Prognostic factors for permanent neurological dysfunction after total aortic arch replacement with regional cerebral oxygen saturation monitoring

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Abstract
Objective: To explore the prognostic factors for permanent neurological dysfunction (PND) after total aortic arch replacement with regional cerebral oxygen saturation (rSO₂) monitoring.

Methods: This retrospective study enrolled 98 type A aortic dissection aneurysm patients who underwent emergency total aortic arch replacement combined with deep hypothermic circulatory arrest and right axillary artery selective antegrade cerebral perfusion (SACP). Data such as age, gender, body mass index, preoperative existing disease, laboratory test results, intraoperative critical operation duration, and intraoperative rSO₂ were collected, and the neurological prognoses in the hospital were recorded and grouped by severity. Multiple logistic regression analysis was performed on the statistically significant differences between the groups to screen the predictors of postoperative neurological complications in these patients.

Results: Forty-two patients had postoperative neurological complications, among which there were 29 cases (29.6%) of transient neurological dysfunction, and 13 cases (13.3%) of PND. Multiple logistic regression results showed that advanced age, preoperative low platelet count, prolonged hemostasis time and lowest relative rSO₂ to baseline (ΔrSO₂min) in each time period were risk factors for postoperative PND. The ROC curve measurement showed that the optimal cut-off value of ΔrSO₂min was 79.7%, and the area under the curve was 0.708 (95% confidence interval = 0.557–0.858), p = 0.016; the optimal cut-off value of ΔrSO₂min in SACP was 81.6%, and the area under the curve was 0.720 (95% confidence interval = 0.570–0.870), p = 0.011; the optimal cut-off value of ΔrSO₂min in cardiopulmonary bypass (CPB) was 80.8%, and the area under the curve was 0.697 (95% confidence interval = 0.554–0.840), p = 0.023.

Conclusion: Intraoperative ΔrSO₂min that is lower than the basal level of about 80%, advanced age, preoperative low platelet count, and prolonged hemostasis time are predictors of PND after total aortic arch replacement.
1 | INTRODUCTION

Total aortic arch replacement with a long duration and complicated operation has a great chance of postoperative complications of various systems. Factors such as ischemia, hypoxia, reperfusion injury, and internal environment disturbance caused by deep hypothermic circulatory arrest (DHCA) during surgery may lead severe damage to central nervous system. Disturbance of consciousness, paresthesia, physical activity disorder, and cognitive impairment are common injuries, and these permanent neurological complications will decrease the quality of life significantly (Minakawa et al., 2010). These difficult complications always confuse clinicians.

Currently, the significance of brain function monitoring during the cardiovascular surgeries is still unclear (Serraino & Murphy, 2017; Zheng et al., 2013). Near-infrared spectroscopy (NIRS) is a technique used for percutaneous monitoring of regional cerebral oxygen saturation ($rSO_2$), which can reflect the oxygen supply and demand balance of brain tissue in a noninvasive, real-time and continuous manner (Jobsis, 1977); it has been applied to monitor perioperative brain function. Some studies have suggested that $rSO_2$ is associated with the prognosis such as postoperative mortality (Hansen et al., 2013), stroke (Tournay-Jette et al., 2011), delirium (Khazi, Al-Safadi, Al, & Aljassim, 2018), cognitive dysfunction (Kakihana et al., 2012), and extended hospital stay (Goldman, Sutter, Ferdinand, & Trace, 2004) of some cardiac surgeries such as coronary artery bypass surgery or valve replacement surgery. However, the range of optimal $rSO_2$ is still lacking.

In this study, Stanford type A aortic dissection patients undergoing emergency total aortic arch replacement were studied, whose correlation between various factors of perioperative surgery including intraoperative $rSO_2$ changes and postoperative neurological complications were analyzed to search for correctable risk factors and to verify the predictive value of $rSO_2$ for neurological prognosis in such surgeries, to provide more references for the clinical practice of predicting and improving the neurological prognosis after total arch replacement.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This is a retrospective study of 98 patients who underwent total aortic arch replacement in our hospital between 2013 and 2015. Inclusion criteria: (a) acute Stanford type A aortic dissection; (b) aged from 20 to 74, male or female; (c) emergency surgery; and (d) intraoperative monitoring of patients with INVOS 4100 NIRS monitor (Somanetics, USA) for bilateral $rSO_2$. Exclusion criteria: (a) noninitial cardiac surgery or preoperative aortic stent implanted; (b) preoperative neurological injury, based on symptoms, signs, and imaging data; (c) preoperative renal insufficiency with dialysis indications; and (d) uncooperative mental abnormalities.

2.2 | Anesthesia and operation protocol

After heparinization, the patients were underwent unilateral femoral artery and right axillary artery cannula, followed by cardiopulmonary bypass (CPB) and total body hypothermia. Cold blood cardioplegia with elevated potassium concentration was infused directly into both the coronary arteries. After cooling down to standard (nasal pharyngeal temperature 18–20°C, bladder temperature 22–25°C), DHCA was started, and unilateral selective antegrade cerebral perfusion (SACP) was performed through the right axillary artery. Triple-branched stent graft implantation technique was applied in all of the surgeries. The lower aortic circulation was restored after anastomosing the opening and the stent proximal end of the descending aortic. Branches of artificial and left subclavian artery, left common carotid artery were anastomosed successively, and distal circulation was restored and began rewarming. Innominate artery and branch of artificial graft were anastomosed. The CPB was routinely terminated, and hemostasis and chest closure were performed.

Anesthesia was performed using intravenous anesthesia combined with inhalation anesthesia, including propofol, sevoflurane, sufentanil, dexmedetomidine and rocuronium. From the start of CPB, ice packs were placed around the head of patients until the start of rewarming. During the hemostasis period, the systolic blood pressure was controlled at 60–90 mmHg (1 mmHg = 0.133 kPa), and Hb ≥ 8.0 g/L and HCT ≥ 24% were maintained. The NIRS monitor was used to monitor the bilateral forehead $rSO_2$. The patients were transferred to ICU with trachea cannula.

2.3 | Data collection and definition

Patients’ information including age, sex, body mass index, preoperative comorbidities and laboratory findings, $rSO_2$ at various key steps during surgery, postoperative mortality and neurological complications were collected. All data recordings were cut-off at discharge. The prognosis of the nervous system was recorded in terms of clinical symptoms and signs by a fixed attending neurologist, which were divided into the following three types according to duration and severity: nonneurological dysfunction (NND), no obvious
neurological damage manifestation on clinical observation; transient neurological dysfunction (TND), postoperative neurological deficit that include conscious disturbances (including coma, lethargy, paralysis, etc.), sensory or motor impairment, and complete disappearance of all neurological damage symptoms before discharge; permanent neurological dysfunction (PND), postoperative neurological deficits that include new onset of coma, sensory or motor impairment, and any neurological damage symptoms that did not completely disappear before discharge.

2.4 | Statistical analysis

All data were statistically analyzed using SPSS 22.0 (International Business Machines Corporation, USA) software. Multiple sets of independent quantitative data were analyzed using analysis of variance (ANOVA) and LSD-t multiple test, and the categorical data were analyzed using chi-square test. The variables were screened by single factor analysis, and p < 0.1 was set as the significant difference. Logistic regression analysis was used to analyze the correlation between the selected variables and the dependent variables. p < 0.05 was set as the significant difference. The best cut-off value was determined using ROC curve.

The statistics related to the rSO₂ variables were defined as follows:

- rSO₂ basal value (%): stable rSO₂ reading that was observed 2 min at each side of forehead after induction of anesthesia.
- Relative rSO₂ (ΔrSO₂, %) = 100% × rSO₂ at each time point/rSO₂ basal value.
- The lowest value of rSO₂: the lowest value of rSO₂ observed in each time period and lasted for more than 3 min.
- Relative rSO₂ lowest value (ΔrSO₂ min, %) = 100% × rSO₂ lowest value/rSO₂ basal value.

3 | RESULTS

There were 98 patients enrolled in our study, the average age was 50.41 ± 11.38 years old, and the mean BMI was 24.31 ± 3.35. The mean operative time was 340.03 ± 66.90 min, the mean SACP time was 38.18 ± 12.05 min, the mean CPB time was 167.39 ± 34.63 min, and the mean hemostasis time (starting from infusion of protamine to the beginning of the chest closure) was 111.96 ± 28.88 min. The average reading of bilateral basal rSO₂ was 66.21 ± 9.87%, and the average intraoperative ΔrSO₂ min was 78.74 ± 14.11%. Postoperative all-cause mortality and neurological prognosis were shown in Table 1. Forty-two patients experienced postoperative neurological complications (including sensory, motor and/or disturbance of consciousness), among which 29 cases (29.6%) were TND, and 13 cases (13.3%) were PND.

Univariate analysis was performed using one-way ANOVA and LSD-t multiple test for continuous variables, and chi-square test for categorical variables between the NND group, TND group and PND group. The results showed that the preoperative platelet counts were lower in the NND group than in the other two groups. The proportion of males in the TND group was higher than that in the NND group. The hemostasis time in the PND group was longer than that in the NND group. The age of the PND group was higher than the other two groups. The ΔrSO₂ min indexes in the PND group during the whole operation, the SACP, the CPB and the hemostasis were lower than that in the other groups (p < 0.1, Table 2).

Multiple logistic regression was further used to analyze the effects of gender, age, preoperative platelet count, hemostasis time, intraoperative ΔrSO₂ min, ΔrSO₂ min in SACP, ΔrSO₂ min in CPB, and ΔrSO₂ min during hemostasis on NND, TND and PND (Tables 3 and 4). The results showed that age, preoperative platelet count, hemostasis time and ΔrSO₂ min were risk factors for postoperative PND. Compared with NND, patients with preoperative low platelet count, prolonged hemostasis time and decreased ΔrSO₂ min in each time period were more likely to experience postoperative PND. Compared with TND, patients with advanced age and decreased ΔrSO₂ min in each time period were more likely to experience postoperative PND. Each factor had no effect on the difference between the TND and NND groups.

The ROC curve was used to measure the ΔrSO₂ min in each time period to predict the cut-off value of PND occurring after total arch replacement. The results suggested that the optimal cut-off value of ΔrSO₂ min for intraoperative PND was 79.7%, the area under the curve was 0.708 (95% confidence interval = 0.557–0.858), p = 0.016; the optimal cut-off value of ΔrSO₂ min in SACP was 81.6%, the area under the curve was 0.720 (95% confidence interval was 0.570–0.870), p = 0.011. The optimal cut-off value of ΔrSO₂ min in CPB was 80.8%, the area under the curve was 0.697 (95% confidence interval is 0.554–0.840), p = 0.023 (Table 5; Figure 1).

### TABLE 1 Overall neurologic outcomes

| Outcome                  | No. (%) |
|--------------------------|---------|
| All-cause mortality      | 15 (15.3) |
| Neurological dysfunction |         |
| NND                      | 56 (57.1) |
| TND                      | 29 (29.6) |
| PND                      | 13 (13.3) |
| Motor or sensory disorder|         |
| Temporary disorder       | 7 (7.1) |
| Permanent disorder       | 8 (8.2) |
| Consciousness disorder   |         |
| Temporary disorder       | 33 (33.7) |
| Permanent disorder       | 3 (3.1) |
| Consciousness outcome    |         |
| Clear consciousness      | 62 (63.3) |
| Delirium                 | 21 (21.4) |
| Lethargy                 | 3 (3.1) |
| Coma                     | 12 (12.2) |

Abbreviations: NND, nonneurological dysfunction; TND, transient neurological dysfunction; PND, permanent neurological dysfunction.
DISCUSSION

Total aortic arch replacement is technically difficult, and it directly involves the anastomosis of blood vessels in both head and neck. Central nervous system injury and brain function protection are always the focus of research in various cooperative disciplines. During the operation, when the autologous blood vessel and artificial blood vessel are anastomosed at the beginning of the descending aorta, the systemic blood supply must be suspended to expose the surgical field. Even with cerebral blood perfusion combined with deep hypothermia and local vascular (often radial or innominate) cannula, its neurological complications are still much higher than other cardiac surgeries (Shelstad, Reeves, Yamanaka, & Reece, 2016). In animal models, it has been found that DHCA can significantly reduce mitochondrial respiratory chain complex 1 and increase reactive oxygen species. Cerebral ischemia indexes (lactic acid/pyruvate ratio) which increase during following subsequent warming may be one of the mechanisms leading to impaired brain function (Mavroudis et al., 2018). Stanford type A aortic dissection is the most common disease requiring total arch replacement that is usually complicated by hypertension, atherosclerosis or Marfan syndrome. Clinically, these conditions are critical and always need emergent operations (Settepani, 2016).

| Variable                  | NND (n = 56) | TND (n = 29) | PND (n = 13) | p-Value |
|---------------------------|--------------|--------------|--------------|---------|
| Male                      | 38 (67.9%)   | 26 (89.7%)   | 10 (76.9%)   | 0.085   |
| Age (years)               | 50.48 ± 10.6 | 47.52 ± 12.83| 56.54 ± 9.32| 0.058   |
| BMI (kg/m²)               | 24.42 ± 3.54 | 24.27 ± 3.16 | 23.95 ± 3.07| 0.902   |
| Marfan Syndrome           | 8 (14.3%)    | 3 (10.3%)    | 0 (0.0%)     | 0.165   |
| Hypertension              | 40 (71.4%)   | 22 (75.9%)   | 11 (84.6%)   | 0.605   |
| Diabetes                  | 6 (10.7%)    | 5 (17.2%)    | 2 (15.4%)    | 0.686   |
| LVEF (%)                  | 61.13 ± 15.86| 60.38 ± 18.80| 59.69 ± 18.49| 0.956   |
| NT-proBNP(pg/ml)          | 437.82 ± 715.29| 544.10 ± 690.21| 465.16 ± 667.79| 0.803   |
| Hb (g/L)                  | 124.02 ± 16.39| 129.24 ± 17.77| 130.15 ± 16.39| 0.277   |
| WBC (×10⁹/L)              | 10.76 ± 14.59| 9.99 ± 4.66 | 12.52 ± 4.10 | 0.804   |
| PLT (×10⁹/L)              | 231.68 ± 95.14| 197.90 ± 58.04| 158.62 ± 65.01| 0.011   |
| Alb (g/L)                 | 37.54 ± 6.28 | 40.38 ± 5.17 | 39.38 ± 6.74 | 0.112   |
| ALT (U/L)                 | 33.46 ± 36.58| 39.41 ± 79.87| 30.17 ± 23.83| 0.838   |
| AST (U/L)                 | 29.88 ± 17.80| 35.03 ± 71.45| 54.00 ± 64.66| 0.274   |
| BUN (mmol/L)              | 8.03 ± 1.87  | 6.57 ± 5.22  | 6.42 ± 1.67  | 0.312   |
| Scr (µmol/L)              | 83.23 ± 27.24| 90.93 ± 43.77| 78.77 ± 25.83| 0.458   |
| INR                       | 1.21 ± 1.66  | 0.98 ± 0.21  | 1.00 ± 0.32  | 0.691   |
| Mean rSO₂ basal value     | 64.34 ± 8.84 | 67.05 ± 12.01| 62.23 ± 8.55 | 0.295   |
| ΔrSO₂/min (%)             | 79.37 ± 12.03| 82.62 ± 12.88| 67.38 ± 19.51| 0.004   |
| Throughout operation      | 90.00 ± 17.77| 94.99 ± 15.61| 76.95 ± 19.71| 0.010   |
| During SACP               | 80.76 ± 12.67| 84.79 ± 12.62| 70.67 ± 18.49| 0.009   |
| During hemostasis         | 89.53 ± 12.47| 89.96 ± 20.23| 78.89 ± 16.78| 0.086   |
| Intraoperative factors    |              |              |              |         |
| LNT in DHCA(°C)           | 18.79 ± 1.34 | 18.28 ± 1.14 | 19.02 ± 1.17 | 0.122   |
| Surgery time (min)        | 333.46 ± 67.79| 343.48 ± 67.70| 360.62 ± 60.16| 0.401   |
| SACP time (min)           | 36.86 ± 11.71| 39 ± 13.54   | 42.08 ± 9.55 | 0.342   |
| CPB time (min)            | 165.38 ± 34.54| 172.31 ± 39.35| 165.08 ± 22.99| 0.664   |
| Hemostasis time (min)     | 107.32 ± 29.15| 114.86 ± 26.01| 126.23 ± 29.71| 0.083   |

Abbreviations: NND, nonneurological dysfunction; TND, transient neurological dysfunction; PND, permanent neurological dysfunction; BMI, body mass index; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; Hb, hemoglobin; WBC, white blood cell count; Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Scr, serum creatinine; INR, international normalized ratio; SACP, selective antegrade cerebral perfusion; CPB, cardiopulmonary bypass; LNT, lowest nasopharyngeal temperature; DHCA, deep hypothermic circulatory arrest. Values are presented as the mean ± SD or number (percentage).

Table 2 Preoperative demographics, patient-related factors, laboratory variables and characterizing intraoperative factors in patients with NND, TND or PND

aLSD test was used for post hoc analysis.
In our study, it was found that the optimal cut-off value of ΔrSO_2 for predicting PND in all operation steps was about 80% of the baseline value (Table 5). AUC was about 0.7, and the fit was good, which may be related to the PND sample size that was only 13 cases. Olsson and Thelin (2006) conducted a similar study, which included and observed changes in rSO_2 during SACP in 46 patients undergoing aortic arch surgery, suggesting that the range of 76%–86% of rSO_2 in the SACP process has a suggestive effect on postoperative stroke. Schön et al. (2009) suggested that the incidence of postoperative stroke was higher in the DHCA + arch surgery with rSO_2 <80% baseline value than in the control group. Another study (Fischer et al., 2011) reported that an rSO_2 reading <65% was associated with severe complications after arch surgery, with a stroke rate of 3/30 (10%). Combining the results of this study and previous studies, it is believed that intraoperative ΔrSO_2 decline is associated with postoperative central nervous system complications. Compared with previous studies, this study focused on type A dissection emergency surgery, and stratified analysis results based on neurological prognosis severity: ΔrSO_2 <80% is more strongly correlated with PND than TND, and it is suggested that monitoring ΔrSO_2 in such surgeries can be used to predict severe neurological complications.

It is found in this study that advanced age is associated with postoperative PND, which is clearly associated with decreased functional reserve in older patients. Also, preoperative low platelet count and prolonged hemostasis time are associated with PND. Interestingly, platelet count in the PND group (158.62 ± 65.01 × 10^9/L) was not below normal but significantly lower than in the TND and NND groups. This may be due to the fact that preoperative basal vasculopathy was severe in patients with PND, leading to platelet activation conducted a similar study, which included and observed changes in rSO_2 during SACP in 46 patients undergoing aortic arch surgery, suggesting that the range of 76%–86% of rSO_2 in the SACP process has a suggestive effect on postoperative stroke. Schön et al. (2009) suggested that the incidence of postoperative stroke was higher in the DHCA + arch surgery with rSO_2 <80% baseline value than in the control group. Another study (Fischer et al., 2011) reported that an rSO_2 reading <65% was associated with severe complications after arch surgery, with a stroke rate of 3/30 (10%). Combining the results of this study and previous studies, it is believed that intraoperative ΔrSO_2 decline is associated with postoperative central nervous system complications. Compared with previous studies, this study focused on type A dissection emergency surgery, and stratified analysis results based on neurological prognosis severity: ΔrSO_2 <80% is more strongly correlated with PND than TND, and it is suggested that monitoring ΔrSO_2 in such surgeries can be used to predict severe neurological complications.

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and consumption. On the other hand, CPB itself causes coagulation factor dilution, blood clot formation disorders, fibrinogen dysfunction, platelet dysfunction, platelet destruction, or fibrinolysis, which is one of the important reasons for the difficulty in stopping bleeding in the surgical field post-CPB (Ranucci, 2015). Low temperature during DHCA further inhibits platelet function and aggravates coagulation factor dilution by prolonging CPB time (Hanna et al., 2016). Therefore, patients with normal preoperative coagulation function often experience coagulopathy during hemostasis after CPB. The controlled hypotension used in combination with surgical hemostasis reduce systemic organ perfusion including brain tissue, and low-level brain tissue oxygen supply for a long time shows low levels of ΔrSO₂, which may be the one of the reasons for postoperative PND. Perhaps the use of point of care platelet counts and functional monitoring in such surgeries can help early detection and correction platelet count or function disorders after CPB to decrease the time of hemostasis and controlled hypotension.

The study still has the following shortcomings. It was a single-center retrospective study, and data collection was inevitably biased. In addition, the intraoperative rSO₂ data collected were characteristic rather than continuous, which might be inaccurate with the real situation and mask some actual correlations, requiring further studies.

In summary, low ΔrSO₂ min during all stages of surgery (the whole surgery, CPB, SACP, and hemostasis), advanced age, preoperative low platelet count, and prolonged hemostasis time are all predictors of PND after thoracic aortic total arch replacement. For elderly patients, positive correction of the platelet count perioperatively,
positive correction and maintenance of $\Delta rSO_2$ higher than 80% of the baseline value intraoperatively may effectively reduce postoperative PND and improve postoperative quality of life.

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AUTHOR CONTRIBUTIONS

YY, YL, and GK formulated the design of the study, carried out the execution and analysis of the study, and drafted the manuscript. LJ, LX, HW, and YR were involved in data collection.

ETHICAL APPROVEMENT

This study was approved by the hospital ethics committee. Approval number: B2016-128, Zhongshan Hospital, Fudan University, Shanghai, China.

DATA AVAILABILITY STATEMENT

All original data will be available when you contact the correspondence author.

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