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Impaired Autoregulation of Cerebral Blood Flow During Rewarming from Hypothermic Cardiopulmonary Bypass and Its Potential Association with Stroke

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Abstract

BACKGROUND—Patient rewarming after hypothermic cardiopulmonary bypass (CPB) has been linked to brain injury after cardiac surgery. In this study, we evaluated whether cooling and then rewarming of body temperature during CPB in adult patients is associated with alterations in cerebral blood flow (CBF)–blood pressure autoregulation.

METHODS—One hundred twenty-seven adult patients undergoing CPB during cardiac surgery had transcranial Doppler monitoring of the right and left middle cerebral artery blood flow velocity. Eleven patients undergoing CPB who had arterial inflow maintained at >35°C served as controls. 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. Intact CBF–blood pressure autoregulation is associated with an Mx that approaches 0. Impaired autoregulation results in an increasing Mx approaching 1.0. Comparisons of time-averaged Mx values were made between the following periods: before CPB (baseline), during the cooling and rewarming phases of CPB, and after CPB. The number of patients in each phase of CPB with an Mx >4.0, indicative of impaired CBF autoregulation, was determined.

RESULTS—During cooling, Mx (left, 0.29 ± 0.18; right, 0.28 ± 0.18 [mean ± SD]) was greater than that at baseline (left, 0.17 ± 0.21; right, 0.17 ± 0.20; $P \leq 0.0001$). Mx increased during the rewarming phase of CPB (left, 0.40 ± 0.19; right, 0.39 ± 0.19) compared with baseline ($P \leq 0.001$) and the cooling phase ($P \leq 0.0001$), indicating impaired CBF autoregulation. After CPB, Mx (left, 0.27 ± 0.20; right, 0.28 ± 0.21) was higher than at baseline (left, $P = 0.0004$; right, $P = 0.0003$), no different than during the cooling phase, but lower than during rewarming (left, $P \leq 0.0001$; right, P

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≤ 0.0005). Forty-three patients (34%) had an Mx ≥0.4 during the cooling phase of CPB and 68 (53%) had an average Mx ≥0.4 during rewarming. Nine of the 11 warm controls had an average Mx ≥0.4 during the entire CPB period. There were 7 strokes and 1 TIA after surgery. All strokes were in patients with Mx ≥ 0.4 during rewarming ($P = 0.015$). The unadjusted odds ratio for any neurologic event (stroke or transient ischemic attack) for patients with Mx ≥ 0.4 during rewarming was 6.57 (95% confidence interval, 0.79 to 55.0, $P < 0.08$).

CONCLUSIONS—Hypothermic CPB is associated with abnormal CBF–blood pressure autoregulation that is worsened with rewarming. We found a high rate of strokes in patients with evidence of impaired CBF autoregulation. Whether a pressure-passive CBF state during rewarming is associated with risk for ischemic brain injury requires further investigation.

Restoring body temperature (“rewarming”) after hypothermic cardiopulmonary bypass (CPB) is reported to be a period of enhanced risk for brain injury.[1–4] The reason for this vulnerability is not known but it may be related to inadvertent cerebral hyperthermia.[5] Cerebral blood flow (CBF) is normally autoregulated to ensure a stable supply of oxygenated blood to the brain over a range of arterial blood pressures. Impaired cerebral vascular reactivity has been reported in patients with traumatic brain injury when their temperatures exceeded 37°C after rewarming from therapeutic hypothermia.[6] Loss of CBF autoregulation may result in cerebral ischemia at low arterial blood pressure and cerebral hyperemia at high blood pressure. During cardiac surgery, the latter may increase cerebral embolic load, which has been implicated in cerebral injury, or it may lead to cerebral edema that results from inflammation-related microcirculatory changes secondary to cardiac surgery.[5,7,8] Whether the rewarming phase of CPB is associated with impaired CBF autoregulation is not clear.

Clinical methods of monitoring CBF–blood pressure autoregulation involve evaluating changes in measures of CBF in response to arterial blood pressure perturbations.[9] Time domain analysis of slow wave changes in transcranial Doppler (TCD)-derived CBF velocity in response to spontaneous changes in arterial blood pressure has been validated as a means for continuous monitoring of CBF autoregulation.[10–14] This approach does not rely on the assumption of linearity or stationarity of CBF or arterial blood pressure measurements that are often absent in the surgical or critically ill patient. Linear regression analysis of the relationship between cerebral perfusion pressure and TCD-measured CBF velocity provides a dimensionless correlation coefficient termed mean velocity index (Mx). When CBF and arterial blood pressure are autoregulated, Mx is near 0 or negative (i.e., little correlation), whereas Mx approaches 1.0 (i.e., increasing correlation) when blood pressure is outside the autoregulatory limits.

The purpose of this study was to evaluate whether cooling and then rewarming of body temperature during CPB in adult patients is associated with alterations in CBF–blood pressure autoregulation measured continuously with TCD. We hypothesized that, similar to what has been observed in patients with traumatic brain injury, rewarming from hypothermic CPB will result in impaired CBF autoregulation.[6]

METHODS

All study procedures were approved by the IRB of The Johns Hopkins Medical Institutions and were performed after receiving written informed patient consent. Patients included in this study were aged ≥45 yr undergoing coronary artery bypass graft surgery and/or valvular surgery that required CPB.

Perioperative Care

Routine perioperative care was used in all patients, including direct radial arterial blood pressure and near infrared spectroscopy (NIRS) monitoring (using either an INVOS [Somanetics, Troy, MI] or Foresight [CAS Medical Systems, Branford, CT] monitor depending on availability). Patients were anesthetized with midazolam, fentanyl, and isoflurane, and pancuronium was given for neuromuscular blockade. Body temperature was measured every 5 min with a nasal pharyngeal temperature probe. During the non-CPB portion of surgery, end-tidal isoflurane concentrations were kept between 0.2% and 1.2%. During CPB, the isoflurane concentration varied between 0.7% and 1% using a vaporizer that was connected to the fresh gas inflow of the membrane oxygenator. Nonpulsatile CPB with a nonocclusive roller pump was used, and CPB flow was maintained between 2.0 and 2.4 $L \cdot min^{-1} \cdot m^{-2}$. The CPB circuit included a membrane oxygenator and a 40-μm arterial line filter. Arterial blood pressure targets during surgery were based on usual clinical practice. Arterial blood gases were measured after tracheal intubation, 10 min after initiation of CPB, and then hourly. Alpha-stat pH management was used during CPB. Mechanical ventilation and CPB gas flow were altered to maintain normocarbia based on arterial $PaCO_2$ results, $ETCO_2$ measurements, or continuous in-line arterial blood gas monitoring during CPB. The rate of rewarming was not standardized. Institutional policy is to maintain the temperature of the perfusate blood at ≤37°C.

The patients received routine institutional postoperative care. Clinical outcomes were recorded from the medical record and included new stroke and transient neurologic ischemic events. Stroke was defined as a new persistent motor focal neurologic deficit; a transient ischemic attack was defined as a similar deficit that resolved within 24 h.

CBF Autoregulation Monitoring

TCD monitoring (Doppler Box, DWL, Compumedics USA, Charlotte, NC) was performed by insonating the right and left middle cerebral arteries with 2.5-MHz transducers at a depth of 35 and 52 mm. The transducers were held in place with a headband. Arterial blood pressure data and TCD 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.[10–14] The signals were time integrated as nonoverlapping 10-s mean values, analogous to applying a moving average filter with a 10-s time window and resampling at 0.1 Hz. This process eliminates high-frequency noise from the respiratory and pulse frequencies while allowing for the detection of oscillations occurring below 0.05 Hz. Signals were further high-pass filtered with a direct current cutoff set at 0.003 Hz. A continuous, moving Pearson correlation coefficient was calculated between the mean arterial blood pressure (MAP) and TCD blood flow velocities rendering the variable Mx.

Data Analysis

Data for this analysis were from patients enrolled in a study to evaluate the use of NIRS for monitoring CBF autoregulation (www.clinicaltrials.gov, NCT00769691). The power analysis for that study was based on the differences in MAP values at the CBF autoregulatory threshold as measured by TCD and NIRS determined from pilot data. A sample size of 144 patients was determined to provide an estimated power of 98% to establish equivalence between the 2 methods of assessing the CBF autoregulatory limit. Patients were included in the present analysis if during CPB there was a period of active or passive cooling with an arterial inflow temperature <34°C (cooling phase of surgery). The rewarming phase of CPB was the period during which the patient was actively warmed to a target temperature of 36°C. In an attempt to evaluate the effects of duration of CPB on Mx, we included a group of patients from this same cohort who underwent CPB with constant warming of arterial inflow temperature ≥35°C (warm controls). For warm control patients with a CPB duration >1.5 h, average Mx was calculated separately for the first hour and for the remaining duration of CPB.

For analysis, we used time-averaged values for MAP and TCD data that were obtained after anesthesia induction but before CPB (baseline), during the respective CPB periods, and after CPB until the conclusion of surgery. Denoting an absolute Mx cutoff indicative of definitive impaired autoregulation is difficult, but it is likely between 0.3 and 0.5.[9,15] To provide an indication of how many patients might have been at this level, we determined the number of patients with an Mx ≥0.4 in the cooling and rewarming phases of CPB. Continuous data were analyzed with analysis of variance and discrete data with χ^2 or Fisher's exact test. Nonnormally distributed continuous data were log transformed for testing. Logistic regression was used to assess the relation between neurologic outcomes and abnormal CBF autoregulation. Stata software (version 9.0, StataCorp, College Station, TX) was used for data analysis.

RESULTS

Of 144 enrolled patients, 127 met the criteria for the present analysis. An additional 11 patients met criteria as warm controls. Six patients had arterial inflow during surgery that varied between >34°C and <35°C and therefore were not included. Demographic and medical data for the 138 study patients are listed in Table 1. Warm control patients were more likely to have had a prior myocardial infarction and to have shorter duration of CPB and aortic cross-clamping compared with the patients who had hypothermia and rewarming during CPB.

Average body temperature, MAP, and other physiologic data are listed in Table 2 for the hypothermia/rewarming group. Seventy-eight patients (61%) had a peak nasopharyngeal temperature ≥37°C during the rewarming phase of CPB, and 8 patients (6%) had a peak nasopharyngeal temperature ≥38°C.

MAP was lower during the cooling phase of CPB than at baseline and decreased further during rewarming. CBF velocity decreased during the cooling phase and then rebounded toward the baseline level during rewarming. NIRS O_2 saturation decreased during the

cooling phase and did not change upon rewarming. Cooling during CPB was associated with a decrease in pH, Pao_2, and hemoglobin levels compared with baseline. During rewarming, these values remained below baseline levels. In contrast, $Paco_2$ increased during cooling and remained higher than baseline during rewarming. Compared with the cooling phase of CPB, pH was lower during rewarming, but there were no differences in $Paco_2$, Pao_2, or hemoglobin.

CBF autoregulation was monitored for 74.1 ± 30.6 min (mean ± SD) before CPB. Because of electrical interference and transducer movement, stable TCD data for calculating Mx were available for only 25.6 ± 19.9 min before CPB. CBF autoregulation was monitored for 59.0 ± 24.8 min during the cooling phase, 47.9 ± 19.9 min ($P \leq 0.00001$) during the rewarming phase, and 27.3 ± 7.5 min after CPB until wound closure. CBF was monitored for 78.6 ± 24.7 min during CPB in the warm controls. Figure 1[16–18] shows Mx results from baseline, during the cooling and rewarming phases of CPB, and from the period after CPB until wound closure. During cooling, Mx (left, 0.29 ± 0.18; right, 0.28 ± 0.18) was higher than at baseline (left, 0.17 ± 0.21; right, 0.17 ± 0.20; $P \leq 0.0001$). Mx increased during the rewarming phase of CPB (left, 0.40 ± 0.19; right, 0.39 ± 0.19) compared with baseline ($P \leq 0.0001$) and compared with the cooling phase ($P \leq 0.0001$), indicating impaired CBF autoregulation. After CPB but before wound closure, Mx (left, 0.27 ± 0.20; right, 0.28 ± 0.21) was higher than at baseline (left, $P = 0.0004$; right, $P = 0.0003$), no different than during the cooling phase of CPB ($P = 0.8996$), but lower than during the rewarming phase of CPB (left, $P \leq 0.0001$; right, $P \leq 0.0005$). Forty-three patients (34%) had an Mx ≥0.4 during the cooling phase and 68 (53%) had an average Mx ≥0.4 during rewarming. Of the patients with an average Mx ≥0.4, 31 (24%) had an Mx ≥0.4 during both the cooling and rewarming phases of CPB. During rewarming, 18 patients had an Mx ≥0.5 but <0.6, 13 patients had Mx ≥0.6 but <0.7, and 6 patients had Mx ≥0.7. In 23 of the 68 patients with impaired CBF autoregulation during CPB, Mx remained ≥0.4 during the post-CPB recording period in the operating room. Nine of the 11 warm controls (82%) had an average Mx ≥0.4 during the entire CPB period. In 7 of these patients, the duration of CPB was >1.5 h, allowing for categorization of the CPB into 2 periods (first hour and the remaining CPB period). In these patients, the average Mx from the left and right side during the first hour of CPB was 0.50 ± 0.11 and 0.47 ± 0.15, respectively. During the second hour of CPB, the average Mx on the left and right sides was 0.61 ± 14 and 0.58 ± 0.08, respectively. There was no difference between left-sided ($P = 0.2948$) or right-sided ($P = 0.2476$) Mx between the first and second hour of CPB in the warm control group.

Demographics, average body temperature, MAP, and other physiologic data for patients with and without an average Mx ≥0.4 during rewarming are listed in Tables 3 and 4. With the exception of insulin treatment, there were no demographic or operative differences between patients with and without an average Mx ≥0.4. Additionally, there were no differences in the peak or average temperature between groups or in the frequency of a peak nasopharyngeal temperature >37°C during the rewarming phase of CPB. Four patients in each group had a peak nasopharyngeal temperature ≥38.0°C. Compared with those without evidence of CBF autoregulation impairment, those with an average Mx ≥0.4 had higher left middle CBF velocity and a lower pH. Except for temperature and hemoglobin level, there were no

differences between the warm controls and patients with and without impaired CBF autoregulation.

Clinical neurologic outcomes are listed in Table 5. Seven of the 138 (5.1%) patients experienced a new perioperative stroke and 1 patient experienced a transient ischemic attack. All 7 patients with stroke had Mx ≥ 0.4 during rewarming on CPB ($P = 0.015$) indicating impaired CBF autoregulation. The unadjusted odds ratio for any neurologic event (stroke or transient ischemic attack) for patients with Mx ≥ 0.4 during rewarming was 6.57 (95% confidence interval, 0.79 to 55.0, $P < 0.08$).

DISCUSSION

These data show that initiation of hypothermic CPB is associated with an increase in Mx from baseline, indicating some degree of CBF autoregulation dysfunction. Patient rewarming was associated with a marked increase in Mx compared with that at baseline and during the cooling phase of CPB. Thirty-four percent of patients had an average Mx ≥0.4 during the cooling phase, and 53% had an average Mx ≥0.4 during the rewarming phase of CPB, consistent with impaired CBF autoregulation. Time-averaged Mx did not recover to baseline during the period between separation from CPB and the end of surgery, although it returned to a level similar to that at the cooling phase of CPB. In patients whose body temperature was maintained at >35°C during CPB (warm controls), Mx was high throughout surgery, with 9 of 11 patients (82%) demonstrating a time-averaged Mx ≥0.4. All 7 strokes that occurred perioperatively were in patients with impaired CBF autoregulation during CPB rewarming.

Hypothermia is widely used during CPB to provide organ protection, although limited data support its effectiveness.[5,19] One explanation for the limited beneficial effects of hypothermia is that its neuroprotective effects may be offset by inadvertent cerebral hyperthermia that can occur during rewarming.[5] Cerebral hyperthermia might easily occur because the aortic cannula returning warmed blood to the central circulation is positioned at the base of the cerebral vessels. Moreover, brain temperature is likely to be clinically underestimated from usual temperature monitoring sites.[5]

Our results demonstrate that patient rewarming from mild or moderate hypothermic CPB is associated with impairment of CBF autoregulation based on an Mx ≥0.4. During the rewarming phase of CPB, pressure-passive CBF could have deleterious effects on cerebral perfusion, particularly for patients with cerebral vascular disease, because MAP often decreases during this phase. The exact Mx associated with CBF autoregulatory failure is not clearly known. Our estimate of an Mx ≥0.4 is derived from animal data and is likely conservative.[15] Furthermore, it has been reported that an average Mx >0.3 is associated with delirium in patients with sepsis.[16] Autoregulatory control could greatly affect patient outcome because studies have shown that impaired autoregulation is associated with poor outcome after traumatic brain injury and that outcomes improve when arterial blood pressure is optimized within the autoregulatory range.[10,20]

Body temperature, and hence, cerebral metabolic rate for O_2, is a major determinant of CBF during CPB.[21] During rewarming, CBF is reported to return to or even exceed baseline measurements, but CBF–blood pressure autoregulation is widely believed to remain functional.[21–24] In a study of 29 patients undergoing coronary artery bypass graft surgery, however, Henriksen et al.[25] reported impaired CBF autoregulation during rewarming from hypothermic CPB. Furthermore, reductions in jugular bulb O_2 saturation have been reported in 17%–23% of patients during CPB rewarming, indicating cerebral O_2 supply versus demand imbalance and risk for postoperative neurocognitive dysfunction.[1,26] We found that NIRS was lower during rewarming than at baseline despite normalization of CBF velocity. These results and other data indicate that, at least in some individuals, global cerebral O_2 delivery might be compromised during rewarming from hypothermic CPB.

Prior studies evaluating the effects of CPB on CBF autoregulation have been derived by using the xenon washout technique or Kety-Schmidt methodology.[21] Both techniques provide only intermittent assessments of CBF autoregulation, and not all of these reports included paired measurements in studied patients. Furthermore, these investigations were performed mostly in patients who were younger and had fewer risk factors for cerebral vascular disease than those seen in contemporary practices.[27]

Those prior studies of CBF autoregulation during CPB that did include multiple measurements within individuals have noted a slightly positive slope to the CBF autoregulation plateau.[22,28,29] Those findings might explain our positive Mx with hypothermic CPB. However, the mechanism by which the Mx becomes markedly positive during CPB is not clear. Abnormal CBF autoregulation might be a manifestation of microcirculatory dysfunction that results from multiple causes during CPB including hypothermia, nonpulsatile CPB flow, and inflammatory responses to surgery.[16,30] Arterial blood pressure below an individual's lower autoregulatory threshold would result in a positive Mx. The fact that MAP was not different between patients with and without high Mx during rewarming (Table 3) suggests that factors other than low MAP may contribute to the impaired CBF autoregulation. Other physiologic factors such as $Paco_2$ or anemia might influence CBF. Although still within a normal range, $Paco_2$ during rewarming was slightly higher in patients with high Mx than in those without high Mx. Whether this small difference between groups contributed to our findings is not known, but it is unlikely, because we observed high Mx in a high percentage of warm control patients despite their having a $Paco_2$ similar to that of patients without CBF autoregulation impairment.

Our findings might simply indicate cerebral vasodilation in response to increased cerebral metabolic rate for O_2 from rewarming. Nonetheless, the latter would not explain susceptibility to impaired CBF autoregulation in only some patients despite a similar degree of rewarming. The rate of rewarming after hypothermic CPB has been suggested to be associated with risk for postoperative neurocognitive dysfunction.[2] Hypothermia and rapid rewarming might also lead to vascular oxidative stress and endothelial dysfunction.[31,32] We were unable to determine whether rate of rewarming might also affect CBF autoregulation. We found that CBF autoregulation was impaired during the cooling phase in 25% of patients.

We found abnormal CBF autoregulation in all patients with a perioperative stroke. This finding is tempered by the small number of enrolled patients. Thus, we are unable to risk adjust these results to evaluate whether there is an independent association between high Mx and stroke. Furthermore, this finding was based on clinical assessment and not on detailed neurologic examination. We did not perform detailed neuropsychological testing or brain imaging studies that might have revealed evidence of brain injury in patients who did not have high Mx during CPB. Regardless, if confirmed in larger studies, the finding of an association between neurologic injury in patients with high Mx during cardiac surgery would be consistent with data from patients with traumatic brain injury, in whom evidence of impaired CBF autoregulation is associated with poor outcome and mortality.[10,20] It is possible that patients experiencing a new stroke during surgery may have developed abnormal CBF autoregulation during CPB, explaining our observations. Conversely, impaired CBF autoregulation may have predisposed patients to cerebral ischemia with low arterial blood pressure.

Our study has several limitations. CBF autoregulation is influenced by many factors during surgery including volatile anesthetics and anemia.[6,33–35] High concentrations of isoflurane might attenuate the range of blood pressures over which CBF is autoregulated.[33] Concentrations of isoflurane used in this study would not likely influence the CBF autoregulatory threshold, and opioids and benzodiazepines used in our patients would not affect CBF autoregulation.[35] We chose an Mx value ≥0.4 to indicate impaired CBF autoregulation based on our experimental findings that this level is associated with definite CBF dysregulation.[17] Impairment in autoregulation might, in fact, occur at lower levels of Mx. It is possible that an Mx ≥0.4 in the latter phases of CPB might result from the duration of CPB and not necessarily rewarming. We included a small number of patients who did not undergo hypothermic CPB or rewarming as controls. Our finding that the majority of these patients had an Mx ≥0.4 throughout CPB suggests that our observations of impaired CBF autoregulation are not merely a consequence of CPB duration. Our time domain methods of monitoring CBF autoregulation are based on analysis of low-frequency waves of TCD and MAP that filters variations caused by respiration and pulsatility. The presence or absence of pulsatility during CPB should not affect the fidelity of the measurements. Finally, the frequency of stroke in this cohort (5%) is higher than other larger series (approximately 1%–3%).[5] This may have resulted from our nonconsecutive enrollment of patients that led to inclusion of a group at high risk for stroke.

In conclusion, hypothermic CPB is associated with abnormal CBF–blood pressure autoregulation in some patients, which worsened with rewarming. During rewarming, more than half of the patients had an Mx value that indicated impaired CBF autoregulation. We also found a higher rate of strokes in patients with evidence of impaired CBF autoregulation. Whether a pressure-passive CBF state during rewarming is associated with risk for ischemic brain injury requires further investigation.

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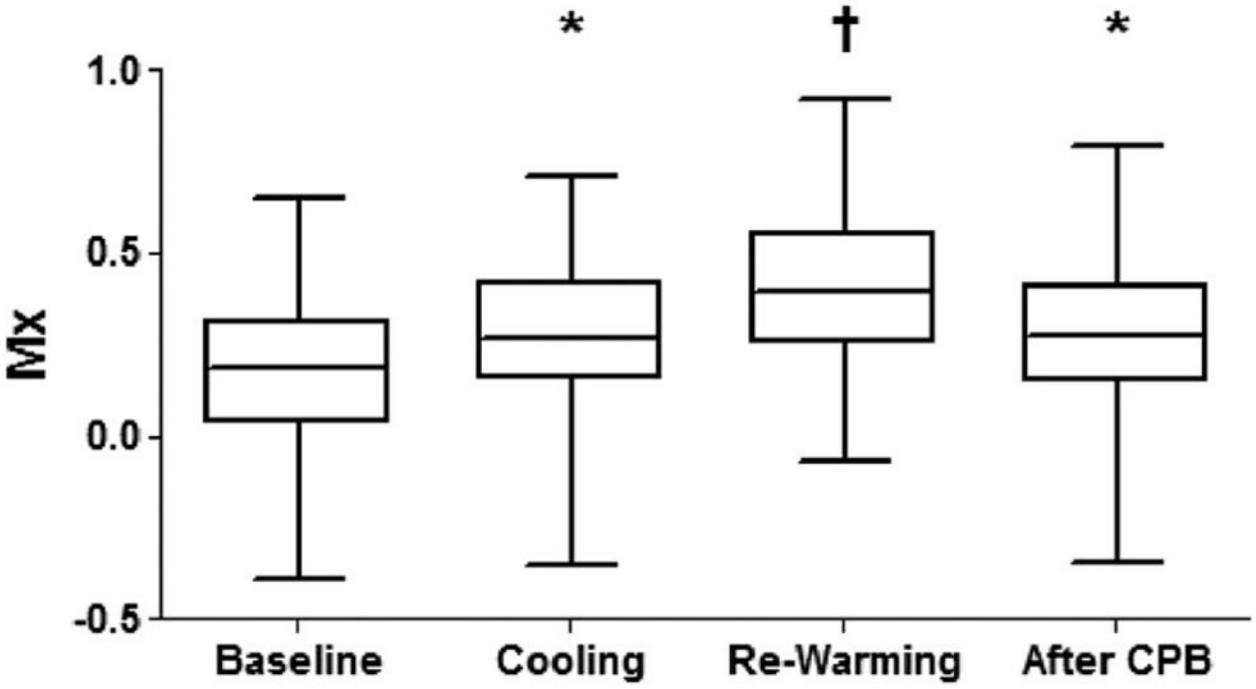

Figure 1.

Mean velocity index (Mx) values obtained after anesthesia induction but before cardiopulmonary bypass (CPB) initiation (baseline) and during the cooling and rewarming phases of CPB. Mx is derived as the nonlinear correlation between cerebral blood flow (CBF) velocity of the right and left middle cerebral arteries and mean arterial blood pressure. This unitless measurement is obtained from 300-s windows of data that are updated every 10 s. Functional CBF autoregulation is indicated by values of Mx that approach 0; dysregulation is indicated by Mx values approaching 1.0. An Mx value between 0.3 and 0.5 is likely associated with autoregulation failure.[16–18] $*P \leq 0.001$ versus baseline; $\dagger P \leq 0.0001$ versus cooling phase and baseline.

Table 1

Demographic and Medical Data for the Enrolled Patients

Variable	Hypothermia/rewarming group (*n* = 127)	Warm controls (*n* = 11)	*P*
Age (mean ± SD, yr)	65 ± 11	67 ± 13	0.4719
Male/female	103 (80%)/24 (20%)	10/1	0.320
Prior stroke (*n*, %)	11 (9%)	2 (17%)	0.318
Prior TIA (*n*, %)	9 (7%)	1 (8%)	0.613
Hypertension (*n*, %)	88 (70%)	9 (75%)	0.515
Diabetes (*n*, %)	41 (34%)	3 (25%)	0.400
Insulin treatment (*n*, %)	34 (44%)	3 (27%)	0.095
Prior myocardial infarction (*n*, %)	39 (41%)	8 (67%)	0.018
Congestive heart failure (*n*, %)	17 (14%)	3 (25%)	0.245
Peripheral vascular disease (*n*, %)	16 (13%)	1 (8%)	0.545
Chronic obstructive lung disease (*n*, %)	13 (10%)	2 (17%)	0.388
Current smoker (*n*, %)	14 (12%)	1 (8%)	0.597
Left ventricular ejection fraction <30% (*n*, %)	21 (17%)	4 (33%)	0.149
Preoperative medication			
Beta-blockers (*n*, %)	68 (55%)	10 (83%)	0.054
Statins (*n*, %)	84 (68%)	9 (75%)	0.454
Aspirin (*n*, %)	81 (66%)	10 (83%)	0.183
ACE inhibitors (*n*, %)	37 (30%)	7 (58%)	0.051
Ca^{++} channel blockers (*n*, %)	24 (19%)	0	0.104
Surgical procedure			
CABG only (*n*, %)	76 (60%)	11	
CABG with aortic valve replacement (*n*, %)	13 (10%)	0	0.353
CABG with mitral valve replacement/repair (*n*, %)	5 (4%)	0	
Aortic valve replacement (*n*, %)	24 (19%)	0	
Mitral valve replacement (*n*, %)	6 (5%)	0	
Other (*n*, %)	3 (2%)	0	
Duration of CPB (mean ± SD, min)	119 ± 46	85 ± 24	0.0127
Duration of aortic cross-clamping (mean ± SD, min)	75 ± 31	34 ± 28	≤0.0001

CPB = cardiopulmonary bypass; TIA = transient ischemic attack; ACE = angiotensin converting enzyme; CABG = coronary artery bypass graft.

Table 2

Physiologic Variables Obtained Before (Baseline) and During the Cooling and Rewarming Phases of Cardiopulmonary Bypass

Variable	Baseline	Cooling	*P* value versus baseline	Rewarming	*P* value versus baseline	*P* value versus cooling
Nadir/peak temperature (°C)	35.2 ± 1.2	30.9 ± 2.9	≤0.0001	37.0 ± 11.0.7	≤0.0001	≤0.0001
MAP (mm Hg)	77.3 ± 11.1	73.5 ± 10.2	0.0176	70.0 ± 9.6	≤0.0001	0.0193
Left CBF velocity (cm/s)	41.4 ± 11.0	31.7 ± 9.0	0.0062	37.7 ± 10.7	0.4738	0.0216
Right CBF velocity (cm/s)	36.1 ± 11.3	32.0 ± 10.1	0.0139	37.2 ± 11.9	0.7306	0.0014
Left frontal NIRS O_2 Saturation						
$SctO_2$ %[a] (*n* = 35)	70.1 ± 5.6	63.0 ± 5.7	≤0.0001	60.9 ± 7.9	≤0.0001	0.1640
Regional O_2 %[b] (*n* = 92)	65.5 ± 11.9	54.3 ± 10.2	≤0.0001	54.5 ± 11.2	≤0.0001	0.9687
Right frontal NIRS O_2 saturation						
$SctO_2$ %[a] (*n* = 35)	69.4 ± 4.8	62.5 ± 5.9	≤0.0001	61.6 ± 5.8	≤0.0001	0.4980
Regional O_2 %[b] (*n* = 92)	66.0 ± 11.5	54.1 ± 11.5	≤0.0001	53.5 ± 11.8	0.0001	0.8443
Average pH	7.41 ± 0.04	7.40 ± 0.04	0.0342	7.39 ± 0.03	≤0.0001	0.0068
Average $PaCO_2$ (mm Hg)	37.9 ± 4.1	39.1 ± 3.5	0.0150	38.85 ± 3.0	≤0.0001	0.2873
Average PaO_2 (mm Hg)	341.8 ± 89.1	259.2 ± 41.4	≤0.0001	247.2 ± 48.2	≤0.0001	0.140
Hemoglobin (gm/dL)	11.46 ± 1.9	9.5 ± 1.70	≤0.0001	9.3 ± 1.4	≤0.0001	0.2151

Values are listed as mean ± SD with minimum to maximum values listed in parenthesis where noted.

CBF = cerebral blood pressure; MAP = mean arterial blood pressure; NIRS = near infrared spectroscopy.

[a]NIRS measured with Foresight™ (CAS Medical Systems, Branford, CT).

[b]NIRS measured with Invos™ (Somenetics, Troy, MI).

Table 3

Demographic and Perioperative Data for Patients with (Impairment) and Without (No Impairment) Impaired CBF Autoregulation (Mx ≥ 0.4) During the Rewarming Phase of Cardiopulmonary Bypass

Variables	No impairment (*n* = 60)	Impairment (*n* = 67)	*P*
Age (mean ± SD, yr)	66 ± 11	64 ± 10	0.3170
Male/female	48/11	53/13	0.514
Prior Stroke (*n*, %)	5 (8%)	6 (9%)	0.876
Prior TIA (*n*, %)	7 (12%)	3 (4%)	0.186
Hypertension (*n*, %)	44 (75%)	45 (66%)	0.174
Diabetes (*n*, %)	20 (34%)	21 (31%)	0.2750
Insulin treatment	18 (30%)	17 (25%)	0.012
Prior myocardial infarction (*n*, %)	20 (34%)	20 (29%)	0.875
Congestive heart failure (*n*, %)	11 (19%)	9 (13%)	0.599
Peripheral vascular disease (*n*, %)	10 (17%)	5 (7%)	0.148
Chronic obstructive lung disease (*n*, %)	6 (10%)	6 (9%)	0.216
Current Smoker (*n*, %)	9 (15%)	7 (10%)	0.303
Left ventricular ejection fraction <30% (*n*, %)	9 (15%)	17 (25%)	0.102
Preoperative medication			
Beta-blockers (*n*, %)	35 (60%)	33 (46%)	0.2860
Statins (*n*, %)	40 (68%)	41 (60%)	0.8800
Aspirin (*n*, %)	37 (63%)	44 (65%)	0.6490
ACE inhibitors (*n*, %)	19 (63%)	18 (26%)	0.5410
Ca^{++} channel blockers (*n*, %)	8 (14%)	16 (23%)	0.131
Surgical procedure			
CABG only (*n*, %)	35 (59%)	42 (62%)	
CABG with aortic valve replacement (*n*, %)	6 (10%)	7 (10%)	
CABG with mitral valve replacement/repair (*n*, %)	3 (5%)	1 (2%)	0.514
Aortic valve replacement (*n*, %)	10 (17%)	14 (20%)	
Mitral valve replacement (*n*, %)	4 (7%)	2 (3%)	
Other (*n*, %)	1 (2%)	2 (3%)	
Duration of CPB (mean ± SD, min)	116 ± 45	121 ± 47	0.5907
Duration of Aortic Cross-Clamping (mean ± SD, min)	73 ± 28	76 ± 33	0.6578

CBF = cerebral blood flow; TIA = transient ischemic attack; ACE = angiotensin converting enzyme; CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass.

Table 4

Physiologic Data for Patients with and Without Impaired CBF-Blood Pressure Autoregulation During Rewarming Phase of Cardiopulmonary Bypass

	No impairment (*n* = 60)	Impairment (*n* = 67)	*P*	Warm controls with impairment (*n* = 9)	*P* value versus no impairment	*P* value versus impairment
Peak temperature during rewarming (°C)	37.0 ± 0.8	37.0 ± 1.3	0.6072	36.8 ± 0.5	0.3287	0.7034
Nadir temperature during hypothermia (°C)	30.4 ± 3.0	31.2 ± 2.8	0.0969	36.7 ± 0.4	≤0.0001	0.0003
MAP (mm Hg)	70.0 ± 7.0	69.9 ± 11.4	0.7067	74.8 ± 8.0	0.3669	0.4498
Left CBF velocity (cm/s)	34.6 ± 10.0	40.0 ± 11.7	0.0056	38.7 ± 12.0	0.0929	0.6525
Right CBF velocity (cm/s)	35.0 ± 12.0	39.0 ± 11.7	0.0718	35.3 ± 9.7	0.5793	0.8148
Mx left (mean ± SD)	0.25 ± 0.13	0.52 ± 0.14	≤0.0001	0.434 ± 0.21	0.0010	0.2523.
Mx right (mean ± SD)	0.26 ± 0.15	0.49 ± 0.16	≤0.0001	0.40 ± 0.19	0.0018	0.2030
Duration of recording (min)	43.7 ± 13.9	54.0 ± 24.7	0.0718	78.6 ± 24.6	0.6364	0.1897
Left NIRS O_2 saturation						
$SctO_2$ %[a] (*n* = 35)	59.3 ± 9.1	62.2 ± 6.6	0.2901			
Regional O_2 %[b] (*n* = 92)	53.4 ± 11.1	55.5 ± 11.36	0.3859	54.2 ± 8.7	0.9725	0.6780
Right NIRS O_2 saturation						
$SctO_2$ %[a] (*n* = 35)	61.3 ± 0.8	61.8 ± 6.7	0.8199			
Regional O_2 %[b] (*n* = 92)	53.5 ± 12.8	53.4 ± 11.0	0.9739	55.8 ± 9.1	0.7750	0.7276
Average pH	7.40 ± 0.03	7.38 ± 0.03	0.0389	7.38 ± 0.05	0.4535	0.8738
Average $PaCO_2$ (mm Hg)	38.2 ± 3.2	39.2 ± 2.8	0.0515	40.4 ± 3.7	0.1226	0.7174
Average PaO_2 (mm Hg)	249.9 ± 4.0	244.7 ± 42.7	0.6652	267.1 ± 19.9	0.2599	0.0193
Hemoglobin (gm/dL)	9.4 ± 1.6	9.2 ± 1.3	0.4146	9.0 ± 1.6	0.32220.0228	0.0210

Impaired CBF-blood pressure autoregulation was defined as an average mean velocity index (Mx) ≥0.4 (see text). Warm controls consisted of patients whose arterial inflow temperature was maintained ≥35°C throughout cardiopulmonary bypass and whose Mx was ≥0.4.

CBF = cerebral blood pressure; MAP = mean arterial blood pressure; NIRS = near infrared spectroscopy.

[a]NIR measured with Foresight™ (CAS Medical Systems, Branford, CT).

[b]NIR measured with Invos™ (Somenetics, Troy, MI).

Table 5

Neurological Outcomes for Patients with and Without Impaired Cerebral Blood Flow Autoregulation During Rewarming on Cardiopulmonary Bypass

Outcome	No impairment (*n* = 60)	Impairment (*n* = 67)	*P*
Perioperative stroke	0	7 (10.4%)	0.015
Transient ischemic attack	1 (1.7%)	0	0.463