Selective cerebral perfusion for thoracic aortic surgery: Association with neurocognitive outcome

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Objectives: Optimal brain protection for aortic arch surgery remains unclear. This prospective study examined neurocognitive outcomes in cardiac and thoracic aortic surgical patients, including a small cohort who underwent selective cerebral perfusion.

Methods: Fifty-seven adult cardiac and thoracic aortic surgical patients underwent preoperative and postoperative neurocognitive testing. Patients were divided into 3 groups. Group 1 patients underwent procedures with cardiopulmonary bypass alone ($n = 24$), group 2 patients with cardiopulmonary bypass and hypothermic circulatory arrest ($n = 23$), and group 3 patients with cardiopulmonary bypass, hypothermic circulatory arrest, and antegrade selective cerebral perfusion ($n = 10$). Changes in 14 neurocognitive test scores and 6 neurocognitive domain scores (Attention, Speed, Language, Memory, Executive Function, and Motor Function) were evaluated.

Results: Multiple regression analyses examining the relationships of cardiopulmonary bypass time, hypothermic circulatory arrest time, and selective cerebral perfusion time with change in cognitive test performance revealed that selective cerebral perfusion time (range, 39–83 minutes) was a significant predictor of decline in performance on memory and language tests. Hypothermic circulatory arrest (range, 14–40 minutes) and cardiopulmonary bypass (range, 70–369 minutes) times were unrelated to decline.

Conclusions: Complex thoracic aortic repairs requiring prolonged selective cerebral perfusion were associated with decline in neurocognitive function. It is unclear whether the complexity of the repair necessitating prolonged selective cerebral perfusion or the perfusion technique itself contributed to neurocognitive decline. Prospective multicenter neurocognitive evaluations are necessary to assess the relative merits of current brain protection strategies in thoracic aortic surgery. (*J Thorac Cardiovasc Surg* 2012;143:1205-12)

The technique of thoracic aortic surgery was revolutionized in 1975, when Griep and colleagues¹ introduced hypothermic circulatory arrest (HCA) to allow sufficient time to conduct surgical repairs in a bloodless field with acceptable to excellent neurologic outcomes. As it came to be recognized that the “safe” duration of HCA is limited, adjunct techniques aimed at providing blood flow and metabolic support to the brain were introduced to extend the time available for complex aortic reconstructions. Retrograde cerebral perfusion (RCP) is commonly used as a cerebral perfusion adjunct jointly with HCA. Its efficacy for providing metabolic support and improving neurologic outcomes remains controversial, however, and some data suggest that RCP has deleterious effects.^{2,3} For this reason, and as a result of surgical innovation, antegrade selective cerebral perfusion (SCP) is now used in many centers.

It is difficult to evaluate the relative neuroprotective efficacies of these techniques, because the patient groups differ with respect to multiple variables that potentially influence outcome. The potentially confounding variables include the following: preoperative factors, such as cognitive and neurologic status, overall health, and atherosclerotic disease; operative factors, such as emergency versus elective surgery and surgical complexity; and postoperative factors, such as neurologic morbidity (stroke and transient nonfocal neurologic symptoms), nonneurologic morbidity, and mortality. Moreover, there is marked variability among centers and across time with respect to HCA, RCP, and SCP protocols. Thus the existing literature consists mainly of retrospective reports of gross neurologic outcomes from single-center cohorts. The issue of the optimal methods of brain protection during thoracic aortic surgery remains controversial.⁴⁻⁷

There have been few neurocognitive outcome studies examining the efficacy of intraoperative neuroprotection for thoracic aortic surgery. We found that preoperative to postoperative changes in memory and fine motor function were worse in patients with HCA times of at least 25 minutes, relative to patients with shorter periods of HCA or with cardiopulmonary bypass (CPB) without HCA.⁸ Our subsequent experience with RCP was associated with worse neurocognitive outcome than was HCA alone, consistent with the findings of other studies.⁹⁻¹¹ In more recent years, we

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Abbreviations and Acronyms

CABG	= coronary artery bypass grafting
CPB	= cardiopulmonary bypass
FTT	= Finger Tapping Test
GPB	= Grooved Pegboard Test
HCA	= hypothermic circulatory arrest
HVLT-R	= Hopkins Verbal Learning Test–Revised
RCP	= retrograde cerebral perfusion
SCP	= selective cerebral perfusion
TMT-A	= Trail Making Test A
TMT-B	= Trail Making Test B

have used SCP as the primary adjunct perfusion technique. In this prospective study, we sought to evaluate further the roles of HCA and SCP as predictors of preoperative to postoperative cognitive decline.

MATERIALS AND METHODS**Patients**

The study protocol was approved by the institutional review board. Adult patients undergoing nonemergency cardiac or proximal aortic surgery with CPB or thoracic aortic surgery with HCA between February 28, 2002, and June 16, 2008, were recruited into the study after providing informed consent. Patients were divided into 3 groups. Group 1 patients underwent coronary artery and cardiac valve procedures with CPB. Group 2 patients underwent thoracic aortic procedures with CPB and at least 1 period of HCA. Finally, group 3 patients underwent thoracic aortic procedures with CPB, HCA, and at least 1 period of SCP.

Anesthesia and Monitoring

General anesthesia was induced with a hypnotic agent (etomidate, propofol) and supplemented with an opioid analgesic (fentanyl, sufentanil) and a benzodiazepine (midazolam hydrochloride). Maintenance consisted of isoflurane (0.6–1.5% end-tidal concentration), fentanyl, neuromuscular blockers, and midazolam. All patients had mechanical ventilation with a fraction of inspired oxygen of 1.0 to maintain the P_{aO_2} at 35 to 45 mm Hg.

The following monitors were placed: a radial arterial catheter, a pulmonary arterial catheter, and temperature monitoring of the urinary bladder catheter and the esophagus or nasopharynx. For HCA, a 20-gauge jugular bulb catheter for intermittent sampling of jugular venous blood was placed and confirmed by baseline jugular bulb venous saturation measurement. Patients enrolled during the later years of the series underwent near-infrared spectroscopic monitoring of transcranial cerebral oxygenation and bispectral index monitoring.

Surgical and Perfusion Techniques

All patients underwent midline sternotomy. All patients undergoing HCA had direct right axillary cannulation or end-to-side graft anastomosis for CPB arterial inflow. Antegrade crystalloid or blood cardioplegia was used every 20 to 30 minutes, either through an aortic root cannula or directly into the coronary ostia, and the left ventricle was vented. In patients who did not undergo HCA, operations were performed with standard CPB at mild to moderate hypothermia (28°C–35°C).

The techniques of HCA were consistent throughout the duration of the study and have been described in detail previously.¹² Briefly, cooling during CPB was performed until a core temperature of 12°C to 15°C, as

measured by a urinary bladder thermistor, was achieved. Alpha-stat pH management was used, and cooling times of 45 minutes or longer were generally required. Cooling was continued until jugular venous saturation exceeded 95% in most cases and 90% in all. The head was packed in ice before commencement of HCA for intervals expected to exceed 20 minutes. All patients undergoing HCA were administered 30 mg/kg of methylprednisolone before CPB. In patients with combined HCA and SCP times exceeding 30 minutes, tapering doses of glucocorticoids were continued in the intensive care unit for 48 hours.

In repairs involving the transverse aortic arch, the brachiocephalic vessels were anastomosed to a trifurcated graft during a brief period of HCA.¹³ The proximal end of the trifurcated graft was then clamped, and SCP was instituted through the right axillary cannula. We used alpha-stat management, perfusate temperatures between 15°C and 20°C, hematocrit of 20% to 30%, and flows of approximately 10 mL/(kg/min) titrated to maintain a mean arterial pressure of 40 to 60 mm Hg. Adequacy of cerebral oxygenation was confirmed by near-infrared spectroscopy and cerebral oximetry in the later years of the series, although no specific criteria were set.

On completion of the HCA and SCP portions of the procedures, gradual systemic rewarming was carried out by means of CPB, limiting the gradient between perfusate and urinary bladder temperature to less than 10°C, with a maximum perfusate temperature of 37°C. Rewarming was discontinued once an esophageal temperature of 35°C to 37°C and a urinary bladder temperature of 32°C to 35°C had been achieved.

CPB time was defined as the cumulative time on full-body CPB, exclusive of HCA or SCP. HCA time was defined as the cumulative time on full-body circulatory arrest, exclusive of SCP. Brain perfusion time was defined as the cumulative time on full-body CPB and SCP, which was equivalent to CPB time for groups 1 and 2. CPB onset-to-offset time was defined as the cumulative time from initiation of CPB to weaning from CPB, regardless of whether HCA or SCP was used within that interval. Surgical time was defined as the time from incision to closure.

Neurocognitive Testing

Neurocognitive testing was performed preoperatively at preadmission testing and postoperatively when patients returned to the hospital for surgical follow-up visit. The neurocognitive test battery consisted of 8 tests yielding 14 test scores that assessed 6 domains of function, as summarized in Table 1. The tests used were as follows: Wechsler Memory Scale III Digit Span subtest (Psychological Corporation, New York, NY); Trail Making Test (TMT-A and TMT-B; Neuropsychology Press, Tuscon, Ariz); Symbol Digit Modalities Test, oral version (Western Psychological Services, Los Angeles, Calif); Boston Naming Test–15 item version¹⁴; Hopkins Verbal Learning Test–Revised (HVLT-R; Psychological Assessment Resources, Inc, Odessa Fla); Stroop Color and Word Test (Stoelting Co, Wood Dale, Ill); Finger Tapping Test (FTT; Psychological Assessment Resources); and Grooved Pegboard Test (GPB; Psychological Assessment Resources). Alternate forms of the HVLT-R and Boston Naming Test–15 item version were administered across the preoperative and postoperative test sessions in a counterbalanced fashion. Only the dominant hand was tested with the FTT and GPB.

Statistical Methods

The initial step in analyzing the neurocognitive test data was to convert raw test scores to z scores. The normalized z score reflects where an observed raw data point stands in relation to a reference group, allowing for comparison across tests. For the purpose of standardization, we chose the group of patients who underwent preoperative neurocognitive testing and subsequent surgical procedures with CPB only as the reference group. The difference between preoperative and postoperative z scores was then computed for each test measure and each patient. Logarithmic transformation was performed on the time-related tests (TMT-A, TMT-B, and GPB) to improve normality of the data. Because higher scores reflect poorer

TABLE 1. Neurocognitive battery assessing 6 domains of function

Test	Test score
Attention	
Wechsler Memory Scale III Digit Span subtest	Digits Forward Digits Backward Digit Span
Processing speed	
The Trail Making Test (TMT)	Trail Making Test, Part A (TMT-A) Trail Making Test, Part B (TMT-B)
The Symbol Digit Modalities Test, oral version	SDMT
Language	
Boston Naming Test—15 item version	BNT-15
Memory	
Hopkins Verbal Learning Test—Revised (HVLTR)	HVLTR Total Recall HVLTR Delayed Recall HVLTR Retention HVLTR Recognition
Executive function	
Stroop Color and Word Test	Stroop Interference (Stroop)
Motor function	
Finger Tapping Test	FTT
Grooved Pegboard Test	GPB

performance for these tests, postoperative scores were subtracted from preoperative scores to ensure that negative difference scores would reflect a decline in function for all measures.

To reduce the number of statistical analyses and decrease the risk of type I error, we classified the 14 test scores into 6 domains: Attention, Processing Speed, Language, Memory, Executive Function, and Motor Function. Cluster analysis was used to confirm our conceptual grouping of the neurocognitive tests by the variable cluster analysis (VARCLUS) procedure in the SAS 9.1.3 statistical analysis software package (SAS Institute, Inc, Cary, NC). This procedure uses iterative splitting (until a stopping criterion is met) and factor analysis methods to divide a set of variables into nonoverlapping subgroups. Because the VARCLUS procedure used for variable cluster analysis removes subjects with incomplete data, and the HVLTR Retention, FTT, and GPB variables had greater than 15% missing data, we excluded those variables from the cluster analysis. Complete preoperative neurocognitive test data were available for 83 patients on 11 of the 14 neurocognitive test scores. After controlling for age and education, cluster analysis yielded 5 clusters: Attention (Digits Forward, Digits Backward, Digit Span), Processing Speed (TMT-A, TMT-B, and Symbol Digit Modalities Test, oral version), Language (Boston Naming Test—15 item version), Memory (HVLTR Total Recall, HVLTR Delayed Recall, and HVLTR Recognition), and Executive Function (Stroop). The proportion of variation explained by these five clusters was 78%. We then assigned the HVLTR Retention variable to the Memory domain and the FTT and GPB variables to the Motor Function domain. Finally, a composite score for each domain for each patient was created by averaging the difference in *z* scores for the variables in the cluster.

Statistical analyses were carried out using the SAS statistical software package (version 9.1.3). For group comparisons, χ^2 tests were used for binary categorical variables, Students *t* tests or analysis of variance (allowing heterogeneous variance across the groups) were used for normally distributed continuous variables, and nonparametric Kruskal-Wallis tests were used for nonnormally distributed continuous variables.

Multiple linear regression analysis was used to model the associations between the 3 types of perfusion and arrest times (CPB, HCA, and SCP) and each of the neurocognitive test scores and domain scores, independent of group assignment. The analyses assumed that the practice effects of the tests were independent of the perfusion and arrest times. The models adjusted for preoperative neurocognitive scores and number of days since surgery. Because of the small sample size, we chose not to adjust for age and education level, assuming that the effects of these variables should be reflected in the baseline test scores. The models also adjusted for use of HCA or SCP as binary variables (present or absent). To explore the possibility of nonlinear relationships between CPB, HCA, and SCP times and postoperative neurocognitive performance, a quadratic polynomial term for CPB, HCA, and SCP times was tested for statistical significance. Two-way interactions among use of HCA or SCP and perfusion and arrest times were also tested.

To examine further the association between SCP time and neurocognitive decline, we performed propensity score analysis that matched 10 patients from the HCA group with 10 from the SCP group. We used the sampling with replacement technique to test the effects of SCP when the matched pairs had similar brain perfusion time and HCA time. From the sample of SCP group and HCA group subjects, a logistic regression was performed to predict the probability (propensity score) of SCP group membership by using age, education, brain perfusion time, and HCA time as predictors. The balance of the covariates (age, education, time of postoperative testing, baseline neurocognitive domain *z* scores, brain perfusion time, and HCA time) between the resulting matched pairs were compared with *t* tests, and all differences were nonsignificant. In the next step, we repeated the multiple regression analysis for SCP time, adjusting for SCP use, preoperative neurocognitive scores, and time of postoperative testing.

RESULTS
Demographic Characteristics

A total of 178 cardiac and thoracic aortic surgical patients underwent preoperative neuropsychologic testing: 88 (49.4%) in group 1, 61 (34.3%) in group 2, and 29 (16.3%) in group 3. Fifty-seven of those patients (32%) underwent postoperative neuropsychologic testing at the outpatient follow-up visit: 24 (42.1%) in group 1, 23 (40.4%) in group 2, and 10 (17.5%) in group 3. The return rates for postoperative neuropsychologic testing were 27%, 38%, and 34% for groups 1, 2, and 3, respectively (*P* = .34). Postoperative testing occurred 15 to 233 days (median, 44 days) after surgery.

Of the 121 patients unavailable for follow-up, 3 (0, 2, and 1 for groups 1 through 3, respectively) died before hospital discharge, 2 (0, 1, and 1) had strokes, and 9 (4, 3, and 2) had medical complications necessitating their discharge to other facilities (rehabilitation, acute care, or skilled nursing facilities). Relative to patients who were unavailable for follow-up (*n* = 121), patients who underwent postoperative neuropsychologic testing (*n* = 57) were on average 5 years younger (58 years vs 63 years; *P* = .03). They did not differ with respect to level of education (*P* = .97) or postsurgical hospital stay (*P* = .30).

The surgical procedures of patients in group 1 (*n* = 24) were single valve repairs (*n* = 11), multiple valve repairs (*n* = 6), coronary artery bypass grafting (CABG; *n* = 2), CABG and valve repair (*n* = 2), and ascending aortic

repairs (n = 3). The surgical procedures of patients in group 2 (n = 23) were ascending aortic repairs (n = 13), ascending aortic repairs with CABG (n = 5), ascending aortic repairs with mitral valve repair (n = 1), ascending aortic repairs with CABG and aortic valve repair (n = 2), hemiarch replacement with aortic valve repair (n = 1), and aortic arch repair (n = 1). The surgical procedures of patients in group 3 (n = 10) were aortic arch replacement (n = 8), ascending aortic repair (n = 1), and thoracoabdominal aortic repair (n = 1).

Group Comparisons

Table 2 presents the characteristics of patients who underwent both preoperative and postoperative neurocognitive testing. The treatment groups were similar with respect to age and education. Group 1 had significantly more men than did group 3. The groups differed with respect to hospital stay and time to postoperative testing, with group 1 having significantly shorter intervals from surgery to hospital discharge and from surgery to postoperative testing. Duration and complexity of surgery, as assessed by surgical duration and CPB onset-to-offset time, was significantly greater in groups 2 and 3 relative to group 1. Group 3 underwent significantly longer intervals of HCA than did group 2. Total brain perfusion time was not significantly different between groups 2 and 3.

Table 3 summarizes the raw preoperative and postoperative test scores and z score differences. Overall, the 3 groups differed on 3 of the 14 difference scores (TMT-B, HVLT-R

Total Recall, and FTT), with group 3 performing significantly worse than group 2.

Relationships of Perfusion and Arrest Times to Neurocognitive Outcomes

Table 4 presents the results of multiple regression analyses examining the relationships of CPB, HCA, and SCP times (independent of group assignment) with the 6 neurocognitive domain scores after adjustment for potential confounders. The results indicate that SCP time (range, 39–83 minutes) was a significant predictor of decline in the domains of Memory and Language. HCA time (range, 14–40 minutes) was not a significant predictor of decline in any domain, and there was no significant interaction between HCA time and SCP use. CPB time (range, 70–369 minutes) was not a significant predictor of decline in any domain, and there was no significant interaction between CPB time and HCA use or SCP use. As a sensitivity analysis, the propensity score analysis (Table 4) that used 10 matched pairs from the SCP and HCA groups confirmed a significant association between SCP time and decline in language ($P = .002$). The effect of SCP on the memory decline trended in the same direction as that seen from the traditional regression analysis, with a P value of .063 (Table 4). The lack of statistical significance could be the result of low study power, with only 10 SCP matched pairs.

Figure 1 presents the relationships between SCP time and the neurocognitive domain scores. The correlations between SCP time and Memory and Language domain scores

TABLE 2. Group characteristics

Variable	Group 1, CPB only (N = 24)	Group 2, CPB + HCA (N = 23)	Group 3, CPB + HCA + SCP (N = 10)	P value
Age (y, mean $\pm$ SD)	54.7 $\pm$ 11.6	61.6 $\pm$ 15.9	57.3 $\pm$ 15.9	.25*
Education (y, mean $\pm$ SD)	15.6 $\pm$ 2.7	14.6 $\pm$ 2.5	13.5 $\pm$ 2.1	.09*
Education >12 y (%)	71%	65%	40%	.23†
Sex (% male)	79%	74%	40%	.07†,‡
Stay (d, median and range)	6 (4–9)	8 (5–25)	8 (6–30)	<.01§,
Postoperative testing (d, median and range)	39 (22–233)	50 (15–132)	48 (31–66)	.038§,
CPB time (min, median and range)¶	170 (70–307)	247 (143–369)	120.5 (83–237)	<.01§, ,#
HCA time (min, median and range)**	—	21 (14–31)	30 (14–40)	.02§
SCP time (min, median and range)	—	—	68.5 (39–83)	
Brain perfusion time (min, median and range)††	170 (70–307)	247 (143–369)	198 (128–284)	.01§,
CPB onset-to-offset time (min, median and range)‡‡	170 (70–307)	270 (171–390)	232 (162–309)	<.01‡,§,
Surgical time (min, median and range)§§	320 (194–451)	443 (329–713)	494 (401–660)	<.01‡,§,

CPB, Cardiopulmonary bypass; HCA, hypothermic cardiac arrest; SCP, selective cerebral perfusion. * P value obtained with analysis of variance. † P value obtained with χ^2 test.

‡Group 3 differed significantly from group 1 ($P < .05$). § P value obtained with Wilcoxon/Kruskal-Wallis test. ||Group 2 differed significantly from group 1 ($P < .05$).

¶Cardiopulmonary bypass time is exclusive of hypothermic cardiac arrest and/or selective cerebral perfusion time. #Group 3 differed significantly from group 2 ($P < .05$). **Hypothermic circulatory arrest time is exclusive of selective cerebral perfusion time. ††Brain perfusion time is the cumulative time of cardiopulmonary bypass and selective cerebral perfusion time, exclusive of hypothermic circulatory arrest. ‡‡Cardiopulmonary bypass onset-to-offset is the time from cardiopulmonary bypass initiation to weaning. §§Surgical time is the time from incision to closure.

TABLE 3. Raw preoperative and postoperative neurocognitive test scores and z score differences by group

Test	Group 1 CPB only (N = 24)	Group 2 CPB + HCA (N = 23)	Group 3 CPB + HCA + SCP (N = 10)	P value
Digits Forward				.870
Preoperative	10.67 ± 2.44	9.26 ± 2.22	9.60 ± 2.07	
Postoperative	10.83 ± 2.75	9.57 ± 1.95	9.60 ± 1.78	
Difference in z score	0.08 ± 0.75	0.14 ± 0.80	0.00 ± 0.65	
Digits Backward				.397
Preoperative	7.25 ± 2.88	6.04 ± 1.69	6.10 ± 2.77	
Postoperative	7.46 ± 3.11	6.04 ± 1.92	5.50 ± 2.64	
Difference in z score	0.08 ± 0.65	0.00 ± 0.64	-0.22 ± 0.56	
Digit Span				.343
Preoperative	17.92 ± 4.97	15.30 ± 3.48	15.70 ± 4.55	
Postoperative	18.29 ± 5.46	15.61 ± 3.31	15.10 ± 3.84	
Difference in z score	0.09 ± 0.64	0.07 ± 0.52	-0.14 ± 0.38	
TMT-A*				.388
Preoperative	24.50 (21-30)	32 (25-41)	31.5 (29-37)	
Postoperative	25.0 (21-30)	30 (27-49)	32.0 (21-39)	
Difference in z score	0.00 (-0.40 to 0.32)	-0.27 (-0.55 to 0.12)	-0.14 (-0.60 to 0.18)	
TMT-B*				.032†,‡,§
Preoperative	58 (47-78)	85 (68-142)	86 (59-86)	
Postoperative	60 (40-72)	88 (51-107)	91.5 (56-163)	
Difference in z score	0.14 (-0.11 to 0.38)	0.20 (-0.21 to 0.65)	-0.19 (-0.41 to 0.03)	
SDMT				.482
Preoperative	48.83 ± 12.12	46.05 ± 10.78	44.89 ± 8.95	
Postoperative	51.71 ± 14.07	46.21 ± 13.19	44.80 ± 8.82	
Difference in z score	0.22 ± 0.7	0.01 ± 0.49	0.02 ± 0.30	
BNT-15				.172
Preoperative	13.43 ± 2.02	13.09 ± 1.50	13.80 ± 1.03	
Postoperative	13.78 ± 1.62	13.83 ± 1.47	13.60 ± 1.17	
Difference in z score	0.17 ± 0.66	0.35 ± 0.50	-0.09 ± 0.70	
HVLT-R Total Recall				.024 ,¶
Preoperative	22.83 ± 4.80	19.83 ± 4.51	22.20 ± 6.07	
Postoperative	22.67 ± 4.48	21.61 ± 5.80	19.10 ± 5.17	
Difference in z score	-0.03 ± 0.83	0.35 ± 0.81	-0.61 ± 0.98	
HVLT-R Delayed Recall				.931
Preoperative	7.75 ± 2.80	6.87 ± 2.42	7.90 ± 2.28	
Postoperative	7.83 ± 2.12	7.00 ± 2.63	7.60 ± 5.38	
Difference in z score	-0.02 ± 0.85	0.05 ± 0.87	-0.11 ± 1.34	
HVLT-R Retention				.666
Preoperative	87.38 ± 17.58	83.28 ± 21.05	111.63 ± 51.25	
Postoperative	86.89 ± 15.44	83.67 ± 24.42	90.14 ± 37.71	
Difference in z score	0.00 ± 0.48	-0.01 ± 0.71	-0.45 ± 1.28	
HVLT-R Recognition				.388
Preoperative	10.00 ± 1.91	10.39 ± 1.23	9.80 ± 1.48	
Postoperative	10.42 ± 1.50	10.09 ± 2.37	10.50 ± 2.17	
Difference in z score	0.20 ± 0.79	-0.15 ± 1.23	0.34 ± 0.85	
Stroop				.799
Preoperative	-1.35 ± 5.51	-2.14 ± 4.89	-3.25 ± 6.66	
Postoperative	-1.38 ± 6.73	-0.75 ± 5.57	-2.85 ± 6.52	
Difference in z score	0.00 ± 0.70	0.14 ± 0.71	0.05 ± 0.66	
FTT				.019†,§,
Preoperative	49.76 ± 10.12	46.19 ± 12.75	45.70 ± 13.21	
Postoperative	50.18 ± 12.04	44.64 ± 12.47	42.20 ± 13.41	
Difference in z score	0.15 ± 0.33	-0.12 ± 1.03	-0.32 ± 0.63	

(Continued)

TABLE 3. Continued

Test	Group 1 CPB only (N = 24)	Group 2 CPB + HCA (N = 23)	Group 3 CPB + HCA + SCP (N = 10)	P value
GPB*				.499
Preoperative	69 (66–77)	83.5 (74–101)	79 (72–88)	
Postoperative	69 (63–76)	80.5 (74–116)	75 (63–105)	
Difference in z score	0.24 (–0.19 to 0.61)	–0.13 (–0.35 to 0.55)	–0.28 (–0.45 to 0.38)	

Tests are as listed in Table 1. CPB, Cardiopulmonary bypass; HCA, hypothermic cardiac arrest; SCP, selective cerebral perfusion. For normally distributed test scores, mean $\pm$ SD is given. For nonnormally distributed test scores (TMT-A, TMT-B, and GPB), median with interquartile range is given. *For TMT-A, TMT-B, and GPB, the signs are reversed from the original scales, to reflect that longer time is associated with greater decline in cognitive function. †P value obtained with Wilcoxon/Kruskal-Wallis Test. ‡The selective cerebral perfusion group differed significantly from the cardiopulmonary bypass group ($P < .05$). §The selective cerebral perfusion group differed significantly from the hypothermic circulatory arrest group ($P < .05$). ||P value obtained with analysis of variance. ¶The hypothermic circulatory arrest group differed significantly from the cardiopulmonary bypass group ($P < .05$).

were statistically significant. Multiple regression analyses showed no statistically significant relationships between SCP time and the other domain scores; however, the correlations between SCP time and Attention, Executive Function, and Motor Function domain scores were negative and in the range of –0.3 to –0.5, which is considered to be of moderate size for data of this nature.

DISCUSSION

This study examined neurocognitive function prospectively in cardiac and thoracic aortic surgical patients who underwent procedures with CPB alone, CPB plus HCA, or CPB plus HCA and SCP. In group comparison analyses, we found that patients who underwent procedures with SCP had significantly greater declines on 3 of 14 test scores. Multiple regression analyses revealed that SCP duration (range, 39–83 minutes) was a significant predictor of decline in performance on Memory and Language domain tests. HCA duration (range, 14–40 minutes) was unrelated to neurocognitive decline across all patients who underwent HCA (independent of group assignment). CPB duration (range, 70–369 minutes) across the entire sample of patients (independent of group assignment) was also unrelated to neurocognitive decline.

Other neurocognitive outcome studies have reported mixed results in patients undergoing thoracic aortic procedures with SCP. A study of 22 patients who underwent aortic arch repair with SCP at moderate hypothermia (26°C) found no significant declines in test scores.¹⁵ Svensson

and colleagues¹¹ compared neurocognitive outcomes in 30 aortic arch surgical patients cooled to less than 20°C and randomly assigned to HCA, HCA plus RCP, or HCA plus SCP and found that mean postoperative test scores were significantly worse in the SCP group than in the HCA group. A study performed by Pacini and colleagues¹⁶ compared 16 patients who underwent aortic arch surgery with SCP with 14 patients who underwent elective CABG. They found no significant neurocognitive test score differences between the 2 groups or within the SCP group across 3 evaluations (preoperative, 1 postoperative week, and 6 postoperative months). By means of diffusion-weighted magnetic resonance imaging, they found that SCP was associated with diffuse vasogenic cerebral edema at 1 postoperative week and that this effect persisted in the temporal lobe at 6 postoperative months. This finding is notable because it is consistent with our finding of decline in performance on Memory and Language domain tests, because neurocognitive profiles characterized by episodic memory and language deficits against a background of otherwise normal cognitive function implicate temporal lobe pathology.

Our finding that HCA duration (range, 14–40 minutes) was unrelated to neurocognitive decline contrasts with our previous findings, in which prolonged HCA durations (≥ 25 minutes) were associated with declines in memory and fine motor function.⁸ Our institutional approach to brain protection has evolved significantly since our 1999 publication, in that HCA periods overall became much shorter as SCP was introduced into clinical practice.

TABLE 4. Multiple regression analyses of the relationships of cardiopulmonary bypass, hypothermic cardiopulmonary bypass, and selective cerebral perfusion times with neurocognitive domain scores, adjusting for potential confounders

Outcome measure	CPB time			HCA time			SCP time			SCP time (propensity score analysis)		
	β^*	SE*	P value	β^*	SE*	P value	β^*	SE*	P value	β^*	SE*	P value
Attention	0.0009	0.0012	.467	–0.0140	0.0156	.373	–0.0070	0.0105	.509	–0.0089	0.0094	.360
Speed	0.0014	0.0010	.166	0.0056	0.0133	.674	0.0090	0.0092	.335	0.0117	0.0103	.274
Language	0.0010	0.0012	.392	0.0018	0.0150	.232	–0.0277	0.0105	.011	–0.0356	0.0092	.002
Memory	–0.0008	0.0013	.530	–0.0132	0.0165	.427	–0.0349	0.0115	.004	–0.0274	0.0137	.063
Executive	0.0001	0.0017	.959	0.0101	0.0215	.640	–0.0093	0.0142	.516	–0.0096	0.0150	.534
Motor	0.0022	0.0012	.063	0.0178	0.0156	.261	–0.0061	0.0117	.604	–0.0185	0.0103	.096

*The β coefficient and its SE were derived from linear regression model.

FIGURE 1. The relationships between selective cerebral perfusion (SCP) duration and neurocognitive domain scores (differences in z scores), with Pearson correlation coefficients.

The nature of complex aortic repairs is that they are performed in referral centers, drawing patients from large geographic regions. This poses significant obstacles to neurocognitive outcomes research because, after hospital discharge, many patients are physically inaccessible for follow-up testing, resulting in high attrition. Those patients who do return to the center after hospital discharge typically are only available for postoperative neurocognitive testing on the day that they are scheduled for follow-up with their surgeons. We believe that such limitations are common in long-term neuropsychologic testing studies of surgical patients at referral centers. Furthermore, it is impractical to generalize findings across small studies from multiple centers or to perform meta-analytic studies because of variations in the ways that HCA, RCP, and SCP are practiced and also in the methods of neurocognitive evaluation.

Although it is reasonable to expect poorer neurocognitive outcomes in patients undergoing extensive reconstructive surgery of the aortic arch requiring SCP, the findings of this study are limited by the small postoperative sample size and the wide variation in timing of postoperative testing. Despite the small sample size, however, the propensity score analysis did confirm the association between SCP

duration and decline in Language domain (naming) test scores. A similar trend of an effect of SCP on decline in Memory domain scores did not retain statistical significance ($P = .06$), however, and the findings regarding memory decline thus should be considered less definitive. We also acknowledge that the number of covariates collected in this study is limited. For example, ranges of hemoglobin concentration, perfusion pressures, and flow rates during CPB and SCP were not investigated. Despite these limitations, the traditional regression analysis and the confirmatory propensity score analysis were concordant. These data indicate that future investigations with larger patient samples and more covariates are warranted.

Neurocognitive outcome studies are essential in evaluating the efficacy of neuroprotection strategies for thoracic aortic surgery. We present these preliminary data to demonstrate that SCP did not eliminate the neurocognitive decline that has been previously identified as a problem in complex aortic arch repairs. Prospective multicenter investigation that uses remote, Internet-based neurocognitive testing, with uniform test selection and test timing, is the most promising approach for such studies. We have previously demonstrated that studying neurocognitive

outcomes with such technology is practical in this patient population.¹⁷

In conclusion, our institution changed its clinical approach to brain protection in complex aortic repairs nearly 15 years ago in response to our clinical and laboratory findings that prolonged HCA was associated with deleterious cognitive outcomes. Our current data do not support the principle that substitution for prolonged HCA with shorter periods of HCA combined with SCP alleviates the problem of cognitive dysfunction after complex aortic arch repairs. Further research is required to validate these findings in larger clinical studies.

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