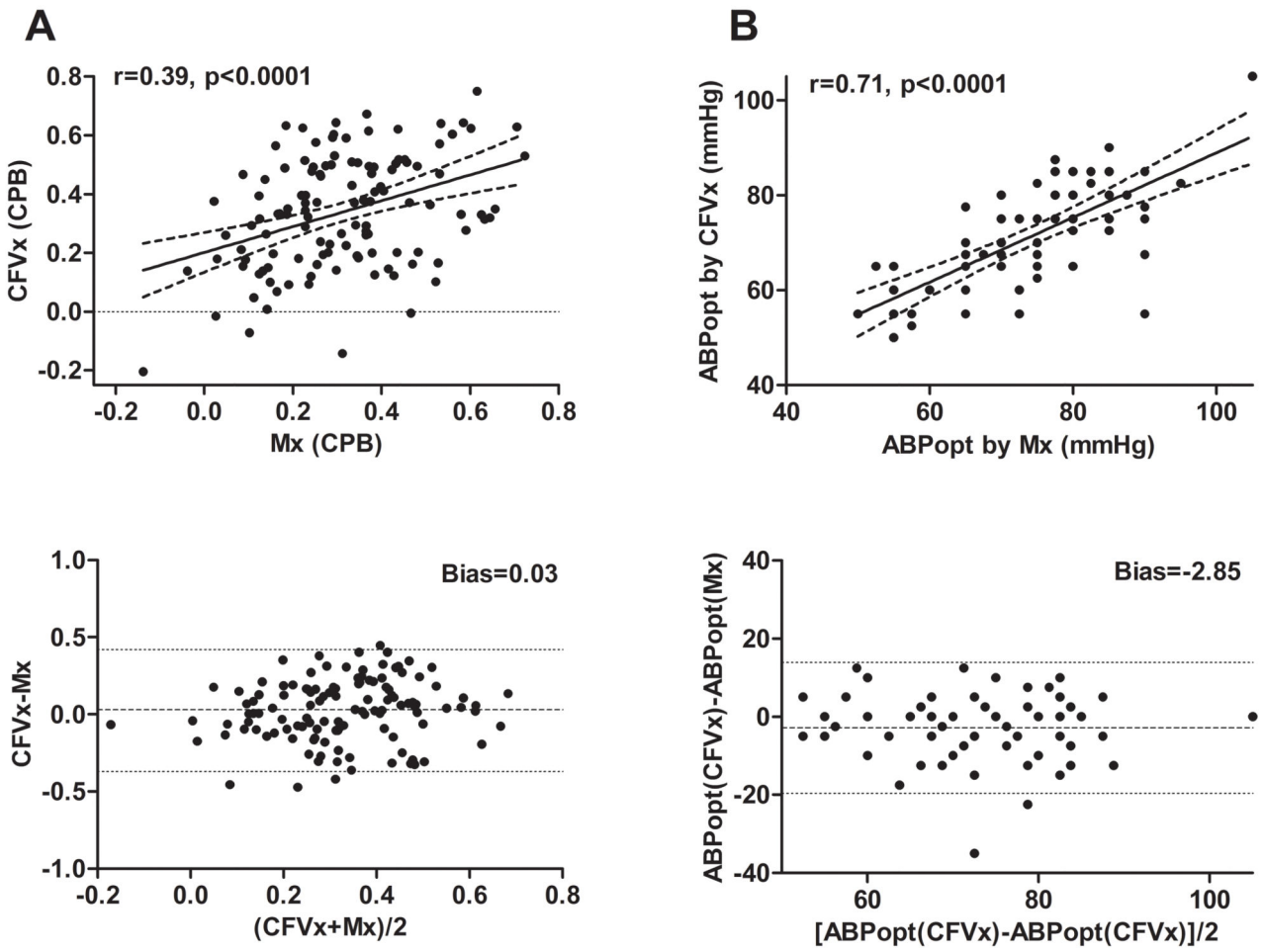

Figure 1.

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.

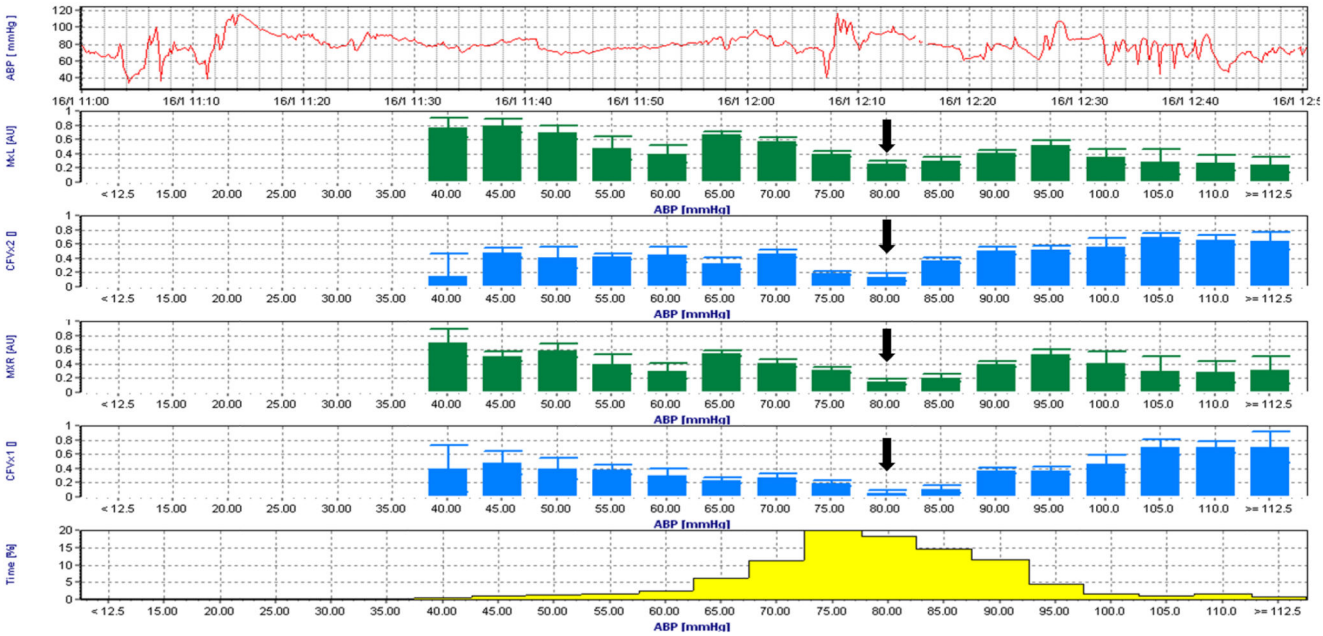

Figure 2.

Average Mx and CFVx during cardiopulmonary bypass in 5mmHg bins. Both Mx and CFVx shows increase in their value as mean arterial pressure moves away from the optimal blood pressure indicating trends towards pressure dependent changes in cerebral blood flow. Mean arterial pressure at lowest Mx or CFVx were 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 80mmHg. MxR=Mx Right; CFVx1=CFVx Right; MxL=Mx Left; CFVx2=CFVx Left;

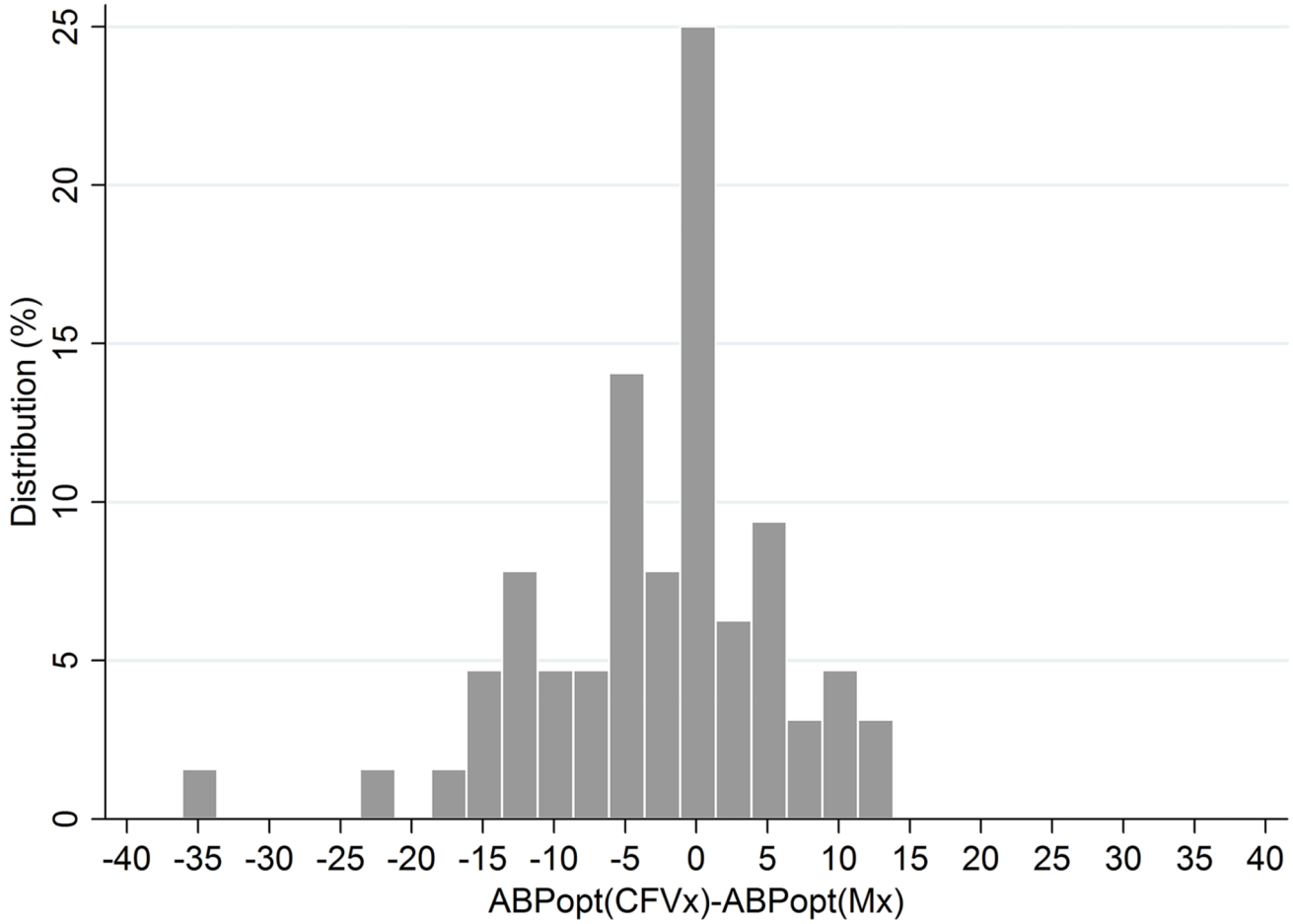

Figure 3.

Histogram showing the percentage of patients versus the differences in optimal blood pressure (ABPopt) measured during cardiopulmonary bypass, as defined by Mx and CFVx respectively.

Table 1

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

Variable	n=64
Age (yrs)*	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%)
Beta 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 (31.3%)
Others (Aortic Root, Asc Aneurysm)	4 (6.2%)
Duration of CPB (min) †	111 (75-148)
Duration of Aortic Cross Clamping (min) †	70 (54-90)
Duration of Hospitalization (days) †	6 (5-9)

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.

*Mean ± Standard Deviation;

†Median with interquartile range in parenthesis.

Table 2

Intraoperative measurements and trans-cranial Doppler and CerOx™ data during CPB.

Variables measured during cardiopulmonary bypass.	
pH*	7.39±0.03
$PaCO_2$ (mmHg) *	41.1±1.95
PaO_2 (mmHg) *	249.9±28.08
Hemoglobin (g/dl) *	9.2±1.07
Average mean arterial pressure (mmHg)*	71±8.2
Maximum Temperature (degrees Celsius) †	36.6 (36.0-37.0)
Minimum Temperature (degrees Celsius) †	32.0 (28.8-33.6)
Average middle cerebral artery flow velocity measured with transcranial Doppler (cm/sec)	
Left*	40±8.9
Right*	40±10.8
Mean Velocity Index (Mx)	
Left*	0.31±0.17
Right*	0.32±0.17
Cerebral Flow Velocity Index (CFI)	
Left*	21.5±10.26
Right*	20.5±9.53
Cerebral Flow Velocity Index (CFVx)	
Left*	0.33 ± 0.19
Right*	0.35 ± 0.19

*Mean ± SD;

†Median (interquartile range)