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The incidence, risk factors and outcomes of impaired cerebral autoregulation in aortic arch surgery: a single-center, retrospective cohort study

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Abstract

Background Impairment of cerebral autoregulation (CA) has been observed in patients undergoing cardiopulmonary bypass (CPB), but little is known about its risks and associations with outcomes. The cerebral oximetry index (COx), which is a moving linear correlation coefficient between regional cerebral oxygen saturation ($rScO_2$) and mean blood pressure (MAP), may reflect CA function. When COx approaches 1, it implies that CA is damaged, whereas the CA is functional when the COx value approaches 0. The objective of this study was to analyze the incidence and risks of impaired CA, based on COx assessment, in patients undergoing total aortic arch replacement under systemic moderate hypothermia and circulatory arrest of the lower body (MHCA). We also evaluated the association between impaired CA and patient outcomes.

Methods One hundred and fifty-four adult patients who underwent total aortic arch replacement with stented elephant trunk implantation under MHCA at our hospital were retrospectively analyzed. Patients were defined as having new-onset impaired CA if pre-CPB COx < 0.3 and post-CPB COx > 0.3. Pre- and intraoperative factors were tested for independent association with impaired CA. Postoperative outcomes were compared between patients with normal and impaired CA.

Results In our 154 patients, 46(29.9%) developed new-onset impaired CA after CPB. Multivariable analysis revealed a prolonged low $rScO_2$ ($rScO_2 < 55\%$) independently associated with onset of impaired CA, and receiver operating charactoristic curve showed a cutoff value at 40 min (sensitivity, 89.5%; specificity, 68.0%). Compared with normal CA patients, those with impaired CA showed a significantly higher rates of in-hospital mortality and postoperative complications.

Conclusions Prolonged low $rScO_2$ ($rScO_2 < 55\%$) during aortic arch surgery was closely related to onset of impaired CA. Impaired CA remained associated with the increased rates of postoperative complications and in-hospital mortality.

Trial registration ChiCTR1800014545 with registered date 20/01/2018.

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Keywords Cerebral autoregulation, Cardiopulmonary bypass, Hypothermia circulatory arrest, Near-infrared spectroscopy

Background

Cerebral autoregulation (CA) ensures a constant supply of oxygenated blood flow to the brain over a wide range of blood pressures [1]. However, when CA is damaged, cerebral blood volume (CBV) may become correlated with blood pressure, leading to cerebral hypo- or hyperperfusion in patients whose blood pressure is uncontrolled. It also predisposes patients with low blood pressure to cerebral ischemia and patients with high blood pressure to hyperemia [1]. CA may become damaged in up to 20–24% of patients undergoing mild hypothermic cardiopulmonary bypass (CPB) [1, 2].

Impaired CA has been linked to neurological dysfunction in patients undergoing hypothermic CPB [1, 3]. Brain ischemic injury with low arterial pressure and increased cerebral embolic load with high arterial pressure are proposed mechanisms of neurological dysfunction in patients with impaired CA [1]. Whether CPB involving hypothermic circulatory arrest (HCA) of lower body and selective cerebral perfusion increase the risk of impaired CA in aortic dissection patients is unclear. On the one hand, Neri et al's work revealed that HCA combined with retrograde cerebral perfusion might damage CA [4]. And on the other hand, Ono et al's study indicated that deep HCA could preserve CA better than moderate hypothermic CPB without circulatory arrest [5]. Therefore, the effect of HCA on CA remains unclear and requires further investigation.

Regional cerebral oxygen saturation ($rScO_2$) monitoring using near-infrared spectroscopy (NIRS) has been widely applied in cardiac surgeries, carotid endarterectomy, and shoulder surgeries in beach-chair position [6–9]. $rScO_2$ takes into account cerebral arterial, capillary, and venous blood, essentially reflecting the balance between cerebral oxygen supply and demand [10]. Particularly for patients who underwent total aortic arch replacement under HCA, $rScO_2$ monitoring could help to manage the flow rate of cerebral perfusion [11–13]. In previous research, it has been demonstrated that the change of $rScO_2$ was coherent with CBV in patients undergoing CPB or in those with an intracranial injury [14, 15]. And the function of CA can be assessed by measuring a moving linear correlation coefficient between $rScO_2$ and mean blood pressure (MAP), which is called the cerebral oximetry index (COx) [14]. If the COx approached 1, it implied that CBV depended on blood pressure and CA was damaged. If the COx value approached 0, it indicated that blood pressure did not correlate with CBV and CA was functional. An average COx > 0.3 was regarded as the threshold of impaired CA [5]. Furthermore, COx analysis has shown high sensitivity (92%) and moderate specificity (63%) for detecting CA impairment [16], and it agrees well with the mean velocity index (Mx) determined by transcranial Doppler (TCD) [14, 17]. The feasibility of using COx to monitor CA during cardiac surgery has been demonstrated for adult and pediatric patients [18, 19].

In this retrospective study, we aimed to identify the incidence and potential risk factors for new-onset impaired CA by COx calculation in patients undergoing total aortic arch replacement involving moderate hypothermic circulatory arrest (MHCA) of lower body and selective cerebral perfusion. We hypothesized that MHCA would have an effect on CA by comparison of COx levels before and after CPB. We also analyzed the associations between impaired CA and short-term outcomes.

Methods

Study design and population

We retrospectively reviewed the electronic medical records of adult patients who underwent total aortic arch replacement with stented elephant trunk implantation for acute type A aortic dissection from February 2017 to December 2018. This study was approved by the Ethics Committee of West China Hospital, Sichuan University (protocol number: 2,017,342). Written informed consent was waived because of retrospective and observational study. All procedures performed in studies involving human participants were in accordance with the Helsinki declaration. Furthermore, the study was registered in the chictr.org.cn with registration number: ChiCTR1800014545.

Perioperative care and anesthesia

Five-lead electrocardiography (ECG), pulse oxygen saturation (SpO_2), nasopharyngeal and rectal temperature, and invasive blood pressures via the bilateral radial arteries and left dorsal pedis artery were routinely monitored. General anesthesia was induced using midazolam (0.04–0.1 mg/kg), sufentanil (1–2 μg/kg), and rocuronium (0.5–1.2 mg/kg), then maintained using sevoflurane inhalation (1–2%) and intermittent administration of sufentanil and cisatracurium besilate. After tracheal intubation, pressure-controlled mechanical ventilation was achieved and adjusted to keep end-tidal carbon dioxide ($EtCO_2$) in the normal range. Transesophageal echocardiographic examination (iE33; Phillips Medical System, Andover, MA, USA) was routinely performed before surgery. Vasoactive

agents were administrated necessarily to stabilize hemodynamics as much as possible.

Surgical procedures

All patients underwent total aortic arch replacement with stented elephant trunk implantation through median sternotomy in supine position. Aortic cannulation, right axillary artery, or femoral artery cannulation was performed for systemic perfusion, and systemic venous return was achieved by vena cava cannulation or trans-femoral venous cannulation. Systemic moderate hypothermia (nasopharyngeal temperature 26–28 °C and rectal temperature 28–30 °C) was reached before the establishing circulatory arrest of the lower body. During the cooling phase before MHCA, the pump flow rate decreased gradually from 2.6 to 2.2 L/min/m^2. If MAP lower than 50 mmHg, vasoconstrictor, including metaraminol (0.2–0.5 mg) or norepinephrine (5–10 μg), was administrated intermittently; when MAP higher than 80 mmHg, vasodilator, including urapidil (3–5 mg) or perdipine (0.3–0.5 mg) was used. After the establishment of MHCA, selective antegrade cerebral perfusion (ACP) was performed initially via innominate artery cannulation. If left $rScO_2$ was 10% lower than right $rScO_2$ during right ACP, unilateral ACP was immediately switched to bilateral ACP through both innominate artery and left common carotid artery cannulations to improve cerebral oxygenation as much as possible. The flow rate of ACP was adjusted between 6 and 12 mL/min/kg under the guidance of right radial artery blood pressure or perfusion pressure. The right radial artery pressue was maintained between 40 and 70 mmHg as possible, while the cerebral perfusion pressure was kept between 40 and 50 mmHg. Alpha–stat management was used during the cooling and rewarming phases, while pH-stat was applied during the MHCA and selective ACP phases. All patients were transferred to the intensive care unit (ICU) after surgery for respiratory and circulatory support.

$rScO_2$ monitoring and COx calculation

Two self-adhesive transcutaneous oximetry sensors (EGOS-600 A, Suzhou Engine Bio-medical Electronics, Suzhou, China) were placed on the right and left sides of the forehead for bilateral $rScO_2$ monitoring. MAPs and $rScO_2$ were sampled with an analog-to-digital converter at 60 Hz and then processed with SAM 1.0 software (Senton Netease, Chengdu, China) and the EGOS-600 A system respectively. For COx calculation, the saved MAP and $rScO_2$ data were extracted and redisplayed by Visual Studio 2013 software (Microsoft Corporation, WA, USA) on a personal computer (Lenovo XiaoXin Air 13 Pro). Of note, the MAP, measured in the left radial artery, was preferred for COx calculation. A continuous, moving Pearson correlation coefficient between MAP and $rScO_2$ was calculated to generate COx [14]. Consecutive, paired, non-overlapping 10-second mean values of MAP and $rScO_2$ were calculated over 300-sec interval, yielding 30 data points, which were used to determine the COx for that interval. This operation was equivalent to applying a moving filter with a 10-second time window and resampling at 0.1 Hz to eliminate high-frequency noise at the same time as allowing detection of oscillations and transients that occur below 0.05 Hz. Then, the mean values of COx of all 300-sec intervals for the pre- and post-CPB periods were used respectively to identify impaired CA. A COx near 1 indicates that CBV depends on blood pressure and so CA is damaged; a COx near 0 indicates that CBV does not correlate with blood pressure and therefore CA is functional [14]. New-onset impaired CA was defined as both right and left mean value of COx > 0.3 after CPB and ≤ 0.3 before CPB at all recorded MAPs [5]. Figure 1 shows one patient's COx data in MAP bins of 5mmHg. The threshold of low $rScO_2$ was defined as lower than 55% according to that $rScO_2$ below 55% was related to the occurrence of neurological events [20, 21].

Data collection and definition

Preoperative variables were age, body mass index, sex, ejection fraction (EF), presence of comorbidities (diabetes, hypertension), baseline creatine, baseline hemoglobin, baseline b-type natriuretic peptide, and preoperative medication. Intraoperative variables were type of cerebral perfusion and systemic perfusion, MAP, central venous pressure, operation time, CPB time, cross-clamp time, cerebral perfusion time, red blood cells transfusion, temperatures and blood gas parameters during HCA, and $rScO_2$ values.

Postoperative outcomes were major complications including delirium, stroke, acute kidney injury (AKI), cardiac dysfunction, mechanical ventilation > 24 h, respiratory infection, and reoperation. Lengths of stay in the ICU and hospital generally were also recorded. Postoperative delirium was measured with the Confusion Assessment Method (CAM) or CAM-ICU for intubated patients. Stroke is defined as a global or focal neurological lesion, mainly detected by cerebral computed tomography (CT). AKI was diagnosed according to the Kidney Disease Improving Global Outcomes (KDIGO) criteria as a 50% increase from baseline serum creatinine level or a 26.4 mmol/L increase from baseline within 48 h [22]. Cardiac dysfunction was defined as the minimal EF < 50% during postoperative hospitalization. Postoperative respiratory infection was identified as follows: if a patient received antibiotics for suspected respiratory infection and met at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever, leukocyte count > $12{,}000 \times 10^9$ L^{-1} [23].

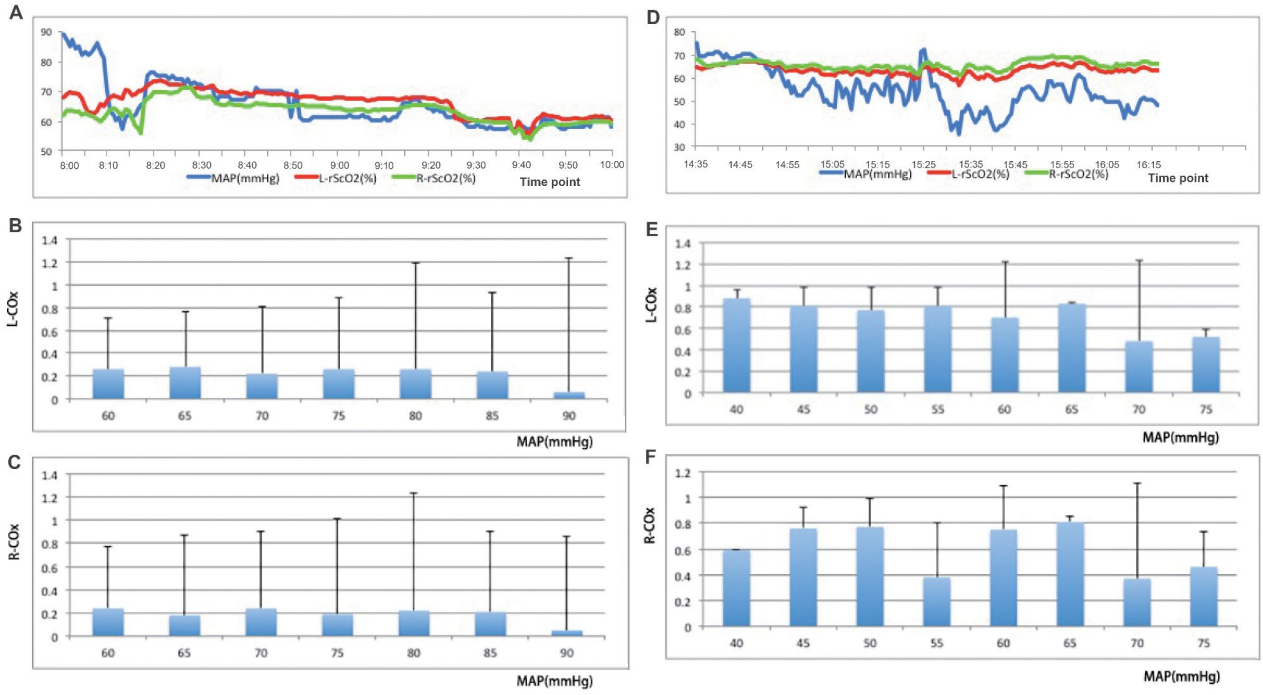

Fig. 1 Examples of $rScO_2$, MAP and COx recordings in a patient with normal CA before CPB but who became impaired after the CPB. A shows MAP, L-$rScO_2$ and R-$rScO_2$ recordings before CPB. B shows L-COx values in MAP bins of 5 mmHg before CPB. C shows R-COx values in MAP bins of 5 mmHg before CPB. D shows MAP, L-$rScO_2$ and R-$rScO_2$ recordings after CPB. E shows L-COx values in MAP bins of 5 mmHg after CPB. F shows R-COx values in MAP bins of 5 mmHg after CPB. $rScO_2$, regional cerebral oxygen saturation; MAP, mean arterial blood pressure; COx, cerebral oximetry index; CA, cerebral autoregulation; CPB, cardiopulmonary bypass; L-$rScO_2$, regional cerebral oxygen saturation of left frontal cerebral; R-$rScO_2$, regional cerebral oxygen saturation of right frontal cerebral; L-COx, cerebral oximetry index of left cerebral; R-COx, cerebral oximetry index of right cerebral

Statistical analysis

Continuous variables were expressed as mean ± standard deviation (SD), and categorical data as frequency in percentage or absolute number. Normality of the continuous data was tested using the Kolmogorov-Smirnov method. Inter-group differences in continuous variables were assessed for significance using Student's *t*-test, and differences in categorical variables were assessed using χ^2 or Fisher's exact test. Preoperative and intraoperative variables were then entered into a univariable logistic regression model to assess for a relationship between each variable and impaired CA. Covariates with an explanatory $P<0.10$ were then manually entered into a multivariable logistic regression model. In cases of intercorrelation, the best single independent variable was chosen. For the predictors of impaired CA, adequate cutoff values were indentified using a receiver operating characteristics curve. According to the previous study, impaired CA occurred in 20% of patients underwent CPB, and the odds ratio was 2 for $PaCO_2$ corresponding to impaired CA [1]. A sample size of 136 patients achieves 90% power at 0.05 significance by logistic regression analysis. Statistical analyses were performed using SPSS version 17.0 (IBM, Chicago, IL, USA), GraphPad Prism 7.0 (GraphPad Software, USA), and PASS 15.0 software. Differences with $P<0.05$ were considered statistically significant.

Results

One hundred and fifty-four adult patients underwent total aortic arch replacement with MHCA were reviewed. Patients with missing NIRS data (n=4), preoperative renal dysfunction (n=1), preoperative stroke (n=5), and impaired CA prior to CPB (pre-CPB COx>0.3) (n=4) were excluded. Finally, 154 cases were enrolled in this study, of which 46 (29.9%) patients presented with new-onset impaired CA after MHCA (Fig. 2).

The preoperative profile and intraoperative data of the two cohort were listed in Table 1. There was no significant difference in the preoperative state between the 2 cohorts. In regards to their intraoperative course, patients who developed new-onset impaired CA had longer antegrade cerebral perfusion time and low $rScO_2$ ($rScO_2$<55%) duration, as well as lower mean value of $rScO_2$ than normal CA patients. The ACP pattern, intraoperative MAP, and CVP showed no significant difference between the two cohorts. Moreover, there were no differences in temperature, pH, carbon dioxide partial pressure ($PaCO_2$), arterial oxygen partial pressure (PaO_2),

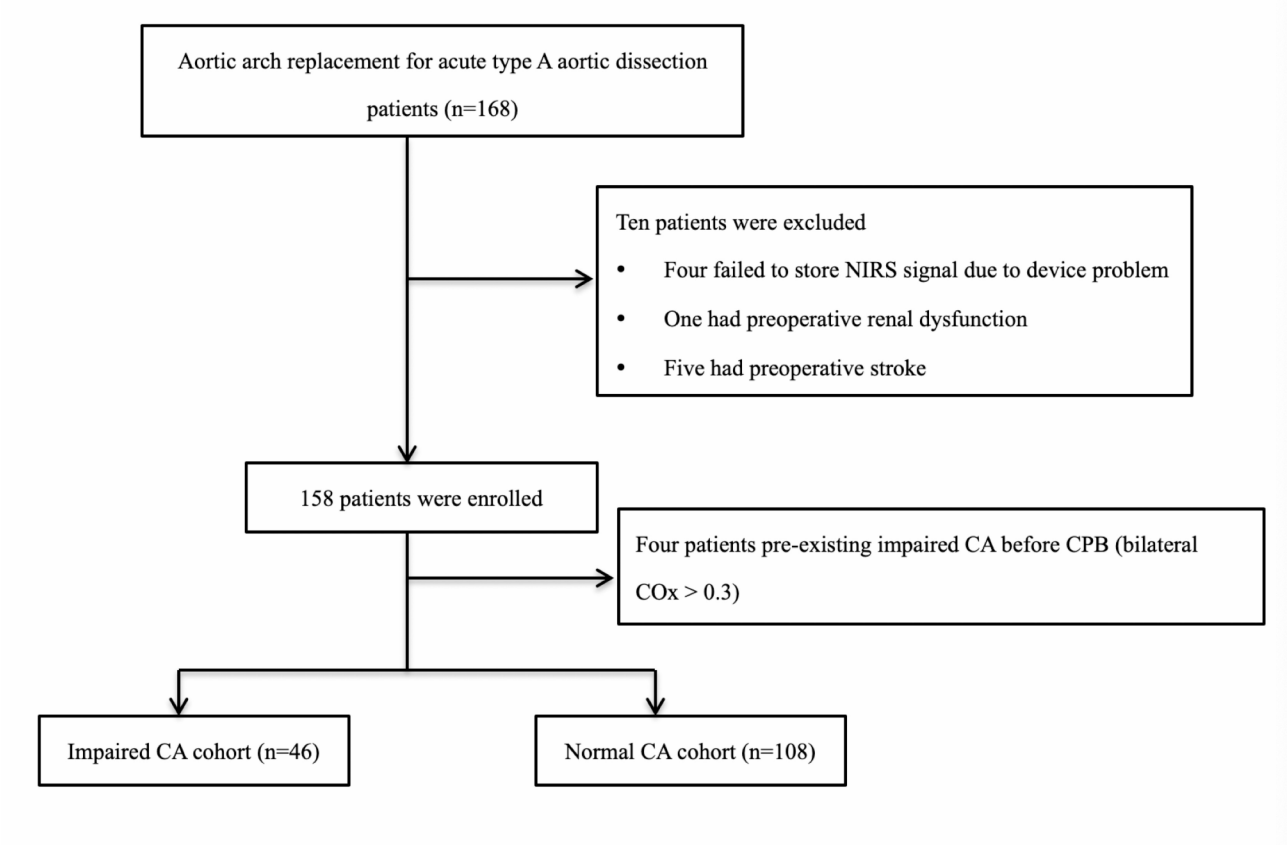

Fig. 2 Flow chart of patient selection. CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; CA, cerebral autoregulation; NIRS, near-infrared spectroscopy

lactate, or hemoglobin between patients with impaired and normal CA during MHCA (Table 2).

The variables listed in Table 1 were tested for univariable association with impaired CA (Table 3). On univariable analysis, only those varibles including bilateral $rScO_2$ mean values and durations of bilateral $rScO_2$<55% were significant. The risk variables with an explanatory *P*<*0.10* at the univariable step were tested with a multivariable analysis. The variables identified in the univariable analysis were tested for intercorrelation. There was a significant correlation between left $rScO_2$ mean value and right $rScO_2$ mean value and between left $rScO_2$<55% duration and right $rScO_2$<55% duration. We therefore included left $rScO_2$ mean value and left $rScO_2$<55% duration in the multivariable models because right side selective cerebral perfusion was mostly performed. After correction for other explanatory facotrs, left $rScO_2$<55% duration independently associated with the occurrence of impaired CA.

To explore the capacity of $rScO_2$<55% duration in predicting impaired CA, a receiver operating characteristic curve was applied. The duration of intraoperative $rScO_2$<55% had an area under the curve of 0.81, with a cutoff value at 40 min (sensitivity, 89.5%; specificity, 68.0%) (Fig. 3).

In-hospital mortality in patients with impaired CA was 26.1% (12/45), of which 33% was cardiogenic shock, 25% neurological, 17% bleeding and 25% other. Compared to patients with normal CA, those who developed impaired CA had higher frequencies of in-hospital mortality, postoperative delirium, AKI, mechanical ventilation>24 h, and respiratory infection, and prolonged ICU stay. Postoperative cerebral CT was only available in 41 patients with impaired CA and 22 patients with normal CA, with no significant difference in the occurrence of stroke between the two cohorts. There was no significant difference in hospital stay between the 2 cohort (Table 4).

Discussion

In our study, 29.9% of aortic arch surgical patients developed new-onset impaired CA after MHCA and with a worse outcomes. The occurrence of impaired CA in adult patients undergoing MHCA was consistent with children in previous reports [24, 25]. Impairment of CA was more likely to be associated with a prolonged low $rScO_2$ ($rScO_2$<55%), in which the critical threshold of $rScO_2$<55% duration was 40 min.

Table 1 Preoperative and intraoperative characteristics of the patients with impaired or normal cerebral autoregulation

Parameter	Impaired autoregulation (n = 46)	Normal autoregulation (n = 108)	*P* value
Frequency (%)	29.9	70.1	
Baseline characteristics			
Age (years)	49.5 ± 11.2	47.2 ± 10.8	0.225
BMI (kg/m^2)	29.3 ± 4.3	25.0 ± 3.7	0.084
Female, n (%)	6(13.0)	21(19.4)	0.339
Preoperative medication, n (%)			
β-blockers	12 (26.3)	22(20.3)	0.434
ACEI	19 (41.3)	38 (35.1)	0.472
CCB	24 (52.1)	43 (39.8)	0.157
Insulin	7 (15.2)	13 (12.0)	0.668
Creatinine (μmol/L)	117.5 ± 121.1	100.6 ± 63.6	0.263
Hemoglobin (g/L)	119.6 ± 22.8	124.5 ± 25.3	0.263
BNP (pg/mL)	1063.1 ± 1643.0	987.8 ± 1981.6	0.826
Diabetes, n (%)	19 (41.3)	36(33.3)	0.345
Hypertension, n (%)	34 (73.9)	71 (65.7)	0.319
Ejection fraction < 50%, n (%)	4(8.7)	9(8.3)	0.941
Moderate to massive pericardial effusion, n (%)	7(15.2)	13(12.0)	0.556
Emergency surgery, n (%)	22 (47.8)	37 (35.2)	0.113
Intraoperative factors			
ACP			
uACP, n (%)	39(84.7)	97(89.8)	0.374
biACP, n (%)	7(15.2)	11(10.2)	0.374
Systemic perfusion			
Trans-femoral artery, n (%)	34(73.9)	73(67.6)	0.531
Trans-aorta, n (%)	12(26.1)	35(32.4)	0.531
MAP (mmHg)			
Pre-CPB	62.3 ± 6.3	62.0 ± 7.6	0.893
During CPB	48.0 ± 5.7	51.1 ± 6.7	0.086
Post-CPB	52.0 ± 3.9	53.9 ± 4.6	0.090
CVP (cmH_2O)			
Pre-CPB	5.7 ± 3.2	7.2 ± 3.8	0.211
Post-CPB	8.1 ± 3.3	10.2 ± 3.5	0.071
Operation time (min)	476.9 ± 100.8	456.6 ± 85.7	0.206
CPB time (min)	257.9 ± 56.2	253.9 ± 73.3	0.754
Pre-CPB time (min)	147.8 ± 32.8	148.3 ± 29.7	0.958
Post-CPB time (min)	144.1 ± 47.9	127.1 ± 48.0	0.136
Cross-clamp time (min)	187.5 ± 49.1	175.7 ± 50.5	0.228
ACP time (min)	37.7 ± 9.1	33.4 ± 9.2	0.008
RBC infusion, n (%)	6 (31.6)	11 (24.4)	0.604
Left $rScO_2$ baseline (%)	61.7 ± 4.5	60.9 ± 3.8	0.562
Right $rScO_2$ baseline (%)	59.6 ± 6.2	61.7 ± 4.5	0.167
Left $rScO_2$ minimum (%)	55.3 ± 3.7	55.1 ± 5.6	0.900
Right $rScO_2$ minimum (%)	55.4 ± 4.6	54.9 ± 5.1	0.254
Left $rScO_2$ mean (%)	57.2 ± 3.6	59.9 ± 5.1	0.041
Right $rScO_2$ mean (%)	57.6 ± 4.8	60.4 ± 4.3	0.035
Left $rScO_2$ < 55% duration (min)	71.5 ± 36.4	33.5 ± 44.2	0.002
Right $rScO_2$ < 55% duration (min)	67.6 ± 24.9	33.5 ± 45.3	0.003
Left $rScO_2$ < 50% duration (min)	4.6 ± 13.0	7.2 ± 20.8	0.627
Right $rScO_2$ < 50% duration (min)	14.5 ± 39.1	11.1 ± 33.8	0.773

Values are n (%) or mean ± SD, unless otherwise noted

Abbreviations: BMI, body mass index; ACEI, angiotensin-converting enzyme inhibitor; CCB, calcium-channel blocker; BNP, b-type natriuretic peptide; ACP, antegrade cerebral perfusion; uACP, unilateral antegrade cerebral perfusion; biACP, bilateral antegrade cerebral perfusion; MAP, mean arterial blood pressure; CVP, central venous pressure; CPB, cardiopulmonary bypass; RBC, red blood cell

P < 0.05

Table 2 Temperatures and blood gas analysis of patients averaged over hypothermic circulatory arrest, stratified by impaired or normal cerebral autoregulation

Parameters	Impaired autoregulation (n = 46)	Normal autoregulation (n = 108)	*P* value
Nasopharyngeal T_{mean}(℃)	26.5 ± 1.7	26.8 ± 2.2	0.522
Nasopharyngeal T_{min}(℃)	26.3 ± 1.7	26.5 ± 2.3	0.732
Rectal T_{mean}(℃)	28.1 ± 2.1	28.5 ± 2.0	0.442
Rectal T_{min}(℃)	27.9 ± 2.0	28.4 ± 1.9	0.407
pH	7.2 ± 0.1	7.2 ± 0.1	0.755
$PaCO_2$ (mmHg)	62.2 ± 13.7	59.6 ± 13.0	0.519
PaO_2 (mmHg)	191.3 ± 85.3	221.2 ± 93.6	0.251
Lactate (mmol/L)	4.8 ± 2.0	5.4 ± 2.7	0.447
BE	-3.6 ± 2.3	-5.0 ± 2.6	0.056
Hemoglobin (g/L)	78.0 ± 10.2	82.2 ± 11.0	0.180
Glucose (mmol/L)	9.8 ± 2.7	11.0 ± 4.1	0.200

Values are mean ± SD, unless otherwise noted

Abbreviations: T, temperature; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; BE, base excess

P < 0.05

Table 3 Univariable and Multivariable Analysis for predictors of impaired cerebral autoregulation

Variables	Odds Ratio	95% Confidence Interval	P-value
Univariate Analysis			
Age (y)	1.014	0.977–1.053	0.464
BMI (kg/m^2)	1.046	0.931–1.176	0.449
Female	1.922	0.636–5.805	0.247
Hemoglobin (g/L)	0.989	0.971–1.006	0.207
Diabetes (Absent, present)	0.791	0.322–1.884	0.596
Hypertension (Absent, present)	0.853	0.347–2.101	0.730
CPB time (min)	1.001	0.995–1.006	0.752
Cross-clamp time (min)	1.005	0.997–1.013	0.228
ACP time (min)	1.038	0.997–1.081	0.073
$PaCO_2$ (mmHg)	1.015	0.972–1.060	0.500
Left $rScO_2$ baseline (%)	1.047	0.899–1.221	0.554
Right $rScO_2$ baseline (%)	0.918	0.812–1.039	0.178
Left $rScO_2$ mean (%)	1.133	1.001–1.282	0.047 *
Right $rScO_2$ mean (%)	1.158	1.013–1.323	0.031 *
Left $rScO_2$ minimum (%)	0.993	0.892–1.103	0.898
Right $rScO_2$ minimum (%)	1.066	0.955–1.189	0.255
Left $rScO_2$ < 55% duration (min)	1.020 1.019(1.005–1.033)	1.005–1.035	0.007 * 0.007
Right $rScO_2$ < 55% duration (min)	1.019	1.005–1.033	0.007 *
Left $rScO_2$ < 50% duration (min)	0.991	0.957–1.027	0.628
Right $rScO_2$ < 50% duration (min)	1.002	0.990–1.014	0.770
Multivariable analysis			
Left $rScO_2$ mean (%)	1.098	0.948–1.272	0.212
Left $rScO_2$ < 55% duration (min)	1.016	1.002–1.031	0.029 *

Abbreviations: BMI, body mass index; CPB, cardiopulmonary bypass; ACP, antegrade cerebral perfusion

*P < 0.05

It is known that the mechanisms for impaired CA have not yet been elucidated. Notably, there was no association between age, body mass index, gender, diabetes, hypertension, preoperative hemoglobin level and impaired CA. During CPB particularly during HCA and selective cerebral perfusion, factors might influence CA include temperature, PaO_2, $PaCO_2$, perfusion pressure, flow rate, and hematocrit [24–27]. Temperature reduction exponentially decreases cerebral metabolism and preserves cellular stores of high-energy adenosine triphosphate [25]. Carbon dioxide is a potent cerebrovasodilator, and elevated $PaCO_2$ can obviously increase CBF volume in both awake and anesthetized states [26]. In our cohort, the patients with impaired or normal CA did not differ significantly in the above factors (Table 2). High $PaCO_2$ might be detrimental to preserve the function of CA. And this variable was independently asscociated with impaired CA [1]. In our study, the $PaCO_2$ was higher than normal range. However, there was no significant difference between patients with impaired and normal CA. The high $PaCO_2$ might be related to that we used pH-stat for blood gas management to ensure sufficient cerebral perfusion during MHCA. Although the seletive cerebral perfusion time showed an obviously difference between impaired CA and normal patients in our study, this variable did not reach a significant association with impaired CA consistent with the result in a literature [20].

Preoperative end-organ malperfusion is common in patients with acute type A aortic dissection, and is associated with significant mortality and morbidity [28]. In particular cerebral malperfusion may result in impairment of the CA. In our study, there was no significant difference in the baseline value of $rScO_2$, which could reflect preoperative cerebral perfusion, between patients with impaired CA and normal CA. Other preoperative variables, that may partially reflect organ malperfusion, such as the tamponade, low cardiac output (EF < 50%), creatinine, BNP, and MAP, did not show significant differences between the two cohorts. Nonetheless, we were still unable to assess potential bias in the occurrence of impaired CA because we cannot obtain comprehensive and accurate assessment data on preoperative organ malperfusion by retrospectively reviewing medical records.

We found that impaired CA seems to associate with intraoperative low $rScO_2$. The period of $rScO_2$ < 55% in impaired CA patients was longer than in normal CA patients. In addition, intraoperative $rScO_2$ less than 55% for more than 40 min was independently associated with the onset of impaired CA. This result was consistent with

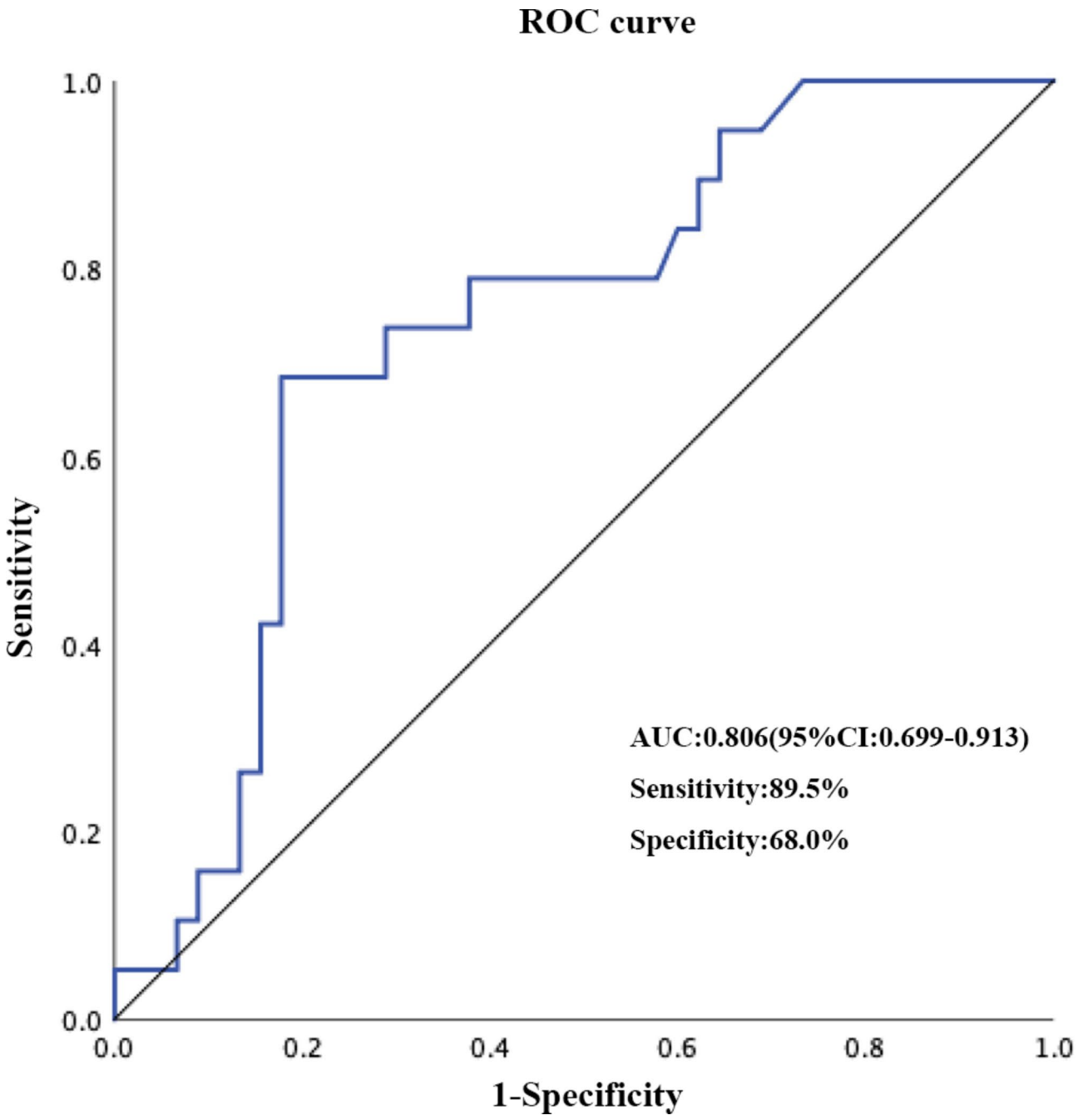

Fig. 3 Receiver operating characteristic curve for the duration of low $rScO_2$ ($rScO_2 < 55\%$) identified as independently associated with impaired cerebral autoregulation. AUC, area under the curve; CI, confidence interval

previous studies that the period of $rScO_2$ less than 55% during aortic surgery was closely related to the occurrence of postoperative neurological events [20, 21]. These results suggest that regulation cerebral perfusion blood flow rate or pressure alone is not sufficient to prevent the occurrence of $rScO_2$ less than 55%. Other methods should also be considered, including switching from unilateral to bilateral cerebral perfusion, increasing hematocrit to improve oxygen delivery, maintaining deep hypothermia to suppress cerebral metabolism, minimizing the duration of HCA, or aggressive upfront antiedema measures [28]. Whereas using α-stat management during moderate hypothermia produces better neurologic outcomes than observed with pH-stat management, it is unclear which strategy is superior in adults when MHCA is used [29].

Our results suggested that patients with impaired CA had a higher rate of postoperative delirium, consistent

Table 4 Outcomes of patients after cardiopulmonary bypass with hypothermic circulatory arrest, stratified by impaired or normal cerebral autoregulation

Outcome	Impaired autoregulation (n = 46)	Normal autoregulation (n = 108)	*P* value
Length of ICU stay (d)	7.3 ± 7.2	4.7 ± 3.5	0.004 *
Hospitalization (d)	19.0 ± 11.1	16.7 ± 7.6	0.146
Re-operation, n (%)	5(10.9)	8 (7.4)	0.946
Ejection fraction < 50%, n (%)	13(28.3)	24(22.2)	0.422
Acute kidney injury, n (%)	17 (37.0)	13(12.1)	< 0.001 *
Delirium, n (%)	31 (67.3)	21(19.4)	< 0.001 *
Postoperative stroke			
Ischemic, n (%)	9 (21.9)	5 (22.7)	0.944
Hemorrhage, n (%)	1 (2.4)	0 (0.0)	0.460
Mechanical ventilation > 24 h, n (%)	32(69.6)	54(50.0)	0.037 *
Lung infection, n (%)	26 (56.5)	39 (36.1)	0.019 *
In-hospital death, n (%)	12(26.1)	9(8.3)	< 0.001 *

Values are n (%) or mean ± SD, unless otherwise noted

Abbreviations: d, days; ICU, intensive care unit

*$P < 0.05$

with previous studies in coronary artery bypass grafting or valve surgery under CPB [30, 31]. Patients with impaired CA were also at increased risks of in-hospital mortality, AKI, mechanical ventilation > 24 h, respiratory infection, and length of ICU stay. Like the present study, other work reported that impaired CA was associated with longer mechanical ventilation and hospital stay [30]. Although there was no significant difference in postoperative stroke between the two cohorts which is inconsistent with the study by Ono M et al., this may be due to the fact that postoperative cerebral CT scan was not performed in all patients in our study [1]. The onsets of AKI, respiratory infection, and postoperative death were affected by many factors, including the cardiac function, bleeding, and the duration of mechnical ventilation. Although the events of low cardiac output and reoperation due to bleeding showed no significant difference between patients with impaired CA and those with normal CA, the causal relationship between impaired CA and postoperative death, AKI and respiratory infection was uncertain from our study which merits prospective studies. Our findings might indicate that impaired CA was one of the manifestations of systemic organ injury in patients who underwent MHCA. These observations suggested the need to comprehensively monitor patients who undergo MHCA to ensure sufficient oxygen delivery to key organs. In particular, patients with impaired CA may require early interventions before postoperative complications onset, such as increasing systemic oxygen delivery, providing renal replacement therapy, and/or giving mild hypothermia therapy.

Our study presents several limitations. First, we were able to enroll only 154 cases because of the relatively small number of total aortic arch replacement surgeries for acute type A aortic dissection at our institution. Second, COx > 0.3 was tested in the animal study as a threshold of impaired CA. Thus, perspective studies were ongoing to explore an absolute value or a certain percentage increase of COx as a measurement tool for impaired CA in adult patients. Third, because $rScO_2$ monitoring was not routinely performed after surgery in our center, we could not further calculate postoperative COx to track the duration of impaired CA. Fourth, not all patients received a rigorous assessment by a neurologist or psychiatrist to identify the postoperative neurological complications. This may lead to an underestimation of the occurrence of postoperative neurological complications. In addition, only the temporary rather than permanent neurological complications were evaluated. Fifth, we did not analyze the potential impact of vasoconstrictors or inotropics on CA because the accuracy of the dosage and usage time could not be ensured. Finally, COx was not calculated during CPB, since considering that the site of blood pressure measurement was not constant due to the interruption of perfusion of the aortic arch branches. Furthermore, there is no control group without MHCA in our study. However, the occurrence of new-onset impaired CA in patients undergoing MHCA was higher than that reported in the literature in patients undergoing CPB alone. This might reveal that MHCA increased the risk of new-onset impaired CA.

Conclusions

Our single-center retrospective study showed that prolonged low $rScO_2$ ($rScO_2 < 55\%$) during aortic arch surgery for type A aortic dissection was closely associated with the development of impaired CA. Impaired CA may be associated with increased rates of postoperative complications and in-hospital mortality.

List of abbreviations

CA	cerebral autoregulation
CBV	cerebral blood volume
CPB	cardiopulmonary bypass
COx	cerebral oximetry index
HCA	hypothermic circulatory arrest
MHCA	moderate hypothermic circulatory arrest
$rScO_2$	regional cerebral oxygen saturation
MAP	mean blood pressure
Mx	mean velocity index
TCD	transcranial Doppler
ECG	electrocardiography
SpO_2	pulse oxygen saturation
$EtCO_2$	end-tidal carbon dioxide
ICU	intensive care unit
CT	computed tomography
AKI	acute kidney injury
KDIGO	Kidney Disease Improving Global Outcomes
EF	ejection fraction
SD	standard deviation

$PaCO_2$	carbon dioxide partial pressure
PaO_2	arterial oxygen partial pressure
BMI	body mass index
ACEI	angiotensin-converting enzyme inhibitor
CCB	calcium-channel blocker
BNP	b-type natriuretic peptide
CVP	central venous pressure
RBC	red blood cell
ACP	antegrade cerebral perfusion
T	temperature
BE	base excess
d	days

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Author contributions
LP, and WW have given substantial contributions to the conception or the design of the manuscript, DG, YHS and JPY to acquisition, analysis and interpretation of the data. All authors participated to draft the manuscript, LP and WW revised it critically. All authors read and approved the manuscript.

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Data Availability
The datasets used and analysed during this study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by Ethics Committee of West China Hospital, Sichuan University (protocol number 2017342). Written informed consent was waived because of retrospective and observational study. All procedures performed in studies involving human participants were in accordance with the Helsinki declaration.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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