BRIEF COMMUNICATIONS

A PROSPECTIVE RANDOMIZED STUDY OF NEUROCOGNITIVE FUNCTION AND S-100 PROTEIN AFTER ANTEGRADE OR RETROGRADE BRAIN PERFUSION WITH HYPOTHERMIC ARREST FOR AORTIC SURGERY

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Several studies in patients undergoing coronary artery bypass (CAB) surgery have shown evidence of postoperative neurocognitive dysfunction or increased levels of the serum brain injury protein S-100.^{1,2} S-100 protein is a calcium-binding dimer found in glial and Schwann cells, and postoperative levels above 0.5 to 1.3 $\mu\text{g/L}$ may be associated with mild neurologic injury.² However, the large series on hypothermic arrest for aortic surgery have not examined these parameters nor compared outcomes according to whether patients had deep hypothermic circulatory arrest alone (DHCA), antegrade brain perfusion (ANTE), or retrograde brain perfusion (RBP).⁽¹⁻⁵⁾ Thus, to determine the incidence and prognosis (temporary or permanent) of brain injury, we compared these parameters in a prospective randomized study.

Methods. Institutional review board approval was obtained for block randomizing a series of 15 patients into 3 equal groups undergoing DHCA, ANTE, and RBP by folded cards in an opaque envelope. In addition, 5 patients undergoing CAB served as controls. Patients who were either undergoing emergency surgery or were older than 75 years were excluded from the study. Patients were operated on between November 1996 and November 1997. DHCA was performed as described previously,³ as was RBP (300-500 mL/min via the occluded superior vena cava to maintain a pressure of 25-35 mm Hg).^{2,3} ANTE was performed by cannulating the right subclavian artery, occluding the innominate artery origin with a balloon catheter, and perfusing the common carotid artery with a balloon catheter while maintaining pressures at 40 to 60 mm Hg. Electroencephalograms were preformed during the operation and the morning after the operation in all patients. A battery of 14 neurocognitive test types (Tables I-IV) were performed before the operation, 4 to 6 days after the operation, 2 to 3 weeks after the operation, and 6 months after

the operation. Serum S-100 protein levels were measured with S-100 immunoradiometric reagents from Sangtec, Bromma, Sweden, before cardiopulmonary bypass (CPB), while CPB was being started, after cooling, after circulatory arrest, after rewarming, at the conclusion of CPB, on leaving the operating room, and at 6, 12, 18, 24, and 48 hours after the operation. Limits of detection were 0.2 $\mu\text{g/L}$ S-100, and normal is less than 0.2 $\mu\text{g/L}$. Statistical analysis was done with the paired Student *t* test for time-related data and comparison between the groups. Regression analysis was performed by means of simple linear regression.

Results. All patients survived the operation, awoke the following morning, and showed no electroencephalographic evidence of seizures or localized deficits. None had a stroke. Hemi-arch replacements required substantially shorter arrest times than did total arch replacements: 21.0 minutes (standard deviation [SD] 12.7 minutes) versus 49.3 minutes (SD 10.3 minutes) ($P = .0003$) (total arch = 6, including 3 elephant trunk procedures). The respective circulatory arrest times for DHCA, ANTE, and RBP were 24.2 (SD 22.7), 39.8 (SD 19.1), and 37.3 (SD 15.0) minutes (P value indicated no significant difference); however, ANTE hemi-arch repairs required longer circulatory arrest times (31 minutes [SD 9.5] vs 10 minutes [SD 3.5] for DHCA/RBP, $P = .004$).

There were no differences in the preoperative neurocognitive tests among the groups (Tables I-IV). Of the preoperative tests, Logical Memory II (Wechsler Memory Scale-Revised, WMS-R) correlated with age ($P = .02$, $r^2 = 0.3$), as did Reaction Time ($P = .03$, $r^2 = 0.3$). Postoperatively, however, 5 tests (including subtests) showed a decline in neurocognitive function ($P < .05$) 4 to 6 days after hypothermic arrest (Table II). Later, neurocognitive tests at 2 to 3 weeks showed no significant difference compared with preoperative values. In comparisons among the groups, at 4 to 6 days after the operation (Tables III and IV), the following were significantly different ($P < .05$): Beck Depression Inventory (RBP patients scored the highest level of depression and physical concerns); Shipley Vocabulary Raw and Age Scores (DHCA scored the highest and ANTE the lowest of the hypothermic arrest patients); Shipley Abstraction Raw and Age Scores (RBP scored the highest and ANTE the lowest); Shipley Total Mental Age (RBP scored the highest and ANTE the lowest); and Shipley Estimated Wechsler Adult Intelligence Score (WAIS) IQ (DHCA scored the highest and ANTE the lowest)

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Table I. *List of neurocognitive tests*

<i>Test: Information and Orientation (WMS-R)</i>	
1	Beck Depression Inventory Mental Control (WMS-R)
2	Digit Span (WAIS-R) Forward Backward WAIS-R scaled score WAIS-R age-adjusted scaled score
3	Visual Memory Span (WMS-R) Maximum forward positions Age group percentile Maximum backward positions Age group percentile
4	Logical Memory I (WMS-R) Age group percentile Logical Memory II Age group percentile Visual Reproduction I (WMS-R) Age group percentile Visual Reproduction II (WMS-R) Age group percentile
5	Shipley Institute of Living Scale Vocabulary raw score Vocabulary—age equivalents Abstraction raw score Abstraction age equivalents Total mental—age Estimated WAIS full-scale IQ
6	Trail Making Test A: Completion time Errors Trail Making Test B: Completion time Errors

Table I. *Continued*

<i>Test: Information and Orientation (WMS-R)</i>	
7	CVLT Trials 1-5 Short delay—free recall Short delay—cued recall Long delay—free recall Long delay—cued recall Recognition trial Cluster Perservations
8	Block Design (WAIS-R) Scaled score Age-adjusted scaled scores
9	PASAT Number Longest string
10	Symbol Digit Test Reaction time (vigil)
11	Finger Oscillation Test Dominant Nondominant
12	Boston Naming Test
13	Controlled Word Association Test (FAS) Number of words Age percentile
14	Hooper Visual Organization Test

WMS-R, Wechsler Memory Scale-Revised; WAIS-R, Wechsler Adult Intelligence Scale-Revised; CVLT, California Verbal Learning Test; PASAT, Paced Auditory Serial Attention Test; FAS, Controlled Word Association Test.

Table II. *Significantly different neurocognitive scores over time*

<i>Test</i>	<i>Baseline</i>		<i>4-6 Days postop</i>		<i>t Values, P values, and 95% CI</i>
	<i>Mean</i>	<i>SD</i>	<i>Mean</i>	<i>SD</i>	
Digit Span (WAIS-R)					
Backward	5.09	2.47	3.91	1.81	$t = 3.634, P = .005 (0.4751, 1.907)$
WAIS-R	7.72	2.33	6.73	1.85	$t = 2.47, P = .033 (9.88, 1.90)$
WAIS-R (age adjusted)	9.64	2.25	7.82	2.14	$t = 4.10, P = .002 (0.8300, 2.806)$
Controlled Word Association					
Number of words	38.82	16.23	32.36	11.84	$t = 2.149, P = .057 (-0.2391, 13.1482)$
Trail Making Tests					
Trail Making Test B	104	53.33	158.82	81.56	$t = -3.19, P = .010 (-93.08, -16.55)$
Symbol Digit Test					
Symbol Digit	55.64	19.27	36	16.14	$t = 2.89, P = .016 (4.51, 34.76)$

SD, Standard deviation; CI, 95% confidence interval for mean differences calculated by subtracting means postoperatively from baseline means.

despite estimated intellectual function being equal before the operation. RBP and DHCA Shipley scores were similar to CAB scores (no significant difference), except that depression (Beck Depression Inventory) was higher in the RBP group. The Shipley scores of ANTE patients were significantly worse than those of CAB patients. Nevertheless, 2 to 3

weeks after discharge from the hospital, there were no significant differences between the groups (including CAB), nor was there a significant difference at 6 months. The in-hospital neurocognitive tests before discharge showed a correlation between age and Wechsler Adult Intelligence Scale—Revised (WAIS-R): Logical Memory I ($P = .03, r^2 = 0.3$),

Table III. Significantly different scores among groups at 4 to 6 days after the operation

Test	CAB vs RBP	RBP vs ANTE	ANTE vs DHCA	CAB vs ANTE
Shipley				
Vocabulary—raw score		$t = 2.49, P = .055$ (-0.7409, 48.74)	$t = 3.886, P = .012$ (-14.12, -2.878)	$t = 5.51, P = .001$ (5.6521, 14.1479)
Vocabulary—age equivalent		$t = 2.801, P = .031$ (1.29, 19.21)	$t = 3.315, P = .021$ (-5.918, 0.7485)	$t = 4.561, P = .003$ (1.8297, 5.7703)
Abstraction—raw score		$t = 2.455, P = .049$ (4.316, 24.96)	$t = -2.75, P = .040$ (-21.62, -0.7161)	$t = 3.442, P = .011$ (4.4439, 23.9561)
Abstraction—age equivalent			$t = 2.714, P = .42$ (-6.17, -0.168)	$t = 3.188, P = .015$ (1.1619, 7.8381)
Total mental age			$t = -3.381, P = .019$ (-32.6, -4.61)	$t = 4.69, P = .002$ (2.3426, 7.2574)
Estimated WAIS full-scale IQ		$t = 2.345, P = .057$ (-0.7923, 37.30)	$t = 3.418, P = .020$ (-7.042, -0.958)	$t = 3.505, P = .010$ (6.6534, 34.2466)
Beck Depression Inventory I Score	$t = 2.591, P = .036$ (-17.5, -0.800)	$t = 3.675, P = .010$ (3.6763, 18.324)		$t = 2.646, P = .038$ (0.2631, 6.74)

There were no significant differences 2 to 3 weeks postoperatively or 6 months postoperatively. Results lacking in statistical significance are excluded from this table. Trends (P values between .005 to .006) are included. CAB, Coronary artery bypass; RBP, retrograde brain perfusion; ANTE, antegrade brain perfusion; WAIS, Wechsler Adult Intelligence Scale.

Table IV. Descriptive statistics for significantly different variables by group

Test	C		RBP		ANTE		DHCA	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Vocabulary—raw	34.4	1.95	31.75	6.5	24.5	3.42	33	1.7321
Vocabulary—age	18.8	0.8367	17.75	2.5	15	1.63	18.33	0.5774
Abstraction—raw	25.2	7.0143	23.5	9	11	4.76	22.67	6.429
Abstraction—age	15	2.65	14.5	3	10.5	1	13.67	2.08
Total mental age	16.8	1.64	16.25	3.5	12	1.412	16	1.732
Estimated WAIS full-scale IQ	116.2	9.88	114	14	95.75	6.8	114.33	7.57
BDI	6.6	5.13	15.75	5.44	4.75	2.5	7.67	7.51

CAB, Coronary artery bypass; RBP, retrograde brain perfusion; ANTE, antegrade brain perfusion; DHCA, deep hypothermic circulatory arrest; SD, Standard deviation; BDI, Beck Depression Inventory. Means were compared via independent t tests and were found to be statistically significant (where $P = < .05$) 4 to 6 days after the operation (see Table III).

Trail Making Test B ($P = .03, r^2 = 0.3$), and Symbol Digit Test ($P = .04, r^2 = 0.3$). However, 2 to 3 weeks after the operation, this correlation no longer existed except for the Symbol Digit Test, and 6 months after the operation this was also no longer significant. The S-100 levels significantly increased transiently after circulatory arrest compared with both baseline and CAB, as shown in Fig 1.

Conclusion. In this small preliminary study, by 2 to 3 weeks after the operation, patients had recovered to their original preoperative levels of neurocognitive function. This study does not take into account the practice effect of learning how to do the tests. Furthermore, we were unable to show any significant difference in brain protection 2 to 3 weeks or 6 months after the operation between the DHCA alone versus ANTE and RBP groups or in comparison between the patients who had DHCA arrest versus CAB. In addition, we also evaluated the patients on the basis of other criteria proposed in the literature.⁵ These criteria for neurocognitive

defects include more than 1 SD decrease in individual neurocognitive tests, or more than a 20% decline in individual tests with more than 20% of individual tests showing a decline. On the basis of these 2 criteria, none of the patients had a significant neurocognitive deficit.

For hemi-arch repairs, the circulatory arrest time is considerably longer with ANTE because of the additional time required for insertion of the innominate and carotid artery catheters for antegrade brain perfusion and later removal of the catheters. However, for longer circulatory arrest times, particularly for total aortic arch replacements, ANTE and RBP may be shown to be beneficial. S-100 levels increased transiently after termination of CPB, indicating some possible brain injury, although these levels returned to normal and undetectable levels within 24 hours and there was no significant difference between the circulatory arrest study groups (Fig 1). This study suggests that brain injury is transient for patients undergoing a relatively brief period of DHCA for

Fig 1. Mean S-100 serum protein values ($\mu\text{g/L}$). CA, Combined mean of circulatory arrest groups (DHCA, ANTE, RBP); CPB, cardiopulmonary bypass; OR, operation.

aortic arch repairs. We are continuing the study to obtain greater statistical power to better define the incidence of neurologic injury, correlation between neurocognitive function and S-100 protein release, and superiority of any method of brain protection.

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