Risks and Association of Impaired Cerebral Autoregulation With Outcomes in Aortic Arch Surgery: A Single-center, Retrospective Cohort Study

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Research Article

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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 objective of this study was to analyze the risks of impaired CA, based on cerebral oximetry index (COx), in patients undergoing total aortic arch replacement with CPB and moderate hypothermic circulatory arrest (MHCA). We also evaluated the association between impaired CA and patient outcomes.

Methods

One hundred fifteen four adult patients who underwent total aortic arch replacement with stented elephant trunk implantation under CPB and MHCA at our hospital were retrospectively analyzed. Patients were defined as having new-onset impaired CA if post-CPB COx > 0.3, calculated based on a moving linear correlation coefficient between regional cerebral oxygen saturation (rScO\textsubscript{2}) and mean blood pressure (MAP). 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 with MHCA. Multivariate analysis revealed a prolonged low rScO\textsubscript{2} (rScO\textsubscript{2} <55%) independently associated with onset of impaired CA, and receiver operating characteristic 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.

Conclusion

Prolonged low rScO\textsubscript{2} (rScO\textsubscript{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.

Introduction

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 and hypothermic circulatory arrest (HCA) 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 CPB and 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 potential risk factors for new-onset impaired CA by COx calculation in patients undergoing total aortic arch replacement involving CPB and moderate hypothermic circulatory arrest (MHCA). 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: 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. Furthermore, the study was registered in the chictro.cn with registration number: ChiCTR1800014545.

**Perioperative care and anesthesia**

Five-lead electrocardiography (ECG), pulse oxygen saturation ($\text{SpO}_2$), 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$\mu$g/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 ($\text{EtCO}_2$) 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. Moderate hypothermia (nasopharyngeal temperature 26-28°C and rectal temperature 28-30°C) was reached after the establishment of circulatory arrest. 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 $\mu$g), 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 was performed initially via innominate artery cannulation. If left $\text{rScO}_2$ was 10% lower than right $\text{rScO}_2$ during right antegrade cerebral perfusion, unilateral antegrade cerebral perfusion was immediately switched to bilateral antegrade cerebral perfusion through both innominate artery and left common carotid artery cannulations. The flow rate of antegrade cerebral perfusion 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 pressure 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 cooling and rewarming phases and pH-stat was applied during MHCA. All patients were transferred to the intensive care unit (ICU) after surgery for respiratory and circulatory support.

**$\text{rScO}_2$ monitoring and COX calculation**

Two self-adhesive transcutaneous oximetry sensors (EGOS-600A, Suzhou Engine Bio-medical Electronics, Suzhou, China) were placed on the right and left sides of the forehead for bilateral $\text{rScO}_2$ monitoring. MAPs and $\text{rScO}_2$ 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-600A system respectively. For COx calculation, the saved MAP and rScO\textsubscript{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\textsubscript{2} was calculated to generate COx [14].

Consecutive, paired, non-overlapping 10-second mean values of MAP and rScO\textsubscript{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\textsubscript{2} was defined as lower than 55% according to that rScO\textsubscript{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\textsubscript{2} values.

Postoperative outcomes were major complications including delirium, 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. 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 × 10\textsuperscript{9} L\textsuperscript{−1} [23].

**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 $\chi^2$ or Fisher's exact test. Preoperative and intraoperative variables were then entered into a univariate 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 identified 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 $\text{PaCO}_2$ 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 sixteen adult patients underwent total aortic arch replacement with CPB and 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 by COx calculation (n=4) were excluded. Finally, 154 cases were enrolled in this study. A total of 46 (29.9%) patients presented new-onset impaired CA after CPB with MHCA (Figure 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 $\text{rScO}_2$ ($\text{rScO}_2<55\%$) duration, as well as lower mean value of $\text{rScO}_2$ than normal CA patients. There were no differences in temperature, pH, carbon dioxide partial pressure ($\text{PaCO}_2$), arterial oxygen partial pressure ($\text{PaO}_2$), lactate, or hemoglobin between patients with impaired and normal CA during MHCA (Table 2).
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                          | 0.225   |
| **Baseline characteristics**     |                               |                               |         |
| Age (years)                      | 29.3±4.3                      | 25.0±3.7                      | 0.339   |
| BMI (kg/m²)                      | 49.5±11.2                     | 47.2±10.8                     | 0.084   |
| Female, n (%)                    | 6(13.0)                       | 21(19.4)                      | 0.434   |
| Preoperative medication, n (%)   |                               |                               |         |
| β-blockers                       | 12 (26.3)                     | 22 (20.3)                     | 0.472   |
| ACEI                             | 19 (41.3)                     | 38 (35.1)                     | 0.157   |
| CCB                              | 24 (52.1)                     | 43 (39.8)                     | 0.668   |
| Insulin                          |                               |                               |         |
| Creatinine (µmol/L)              | 117.5±121.1                   | 100.6±63.6                    |         |
| 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   |

Values are n (%) or mean ± SD, unless otherwise noted.
| Parameter                             | Impaired autoregulation (n=46) | Normal autoregulation (n=108) | P value |
|--------------------------------------|-------------------------------|-------------------------------|---------|
| Hypertension, n (%)                  | 34 (73.9)                     | 71 (65.7)                     | 0.319   |
| Ejection fraction < 50%, n (%)       | 4 (8.7)                       | 9 (8.3)                       | 0.941   |
| Emergency surgery, n (%)             | 22 (47.8)                     | 37 (35.2)                     | 0.113   |
| **Intraoperative factors**           |                               |                               |         |
| ACP                                  | 7 (15.2)                      | 11 (10.2)                     | 0.374   |
| uACP, n (%)                          | 34 (73.9)                     | 73 (67.6)                     | 0.531   |
| biACP, n (%)                         | 12 (26.1)                     | 35 (32.4)                     | 0.531   |
| Systemic perfusion                   | 62.3±6.3                      | 62.0±7.6                      | 0.893   |
| Trans-femoral artery, n (%)          | 48.0±5.7                      | 51.1±6.7                      | 0.086   |
| Trans-aorta, n (%)                   | 52.0±3.9                      | 53.9±4.6                      | 0.090   |
| MAP (mmHg)                           | 8.1±3.3                       | 10.2±3.5                      | 0.071   |
| Pre-CPB                              | 476.9±100.8                   | 456.6±85.7                    | 0.206   |
| During CPB                           | 257.9±56.2                    | 253.9±73.3                    | 0.754   |
| Post-CPB                             | 144.1±47.9                    | 127.1±48.0                    | 0.136   |
| CVP(cmH₂O)                           | 187.5±49.1                    | 175.7±50.5                    | 0.228   |
| Pre-CPB                              | 37.7±9.1                      | 33.4±9.2                      | 0.008   |
| Post-CPB                             | 6 (31.6)                      | 11 (24.4)                     | 0.604   |
| Operation time (min)                 |                               |                               |         |
| CPB time (min)                       |                               |                               |         |
| Post-CPB time (min)                  |                               |                               |         |
| Cross-clamp time (min)               |                               |                               |         |
| ACP time (min)                       |                               |                               |         |
| RBC infusion, n (%)                  |                               |                               |         |
| Left rScO₂ baseline (%)              | 61.7±4.5                      | 60.9±3.8                      | 0.562   |
| Right rScO₂ baseline (%)             | 59.6±6.2                      | 61.7±4.5                      | 0.167   |
| Left rScO₂ minimum (%)               | 55.3±3.7                      | 55.1±5.6                      | 0.900   |

Values are n (%) or mean ± SD, unless otherwise noted.
| Parameter                                      | Impaired autoregulation (n=46) | Normal autoregulation (n=108) | P value |
|------------------------------------------------|-------------------------------|-------------------------------|---------|
| Right rScO₂ minimum (%)                        | 55.4±4.6                      | 54.9±5.1                      | 0.254   |
| Left rScO₂ mean (%)                            | 57.2±3.6                      | 59.9±5.1                      | 0.041   |
| Right rScO₂ mean (%)                           | 57.6±4.8                      | 60.4±4.3                      | 0.035   |
| Left rScO₂<55% duration (min)                  | 71.5±36.4                     | 33.5±44.2                     | 0.002   |
| Right rScO₂<55% duration (min)                 | 67.6±24.9                     | 33.5±45.3                     | 0.003   |
| Left rScO₂<50% duration (min)                  | 4.6±13.0                      | 7.2±20.8                      | 0.627   |
| Right rScO₂<50% duration (min)                 | 14.5±39.1                     | 11.1±33.8                     | 0.773   |

Values are n (%) or mean ± SD, unless otherwise noted.
### 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<sub>mean</sub> (°C) | 26.5±1.7                      | 26.8±2.2                      | 0.522   |
| Nasopharyngeal T<sub>min</sub> (°C) | 26.3±1.7                      | 26.5±2.3                      | 0.732   |
| Rectal T<sub>mean</sub> (°C)  | 28.1±2.1                       | 28.5±2.0                      | 0.442   |
| Rectal T<sub>min</sub> (°C)  | 27.9±2.0                       | 28.4±1.9                      | 0.407   |
| pH                            | 7.2±0.1                        | 7.2±0.1                        | 0.755   |
| PaCO<sub>2</sub> (mmHg)      | 62.2±13.7                      | 59.6±13.0                      | 0.519   |
| PaO<sub>2</sub> (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<sub>2</sub>, partial pressure of carbon dioxide; PaO<sub>2</sub>, partial pressure of oxygen; BE, base excess

P < 0.05

The variables listed in Table 1 were tested for univariable association with impaired CA (Table 3). On univariate analysis, only those variables including bilateral rScO<sub>2</sub> mean values and durations of bilateral rScO<sub>2</sub><55% were significant. The risk variables with an explanatory P<0.10 at the univariate step were tested with a multivariable analysis. The variables identified in the univariate analysis were tested for intercorrelation. There was a significant correlation between left rScO<sub>2</sub> mean value and right rScO<sub>2</sub> mean value and between left rScO<sub>2</sub><55% duration and right rScO<sub>2</sub><55% duration. We therefore included left rScO<sub>2</sub> mean value and left rScO<sub>2</sub><55% duration in the multivariable models because right side selective cerebral perfusion was mostly performed. After correction for other explanatory factors, left rScO<sub>2</sub><55% duration independently associated with the occurrence of impaired CA.
| Variables                          | Odds Ratio | 95% Confidence Interval | P-value |
|-----------------------------------|------------|-------------------------|---------|
| **Univariate Analysis**           |            |                         |         |
| Age (y)                           | 1.014      | 0.977-1.053             | 0.464   |
| BMI (kg/m²)                       | 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   |
| PaCO₂ (mmHg)                      | 1.015      | 0.972-1.060             | 0.500   |
| Left rScO₂ baseline (%)           | 1.047      | 0.899-1.221             | 0.554   |
| Right rScO₂ baseline (%)          | 0.918      | 0.812-1.039             | 0.178   |
| Left rScO₂ mean (%)               | 1.133      | 1.001-1.282             | 0.047*  |
| Right rScO₂ mean (%)              | 1.158      | 1.013-1.323             | 0.031*  |
| Left rScO₂ minimum (%)            | 0.993      | 0.892-1.103             | 0.898   |
| Right rScO₂ minimum (%)           | 1.066      | 0.955-1.189             | 0.255   |
| Left rScO₂ < 55% duration (min)   | 1.020      | 1.005-1.035             | 0.007*  |
|                                  | 1.019(1.005-1.033) |                | 0.007   |
| Right rScO₂ < 55% duration (min)  | 1.019      | 1.005-1.033             | 0.007*  |
| Left rScO₂ < 50% duration (min)   | 0.991      | 0.957-1.027             | 0.628   |
| Right rScO₂<50% duration (min)    | 1.002      | 0.990-1.014             | 0.770   |
| **Multivariable analysis**        |            |                         |         |
| Left rScO₂ < 55% duration (min)   | 1.016      | 1.002-1.031             | 0.029*  |
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%) (Figure 3).

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 (Table 4). There was no significant difference in hospital stay between the 2 cohort.

### 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*   |
| 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.

### Discussion

In our study, 29.9% of aortic arch surgical patients developed new-onset impaired CA after CPB with MHCA and with a worse outcomes. The occurrence of impaired CA in adult patients undergoing CPB with 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.

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, \( \text{PaO}_2 \), \( \text{PaCO}_2 \), 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 \( \text{PaCO}_2 \) 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 \( \text{PaCO}_2 \) might be detrimental to preserve the function of CA. And this variable was independently associated with impaired CA [1]. In our study, the \( \text{PaCO}_2 \) was higher than normal range. However, there was no significant difference between patients with impaired and normal CA. The high \( \text{PaCO}_2 \) might be related to that we used pH-stat for blood gas management to ensure sufficient cerebral perfusion during MHCA. Although the selective 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].

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 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 indicated that by regulating cerebral perfusion blood flow rate and pressure alone might not avoid the events of rScO\(_2\) lower than 55%. Other methods also should be considered, including raising hematocrit to improve oxygen delivery, maintaining deep hypothermia during the circulatory arrest to suppress cerebral metabolism, and minimizing the duration of HCA. 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 [28]. However, given the nature of our study, we cannot confirm a causative relationship between the prolonged low rScO\(_2\) and impaired CA. In other words, improving cerebral oxygen delivery by the strategies above to reduce occurrence of impaired CA should be tested in randomized controlled trials.

Our results suggested that patients with impaired CA had a higher rate of postoperative delirium, consistent with previous studies in coronary artery bypass grafting or valve surgery under CPB [29, 30]. 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 [29]. The onsets of AKI, respiratory infection, and postoperative death were affected by many factors, including the cardiac function, bleeding, and the duration of mechanical 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 CPB with MHCA. These observations suggested the need to comprehensively monitor patients who undergo CPB and 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 158 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, there is no control group without MHCA in our study. But the occurrence of new-onset impaired CA in patients who underwent CPB and HCA was higher than those who underwent CPB alone in literature. This might reveal that CPB with MHCA increased the risk of new-onset impaired CA. Large prospective studies are needed to understand more about the association between COx value and changes of CA over time during all parts of the aortic arch surgery, and the association between COx and patient outcomes.

**Conclusions**

Our single-site retrospective study showed that prolonged low rScO$_2$ (rScO$_2$ <55%) during aortic arch surgery was closely related to onset of impaired CA. Impaired CA might be associated with the increased rates of postoperative complications and in-hospital mortality.

**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, 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,
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.

Availability of data and materials: The datasets used and analysed during this study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Author’s 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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**Figures**

![Figure 1](image)

**Figure 1**

Examples of regional cerebral oxygen saturation ($rScO_2$), mean arterial blood pressure (MAP) and cerebral oximetry index (COx) recording in a patient with normal cerebral autoregulation (CA) before cardiopulmonary bypass (CPB) with hypothermic circulatory arrest (A) but became impaired after the
procedures (B). Graphs in the top row shows MAP, rScO₂ of left brain (L- rScO₂) and right brain (R-rScO₂) from pre-induction of anesthesia until the end of surgery. Graphs in the middle graph show COx values for left side of brain, and graphs in the bottom row show COx for the right side of brain.

**Figure 2**

Flow chart of patient selection. CPB, cardiopulmonary bypass; HCA, hypothermic circulatory arrest; CA, cerebral autoregulation; NIRS, near-infrared spectroscopy
Figure 3

Receiver operating characteristic curve for the duration of low rScO₂ (rScO₂ <55%) identified as independently associated with impaired cerebral autoregulation. AUC, area under the curve; CI, confidence interval.