Comparison of neurocognitive results after coronary artery bypass grafting and thoracic aortic surgery using retrograde cerebral perfusion

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Abstract

Objective: Retrograde cerebral perfusion (RCP) is used as an adjunctive method to hypothermic circulatory arrest to enhance cerebral protection in patients undergoing thoracic aortic surgery. It remains unclear whether RCP provides improved neurological and neuropsychological outcome.
Methods: Forty-six patients undergoing thoracic aortic surgery using RCP, and 28 undergoing coronary artery bypass grafting (CABG; \( n = 28 \)) with CPB, were enrolled in the study. Patients receiving RCP were subdivided into two groups, those with less than 60 min of RCP (S-RCP; \( n = 27 \)) and with 60 min or more (L-RCP; \( n = 19 \)). The patients’ neurocognitive state was assessed by the revised Wechsler Adult Intelligence Scale a few days before operation, at 2–3 weeks and 4–6 months after operation.
Results: There were no stroke, seizure, and hospital mortality in either group. Significant decline between baseline and early scores were seen in three subtests (digit span, arithmetic, and picture completion) for S-RCP and four (digit span, arithmetic, picture completion, and picture arrangement) for L-RCP. Significant decline between baseline and late scores were seen in one subtest (arithmetic) for S-RCP, four (digit span, arithmetic, picture completion, and picture arrangement) for L-RCP, and one (object assembly) for CABG. The mean change of scores for one late test (digit symbol) was significantly lower in S-RCP than in CABG. The mean change of scores for three early tests (digit span, vocabulary, and picture arrangement) and four late tests (information, digit span, picture completion, and picture arrangement) were significantly lower in L-RCP than in CABG. Stepwise logistic regression analysis disclosed that, after considering the other variables, significant difference in test score changes were observed between CABG and L-RCP for two early tests (picture completion and digit symbol) as well as for three late tests (digit span, similarities, and picture completion). None of test score changes showed significant difference between CABG and S-RCP.
Conclusions: The neurocognitive outcome in patients undergoing RCP less than 60 min were comparable with patients undergoing CABG without circulatory arrest. Prolonged RCP of 60 min or more in patients undergoing surgery of the thoracic aorta was associated with postoperative neurocognitive impairment.

Keywords: Neurocognitive function; Retrograde cerebral perfusion; Hypothermic circulatory arrest; Thoracic aortic surgery; Brain protection

1. Introduction

Although there have been remarkable progress in the results of surgery for thoracic aortic aneurysm—including those of the arch—in recent years, cerebral complications remain a major formidable problem. The purpose of this study was to compare the neurological and neurocognitive outcome in patients undergoing thoracic aortic surgery using RCP with those in patients undergoing coronary artery bypass grafting (CABG) using cardiopulmonary bypass (CPB).

2. Materials and methods

2.1. Patient

Out of a consecutive series of 58 patients admitted to elective thoracic aortic operations via median sternotomy using RCP at the Department of Cardiothoracic Surgery, Tokyo University, 46 patients were enrolled in the study. Exclusion criteria included age over 75, previous stroke, transient ischemic attack, reversible neurological attack, or previous psychiatric disorder. Patients receiving RCP were subdivided into two groups, those with less than 60 min of RCP (S-RCP; \( n = 27 \)) and those with 60 min or more of RCP (L-RCP; \( n = 19 \)). This cutoff value was chosen for the following reasons: (1) it nearly represents the mean RCP time (56 min) in this cohort of patients; (2) on review of the pilot data, it represented the point above which neurocognitive disorder became more prevalent.
Out of consecutive 35 patients undergoing elective coronary artery bypass grafting using cardiopulmonary bypass in the same period of time, 28 patients (CABG; n=28) were also included in the study. Exclusion criteria were same as above. We included a control group of CABG patients to negate the practice effects on longitudinal testing for neurocognitive function, anesthesia, and cardiopulmonary bypass. However, because a group of non-operated patients who underwent serial neurocognitive assessment were not included in the study, the practice effect and the effects of anesthesia alone on neurocognitive scores are not corrected.

Although this study was designed prospectively, the analysis of the data was performed as a non-randomized retrospective cohort fashion, because the duration of RCP could be known only postoperatively and therefore the inclusion of the patients undergoing RCP was made only retrospectively.

3. Methods

3.1. Anesthesia

Anesthesia was induced intravenously with fentanyl (5 μg/kg) and midazolam (0.1 mg/kg). Tracheal intubation was performed after pancuronium (0.1 mg/kg). Anesthesia was maintained by a low dose (0.5-1%) of sevoflurane, and additional doses of fentanyl (5 μg/kg) were given.

3.2. Surgical technique

3.2.1. RCP group

The heart, ascending aorta, aortic arch, and arch vessels were exposed through a median sternotomy and left supraclavicular incision. After systemic heparinization, extracorporeal circulation was established with an arterial cannula placed either in the ascending aorta or the femoral artery, and bicaval cannulae through the right atrium for venous return. The left side of the heart was vented through the right superior pulmonary vein.

Core cooling was continued until a rectal temperature or a tympanic temperature of 18 °C or less was obtained. The systemic circulation either from the ascending aorta or the femoral artery was arrested and the ascending aorta or the aortic arch was incised. Myocardial protection was provided with antegrade blood cardioplegia perfused through a balloon catheter placed in the ascending aorta.

After a brief period of circulatory arrest, the CPB bypass circuit was opened and cold oxygenated blood was perfused through the superior vena caval cannula, at a rate of 300-500 ml/min, to keep the central venous pressure between 15 and 25 mmHg. The arterial and inferior vena caval cannulae were clamped during the RCP period.

The descending aorta was transected either just below the origin of the left subclavian artery or distal to the descending aortic aneurysm. Obliteration of the distal false lumen in the descending aorta was performed if necessary. The distal part of the four-limbed vascular graft was anastomosed to the descending aorta. Then the left subclavian and the left common carotid arteries were sutured to each limb of the graft in succession. After the proximal graft was cross-clamped, retrograde cerebral perfusion was interrupted and antegrade systemic perfusion with rewarming through the fourth limb attached to the graft was instituted. Then, the brachiocephalic artery was anastomosed to the last limb. After the proximal graft was anastomosed to the ascending aorta, the aorta and the vascular graft were carefully filled with blood and coronary circulation was restarted. The fourth limb that was used for antegrade systemic perfusion was resected after termination of extracorporeal circulation.

3.2.2. CABG group

Coronary artery bypass grafting was performed using standard cardiopulmonary bypass technique. Patients were hypothermic at 28 °C. The distal anastomosis, preceding the proximal anastomosis, was performed during aortic cross clamping. A tangential occluder was used on the aorta during the proximal anastomosis. Antegrade cardioplegia was intermittently administered in the ascending aorta and the anastomosed vein grafts.

In both groups, cardiotomy suction was used during operation. Autotransfusion was not performed after operation.

3.3. Clinical and neurocognitive assessments

Each patient’s neurological and neuropsychological state was assessed a few days before the operation, 2-3 weeks after the operation, and 4-6 months after the operation. A well-trained psychologist, blinded to the surgical treatment, performed the neurocognitive tests in a standardized manner. We subjected the patients to a battery of core tests that covered memory, language, psychomotor speed, attention, and concentration. This consisted of 11 neuropsychological tests taken from the revised Wechsler Adult Intelligence Scale (WAIS-R), which are accepted tests of global cognitive function. The tests were presented in a fixed order according to conventional practice, and the scores were arranged such that larger scores indicated better neuropsychological performance.

The protocol of this study was approved by the Research Committee, University of Tokyo. Each patient consented to a 11-part psychological examination.

3.4. Statistical analysis

Basic characteristics of each study group, demographic and peri-operative factors, which could reportedly affect neurocognitive performance, were first examined, along with the results of WAIS-R test scores. Based on the means and standard deviations of the test scores obtained preoperatively for each group, Z-scores were calculated, and the difference in test scores between baseline and early/late scores were obtained. Then, the significance of these differences was tested by Wilcoxon matched-paired signed rank tests. The significance of difference between groups in test score changes between baseline and early/late scores were compared by Wilcoxon rank sum tests. Significance levels were adjusted for multiple comparison by Bonferroni’s method.
Significance of difference between CABG and early/late RCP groups: *, between short and long RCP groups: **, between short RCP and CABG: ***

<table>
<thead>
<tr>
<th>Subject characteristics and baseline test scores</th>
<th>CABG (n=28)</th>
<th>Short RCP (n=27)</th>
<th>Long RCP (n=19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>65.0±11.1 (32.75)</td>
<td>65.1±12.2 (29.75)</td>
<td>63.3±10.0 (43.74)</td>
</tr>
<tr>
<td>Sex (m/f)</td>
<td>21/7</td>
<td>20/7</td>
<td>15/4</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>17(61)</td>
<td>15(56)</td>
<td>10(52)</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>12(43)</td>
<td>2(7)**</td>
<td>1(5)**</td>
</tr>
<tr>
<td>Carotid disease (%)</td>
<td>3(11)</td>
<td>2(7)</td>
<td>1(5)</td>
</tr>
<tr>
<td>Myocardial infarction (%)</td>
<td>12(36)</td>
<td>2(7)**</td>
<td>0(0)**</td>
</tr>
<tr>
<td>Aortic lesions (dissection/non-dissection)</td>
<td></td>
<td>4/23</td>
<td>3/16</td>
</tr>
<tr>
<td>Extent of repair (Aortic arch/Acst&amp;hemiaarch)</td>
<td>7/20</td>
<td>2/17</td>
<td></td>
</tr>
<tr>
<td>Pump time (min)</td>
<td>180.8±54.3 (95-314)</td>
<td>229.1±87.7 (120-423)</td>
<td>238.8±37.9 (150-300)**</td>
</tr>
<tr>
<td>Acc time (min)</td>
<td>91.4±38.9 (37-220)</td>
<td>117.0±52.1 (45-232)*</td>
<td>144.7±42.8 (60-224)**,+</td>
</tr>
<tr>
<td>Rcp time (min.)</td>
<td></td>
<td>43.5±10.5 (23-57)</td>
<td>71.1±8.3 (60-90)+ + +</td>
</tr>
<tr>
<td>Rectal temp (°C)</td>
<td>26.4±1.7 (20.4-29.4)</td>
<td>18.8±1.8 (16-22)**</td>
<td>17.9±2.0 (16-21.2)**</td>
</tr>
<tr>
<td>Wakeup time (h)</td>
<td>5.1±2.4 (2.9)</td>
<td>7.1±4.2 (2.24)***</td>
<td>14.4±5.9 (4.24)***, + + +</td>
</tr>
<tr>
<td>Post-op respirator (h)</td>
<td>9.5±4.6 (3-24)</td>
<td>13.8±3.9 (7-20)***</td>
<td>24.1±16.4 (8-86)****, + + +</td>
</tr>
<tr>
<td>Icu stay (day)</td>
<td>2.3±1.4 (1-6)</td>
<td>2.7±1.8 (1-7)</td>
<td>5.8±2.7 (1-15)***, + + +</td>
</tr>
<tr>
<td>Hospital stay (day)</td>
<td>23.5±7.0 (12-32)</td>
<td>23.6±3.7 (16-30)</td>
<td>29.7±8.0 (21-55)**, + +</td>
</tr>
<tr>
<td>Mean cardiac-index postop (l/m²)</td>
<td>3.1±0.8 (2.2-4.5)</td>
<td>3.3±0.9 (2.3-4.7)</td>
<td>3.1±0.1 (2.0-4.8)</td>
</tr>
</tbody>
</table>

Initial (baseline) test scores

Information                                           | 11.7±3.0 (6-15) | 12.9±1.9 (11-18) | 12.8±2.4 (11-18) |
Digit span                                           | 14.1±3.5 (7-19) | 14.4±2.5 (11-18) | 14.4±2.0 (11-17) |
Vocabulary                                           | 11.6±2.2 (6-14) | 11.9±2.8 (6-19) | 12.5±1.7 (10-15) |
Arithmetic                                           | 12.2±3.9 (6-19) | 13.7±2.7 (17-6)** | 13.8±1.7 (11-16)** |
Comprehension                                        | 12.6±2.8 (7-17) | 12.5±1.7 (10-17) | 12.1±2.4 (8-17) |
Similarities                                          | 13.2±3.0 (7-19) | 13.9±2.4 (9-17) | 14.2±1.8 (11-18) |
Picture completion                                   | 11.7±2.8 (6-17) | 11.7±2.0 (6-14) | 11.2±2.9 (7-15) |
Picture arrangement                                  | 11.1±2.6 (5-15) | 12.5±2.3 (7.16)** | 12.6±2.1 (9-15)** |
Block design                                          | 12.2±2.6 (8-18) | 12.4±2.1 (9-17) | 13.0±1.8 (11-18) |
Object assembly                                       | 13.4±2.5 (8-17) | 13.3±1.8 (11-16) | 13.3±1.6 (11-17) |
Digit symbol                                          | 12.0±3.2 (6-19) | 12.2±2.6 (6-16) | 12.1±1.4 (9-16) |

Significance of difference between CABG and early/late RCP groups: *, $P<0.05$; **, $P<0.01$; ***, $P<0.001$ (Wilcoxon rank sum tests). Significance of difference between short and long RCP groups: +, $P<0.05$; ++, $P<0.01$; +++, $P<0.001$ (Wilcoxon rank sum tests). ACC, aortic cross clamp; ASC: ascending aorta.

To find out the set of variables which could best predict the decline in neuropsychological performance, stepwise regression analysis was conducted with the difference in test scores as dependent variables, and the possible predictive factors listed in Table 1, along with dummy variables indicating groups (S-RCP and L-RCP vis-a-vis CABG-group), as independent (explanatory) variables. Those independent variables were entered and removed in a stepwise fashion at the P-level of 0.05, to best predict the dependent variables. All the statistical analysis was done using STATA version 8.1 (Stata Corporation, Texas, USA).

### 4. Results

Basic characteristics of study subjects, demographic and peri-operative factors, which could reportedly affect neuropsychological performance, are presented in Table 1. Baseline scores of WAIS-R test are also presented in raw scores. With the exception of a higher incidence of myocardial infarctions and diabetes in the CABG patients, there was no significant difference between groups with respect to preoperative variables. There were no difference in the cause of aortic aneurysm and the extent of aortic repair between S-RCP and L-RCP patients.

In the CABG group, 6, 15, 7 patients underwent coronary artery bypass grafting for 2, 3, 4 grafts, respectively. In the RCP group, concomitant operative procedures, other than the repair of the aortic arch, included coronary artery bypass grafting in eight (S-RCP=2, L-RCP=6), aortic root replacement in two (L=2), aortic valve replacement in two (S=1, L=1), mitral valve replacement in one (L=1), repair of aortic dissection in six (S=4, L=2), stent-graft insertion in three (S=3), redo aortic surgery in three (L=3), and minimally invasive approach in one patient (S=1).

The duration of cardiac ischemia was significantly shorter in CABG than either in S-RCP or L-RCP. Time to wake up, extubation, ICU discharge and hospital discharge were significantly longer in L-RCP than in CABG or S-RCP. There was no hospital mortality in either group. None suffered a stroke or seizure, including by electroencephalogram.

Postoperative major complications other than neurological disorders included postoperative bleeding in three (CABG=2, S-RCP=1), transient atrial fibrillation in five (CABG=5), respiratory failure in four (S-RCP=2, L-RCP=2), acute renal failure in one (L-RCP=1), gastrointestinal bleeding in two (CABG=1, S-RCP=1), mediastinitis in one (CABG=1), and temporary hoarseness in two (S-RCP=2) of the patients.

All of the 74 patients underwent the neurocognitive tests preoperatively and 2-3 weeks after operation, before discharge from the hospital. Finally, 68 patients (CABG=25, S-RCP=26, L-RCP=17) were tested 4-6 months after operation at the outpatient follow-up visit.

The difference in mean Z-scores between baseline and early/late scores are presented in Table 2. These data are organized according to patient group (CABG, S-RCP, L-RCP), neurocognitive tests (Information, Digit Span, Vocabulary,
Table 2
Difference in scores between baseline and early/late tests

<table>
<thead>
<tr>
<th></th>
<th>CABG group</th>
<th>Short RCP</th>
<th>Long RCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Information</td>
<td>.79 ± 1.66##</td>
<td>.56 ± 2.52</td>
<td>.42 ± 2.69</td>
</tr>
<tr>
<td>Digit span</td>
<td>-.21 ± 2.06</td>
<td>-.93 ± 2.23#</td>
<td>-.163 ± 2.17##</td>
</tr>
<tr>
<td>Vocabulary</td>
<td>.86 ± 1.86##</td>
<td>.11 ± 2.45</td>
<td>-.47 ± 2.01*</td>
</tr>
<tr>
<td>Arithmetic</td>
<td>-.29 ± 2.12</td>
<td>-.85 ± 1.13#</td>
<td>-.95 ± 1.39##</td>
</tr>
<tr>
<td>Comprehension</td>
<td>.071 ± 2.34</td>
<td>.26 ± 2.18</td>
<td>-.53 ± 1.98</td>
</tr>
<tr>
<td>Similarities</td>
<td>-.11 ± 2.92</td>
<td>-.26 ± 2.38</td>
<td>-.90 ± 1.91</td>
</tr>
<tr>
<td>Picture completion</td>
<td>-.86 ± 2.61</td>
<td>-.137 ± 2.12##</td>
<td>-.216 ± 2.14##</td>
</tr>
<tr>
<td>Picture arrangement</td>
<td>.5 ± 1.69</td>
<td>.31 ± 1.30</td>
<td>-.79 ± 1.87##</td>
</tr>
<tr>
<td>Block design</td>
<td>-.25 ± 2.43</td>
<td>.78 ± 2.12</td>
<td>.11 ± 2.54</td>
</tr>
<tr>
<td>Digit symbol</td>
<td>.75 ± 1.99</td>
<td>.52 ± 2.53</td>
<td>-.74 ± 2.08*</td>
</tr>
</tbody>
</table>

Significance of difference in scores between baseline and early/late tests: #, P < 0.05; ##, P < 0.01; ###, P < 0.001 (Wilcoxon matched-pairs signed-ranks tests). Test items with significant difference are shown in bold. Significance of difference between CABG group and short/long RCP groups in test score changes between baseline and early/late test scores: *, P < 0.05; **, P < 0.01; ***, P < 0.001 (Wilcoxon rank sum tests). Significance of difference between short and long RCP groups in test score changes: +, P < 0.05; ++, P < 0.01; ++++, P < 0.001 (Wilcoxon rank sum tests).

Arithmetic, Comprehension, Similarity, Picture Completion, Picture Arrangement, Block Design, Object Assembly, Digit Symbol, and testing interval (Pre-Early and Pre-Late).

Significant decline between baseline and early scores were seen in three subtests (digit span, arithmetic, and picture completion) for S-RCP and four (digit span, arithmetic, picture completion, and picture arrangement) for L-RCP. Significant decline between baseline and late scores were seen in one subtest (arithmetical) for S-RCP, four (digit span, arithmetic, picture completion, and picture arrangement) for L-RCP, and one (object assembly) for CABG. The mean change of scores for one late test (digit symbol) was significantly lower in S-RCP than in CABG. The mean change of scores for three early tests (digit span, vocabulary, and picture arrangement) and four late tests (information, digit span, picture completion, and picture arrangement) were significantly lower in L-RCP than in CABG.

Stepwise logistic regression analysis disclosed that, after considering (or even after controlling for) the other variables, significant difference in test score changes were observed between CABG and L-RCP for two early tests (picture completion and digit symbol) as well as for three late tests (digit span, similarities, and picture completion) (Table 3). None of test score changes showed significant difference between CABG and S-RCP.

5. Discussion

The results of the current study indicate that prolonged RCP of 60 min or more in patients undergoing replacement of the thoracic aorta is associated with impairment in some subtests of WAIS-R both in the early and late postoperative period. In addition, there were no significant differences in

Table 3
Predictors for the difference in test scores between baseline and early/late test results

<table>
<thead>
<tr>
<th></th>
<th>Selected variables</th>
<th>Model</th>
<th>Difference between baseline and early/late test results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>icu</td>
<td></td>
<td>P = 0.0000, Adj R² = 0.3975</td>
</tr>
<tr>
<td>Digit span</td>
<td>resp</td>
<td>P = 0.0000, Adj R² = 0.443</td>
<td>(−0.20 ± 0.09, 0.027)</td>
</tr>
<tr>
<td></td>
<td>(−0.05 ± 0.02, 0.015)</td>
<td></td>
<td>rcplong</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.0000, Adj R² = 0.4811</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(−1.49 ± 0.50, 0.004)</td>
</tr>
<tr>
<td>Arithmetic</td>
<td></td>
<td></td>
<td>Sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.0000, Adj R² = 0.4039</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(−1.28 ± 0.54, 0.021)</td>
</tr>
<tr>
<td>Comprehension</td>
<td></td>
<td></td>
<td>Resp</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.0038, Adj R² = 0.1243</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(0.07 ± 0.03, 0.013)</td>
</tr>
<tr>
<td>Similarities</td>
<td></td>
<td></td>
<td>Sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.0000, Adj R² = 0.5199</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(−1.39 ± 0.52, 0.010), rcplong</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.0000, Adj R² = 0.3666</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(−1.23 ± 0.53, 0.023)</td>
</tr>
<tr>
<td>Picture completion</td>
<td></td>
<td>P = 0.0000, Adj R² = 0.3226</td>
<td></td>
</tr>
<tr>
<td>Picture arrangement</td>
<td></td>
<td>(−1.30 ± 0.51, 0.013)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>icu</td>
<td></td>
<td>(−1.33 ± 0.08, 0.006)</td>
</tr>
<tr>
<td></td>
<td>(−0.21 ± 0.08, 0.006)</td>
<td></td>
<td>Wakeup</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P = 0.0000, Adj R² = 0.2306</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(−0.13 ± 0.05, 0.006)</td>
</tr>
<tr>
<td>Object assembly</td>
<td>Hosp</td>
<td>P = 0.0033, Adj R² = 0.1247</td>
<td></td>
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<tr>
<td></td>
<td>(−0.08 ± 0.04, 0.046)</td>
<td></td>
<td>P = 0.0037, Adj R² = 0.1016</td>
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<tr>
<td></td>
<td>rcplong</td>
<td>P = 0.0000, Adj R² = 0.2975</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(−2.09 ± 0.55, 0.000)</td>
<td></td>
<td>P = 0.0006, Adj R² = 0.1705</td>
</tr>
</tbody>
</table>

rcpshort = 0 (CABG group), one (short CRP group), rcplong = 0 (CABG group), one (long RCP group). Only selected variables are shown except for baseline scores: variable name (partial correlation coefficient ± standard deviation of coefficient, P-value).
In summary, prolonged RCP of 60 min or more in patients undergoing surgery of the thoracic aorta was associated with postoperative neurocognitive impairment. The neurocognitive outcome in patients undergoing RCP less than 60 min were comparable with patients undergoing CABG without circulatory arrest. Although this study provides no information about adjunctive protective effect of RCP over HCA alone, we find it meaningful because it justifies our current strategy for brain protection during thoracic aortic surgery where the method of brain protection is converted from RCP to SCP when the duration of HCA exceeds 60 min, while protective effect of SCP on neurocognitive function has not yet been established.

References