Cognitive Outcomes Three Years After Coronary Artery Bypass Surgery: A Comparison of On-Pump Coronary Artery Bypass Graft Surgery and Nonsurgical Controls

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Background. Coronary artery bypass grafting has been associated with both early and late postoperative cognitive decline, but interpretation of previous studies has been limited by lack of appropriate control groups. We compared changes in cognitive performance from baseline to 3 years in patients undergoing coronary artery bypass grafting with those of a control group of patients with known risk factors for coronary artery disease but without surgery.

Methods. Patients undergoing coronary artery bypass grafting (n = 140) and a demographically similar nonsurgical control group with coronary artery disease (n = 92) completed baseline neuropsychological assessment and were followed up prospectively at 3, 12, and 36 months. Cognitive performance was assessed with a battery of neuropsychological tests, measuring the cognitive domains of attention, language, verbal and visual memory, visuospatial, executive function, and psychomotor and motor speed. The statistical analyses were performed in two ways: using data from all tested individuals, and using a model imputing missing observations for individuals lost to follow-up.

Results. Both the coronary artery bypass grafting and nonsurgical control groups improved from baseline to 1 year, with additional improvement between 1 and 3 years for some cognitive tests. The coronary artery bypass grafting group had statistically significantly greater improvement than the nonsurgical controls for some subtests, and had a comparable longitudinal course for the remainder of the subtests. Both study groups had a trend toward nonsignificant decline at 3 years on some measures, but the overall differences between groups over time were not statistically significant.

Conclusions. Prospective longitudinal neuropsychological performance of patients with coronary artery bypass grafting did not differ from that of a comparable nonsurgical control group of patients with coronary artery disease at 1 or 3 years after baseline examination. This finding suggests that previously reported late cognitive decline after coronary artery bypass grafting may not be specific to the use of cardiopulmonary bypass, but may also occur in patients with similar risk factors for cardiovascular and cerebrovascular disease.

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Although most studies of cognitive outcomes after coronary artery bypass surgery report some decline during the immediate postoperative period, there is still controversy regarding the degree and duration of these changes. More recently, the possibility of a delayed or late decline in cognition after coronary artery bypass grafting (CABG) has been reported. In a large prospective study of patients who had undergone CABG, Newman and colleagues [1] reported that 42% of their patients showed decline when reevaluated 5 years after surgery. In a similar 5-year longitudinal study, Stygall and colleagues [2] reported greater than expected late decline for some cognitive domains. Because neither of these studies included a control group, it cannot be determined if these late cognitive changes are specifically related to the use of cardiopulmonary bypass (CPB) or to other factors. Some studies have suggested that patients with coronary artery disease (CAD) may have mild cognitive impairment even in the absence of cardiac surgery [3], and prospective studies of community-dwelling persons with hypertension, diabetes, or other risk factors for cerebrovascular disease suggest some cognitive decline over time [4]. Therefore, it is unclear whether the late cognitive decline after CABG is specifically associated with the use of CPB or if it represents a separate process related to underlying microvascular disease of the brain or other age-related changes.

To evaluate further the later neurocognitive changes

See page 1104

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after CABG, we prospectively observed patients for 36 months after surgery with a battery of standardized neuropsychological tests. To control for the effects of normal aging and nonspecific cerebrovascular disease, we included a group of patients with CAD diagnosed by cardiac catheterization as our nonsurgical control group. The control patients were similar to the CABG patients in terms of risk factors for both CAD and cerebrovascular disease. We have previously described the baseline characteristics and 3- and 12-month cognitive test results for this cohort [5]. Here, we report the results of the prospective longitudinal changes in neuropsychological test performance from baseline to 36 months, with an emphasis on the changes between 12 and 36 months.

Material and Methods

Patients

The study was approved by the Johns Hopkins Institutional Review Board on July 14, 1997. Eligible candidates for CABG who were native English speaking, not intubated, able to sit upright, and able to give informed consent were approached. Enrollment was completed from September 1997 through March 1999. Of the 1,129 patients who underwent CABG during that period, 140 met study inclusion criteria and completed written informed consent and baseline testing. For the nonsurgical controls, three Johns Hopkins cardiologists identified potential patients who were diagnosed with CAD (by cardiac catheterization). These patients were offered a study pamphlet at their office visit and were then contacted by study coordinators to determine if they were interested in participating. Patients were enrolled with the same inclusion criteria listed above for CABG patients except exclusion for previous cardiac surgery. Ninety-two patients provided written informed consent and completed baseline testing.

Neuropsychological Tests

Study participants were administered a battery of standardized neuropsychological tests at baseline, and at 3, 12, and 36 months. Most of the study participants were tested as outpatients, but about one third of the CABG patients were tested in their hospital rooms shortly before their surgery. The following tests were selected to evaluate performance in eight major areas of cognitive functioning (see Lezak [6] for more complete description of the tests): (1) verbal memory: Rey Auditory Verbal Memory Test, a word-list learning task assessing verbal learning (RAVLT Total), delayed recall (RAVLT Trial 8), retention (RAVLT Retention), and recognition memory (RAVLT Recognition); (2) visual memory: Rey Complex Figure–Recall (RCF Delayed Recall) and retention (RCF Retention), measures of the ability to recall a complex visual design previously copied; (3) language: Boston Naming Test (short form), a measure of visual confrontation naming requiring the subject to name a series of 30 line drawings; (4) attention: Rey Auditory Verbal Learning Test–Trial 1 (RAVLT Trial 1); Attention score from

Table 1. Comparison of Interim Medical Events and Potential Confounding Variables Between Study Groups

Interim Variables	CABG	NSC	*p* Value
Three months	n = 116	n = 84	
Surgery w/general anesthesia	10.3%	2.4%	0.02
Report of chest pain/angina	17.2%	19.0%	0.44
Myocardial infarction	2.6%	1.2%	0.44
Repeat cardiac catheterization	5.2%	1.2%	0.13
PTCA	1.0%	1.2%	0.66
Atrial fibrillation	12.1%	2.4%	0.01
New stroke	0.9%	1.2%	0.66
Transient ischemic attack	1.7%	0	0.33
Antihyperlipidemic agent (statin)	65.5%	63.9%	0.46
Current cigarette smoking	1.7%	7.1%	0.06
Head trauma w/LOC	0.9%	0	0.58
Mortality	0.7%	1.1%	0.63
CES-D >15	23.5%	10.7%	0.01
Mean CES-D	10.1	8.1	0.43
Mean FSQ total score	32.1	32.7	0.31
One year	n = 121	n = 83	
Surgery w/general anesthesia	10.7%	3.6%	0.05
Report of chest pain/angina	22.5%	30.5%	0.13
Myocardial infarction	0.8%	0	0.59
Repeat cardiac catheterization	4.1%	3.6%	0.57
PTCA	1.7%	1.2%	0.63
Atrial fibrillation	10.0%	7.2%	0.33
New stroke	1.7%	1.2%	0.63
Transient ischemic attack	4.1%	1.2%	0.21
Antihyperlipidemic agent (statin)	76.5%	62.2%	0.22
Current cigarette smoking	3.3%	6.0%	0.28
Head trauma w/LOC	0	0	-
Mortality	1.4%	3.3%	0.31
CES-D >15	18.1%	15.9%	0.41
Mean CES-D	9.2	7.7	0.61
Mean FSQ total score	32.2	32.4	0.73
Three years	n = 72	n = 57	
Rehospitalized	36.1%	32.8%	0.41
Surgery w/general anesthesia	15.3%	15.5%	0.57
Report of chest pain/angina	22.2%	36.8%	0.05
Myocardial infarction	1.4%	1.8%	0.68
Repeat cardiac catheterization	13.9%	17.5%	0.37
PTCA	5.6%	12.5%	0.14
Atrial fibrillation	15.3%	8.8%	0.20
New stroke	1.4%	0	0.55
Transient ischemic attack	0	1.8%	0.44
Antihyperlipidemic agent (statin)	70.7%	77.8%	0.24
Current cigarette smoking	5.6%	3.5%	0.45
Head trauma w/LOC	1.4%	1.8%	0.68
Cancer/cancer therapy	12.5%	8.6%	0.33
Mortality	7.1%	7.6%	0.54
CES-D >15	12.9%	10.9%	0.48
Mean CES-D	9.6	6.9	0.10
Mean FSQ total score	31.1	31.2	0.91

CABG = coronary artery bypass graft surgery; CES-D = Center for Epidemiologic Studies-Depression; FSQ = Beth Israel Functional Status Questionnaire (physical functioning); LOC = loss of consciousness; NSC = nonsurgical control group; PTCA = percutaneous transluminal coronary angioplasty.

Table 2. Cross-Sectional Unadjusted Neuropsychological Test Scores at Baseline, 12, and 36 Months by Study Group

Cognitive Domain / Test		Baseline Mean (SD)		12-Month Mean (SD)		36-Month Mean (SD)[a]	
		CABG (n = 140)	NSC (n = 92)	CABG (n = 121)	NSC (n = 83)	CABG (n = 72)	NSC (n = 57)
Verbal memory (RAVLT)							
Total score	All[b]	39.3 (8.8)	41.1 (8.8)	44.5 (11)	45.3 (10)	43.5 (12)	44.1 (11)
	3 yr	39.8 (8.8)	42.0 (8.8)	44.9 (11)	45.4 (10)		
Delayed recall	All	7.09 (3.2)	7.73 (3.1)	8.62 (3.4)	8.85 (3.5)	8.22 (3.4)	8.22 (3.7)
	3 yr	6.90 (3.0)	8.00 (3.0)	8.39 (3.6)	8.94 (3.4)		
Retention score (%)	All	70.3 (25)	76.5 (24)	79.6 (24)	79.6 (23)	76.9 (22)	75.2 (29)
	3 yr	68.9 (22)	77.3 (24)	77.0 (25)	80.8 (23)		
Recognition	All	9.70 (3.6)	10.0 (3.8)	10.7 (3.6)	10.7 (3.9)	10.5 (3.8)	11.0 (3.7)
	3 yr	9.50 (3.1)	10.2 (3.6)	11.0 (3.4)	11.1 (3.6)		
Visual memory (Rey Complex Figure)							
Retention score (%)	All	51.3 (19)	48.9 (19)[c]	58.5 (21)	54.9 (21)	57.3 (18)	56.2 (18)
	3 yr	53.1 (18)	53.9 (15)	57.6 (20)	57.7 (19)		
Delayed recall	All	16.9 (7.0)	16.4 (7.0)[c]	19.7 (7.5)	18.5 (7.7)	19.0 (6.6)	18.9 (6.8)
	3 yr	17.7 (6.9)	18.2 (5.7)	19.5 (7.3)	19.4 (6.8)		
Visuoconstruction (Rey Complex Figure)							
Copy	All	32.5 (4.3)	33.0 (3.2)	33.1 (3.7)	33.0 (3.5)	33.0 (4.2)	33.2 (3.6)
	3 yr	33.0 (4.1)	33.5 (3.0)	33.6 (2.8)	33.5 (2.9)		
Block design	All	23.3 (10)	23.4 (9.5)	26.5 (10)	24.1 (9.8)	26.5 (9.7)	24.4 (9.3)
	3 yr	25.0 (9.7)	24.1 (8.8)	27.1 (10)	24.8 (8.8)		
Language							
Boston Naming Test	All	26.2 (3.8)[c]	26.0 (3.7)[c]	27.1 (3.0)	26.5 (3.4)	27.4 (2.5)	26.6 (3.4)
	3 yr	27.0 (2.7)	26.7 (3.6)	27.4 (2.5)	26.9 (3.4)		
Motor speed (Grooved Pegboard)							
Dominant hand (secs)	All[b]	108 (56)	98.2 (30)	95.3 (30)	90.0 (23)	95.4 (33)	98.5 (30)
	3 yr	100 (34)	94.6 (26)	93.2 (31)	86.8 (16)		
Nondominant hand (secs)	All	119 (67)	108 (39)[c]	105 (46)	102 (38)	105 (36)	110 (36)
	3 yr	108 (32)	100 (32)	99.7 (28)	95.7 (24)		
Psychomotor speed							
Trail Making-Part A (secs)	All	47.1 (24)	43.2 (15)	40.6 (17)	41.4 (16)	41.7 (16)	41.0 (15)
	3 yr	41.9 (14)	42.2 (15)	38.7 (12)	40.5 (13)		
Written Alphabet (secs)	All	26.2 (22)	23.5 (11)	27.2 (29)	24.2 (14)	23.1 (11)	23.7 (11)
	3 yr	21.8 (7.5)	22.5 (7.1)	22.5 (10)	23.3 (9.3)		
Attention							
RAVLT Trial 1	All	5.00 (1.4)	5.36 (1.6)	6.15 (2.1)	6.35 (2.0)	6.30 (1.9)	6.07 (1.8)
	3 yr	5.19 (1.5)	5.38 (1.7)	6.35 (2.3)	6.26 (2.0)		
Mini-Mental Attention Score	All	3.95 (1.4)	4.28 (1.2)	4.26 (1.1)	4.61 (0.7)	4.53 (0.8)	4.34 (0.9)
	3 yr	4.17 (1.3)	4.43 (1.0)	4.39 (1.0)	4.63 (0.7)		
Executive function							
Trail Making-Part B (secs)	All	105 (60)	95.6 (41)	102 (78)	93.5 (45)	96.5 (57)	91.9 (38)
	3 yr	93.6 (40)	94.3 (40)	90.9 (59)	94.4 (41)		

[a] The 36-month values for all individuals and those who completed 3-year follow-up are by definition identical. [b] "All" refers to all subjects who were tested at baseline and "3 yr" to subjects who completed 36-month testing. [c] Significant differences at the 5% level between baseline standardized and adjusted values for those who did and did not complete at 3 years.

CABG = coronary artery bypass graft surgery; NSC = nonsurgical control group; RAVLT = Rey Auditory Verbal Learning Test.

Mini-Mental State Examination (Mini-Mental Attention); (5) visuoconstruction: Rey Complex Figure–Copy (RCF Copy), a measure of visuospatial abilities requiring the subject to copy a complex visual design and block design; (6) psychomotor: Trail Making Test A, a timed task that requires the subject to connect numbered circles in sequence as quickly as possible; Written Alphabet, a timed measure of psychomotor speed in which the subject is asked to write the letters of the alphabet as quickly as possible [7]; (7) motor speed: Grooved Pegboard Dominant (Pegboard Dominant) and Nondominant hand (Pegboard Nondominant), a test of motor speed measuring how quickly the subject is able to place 25 keyed pegs in an array of 5 × 5 holes with randomly positioned slots;

Ann Thorac Surg
2005;79:1201–9

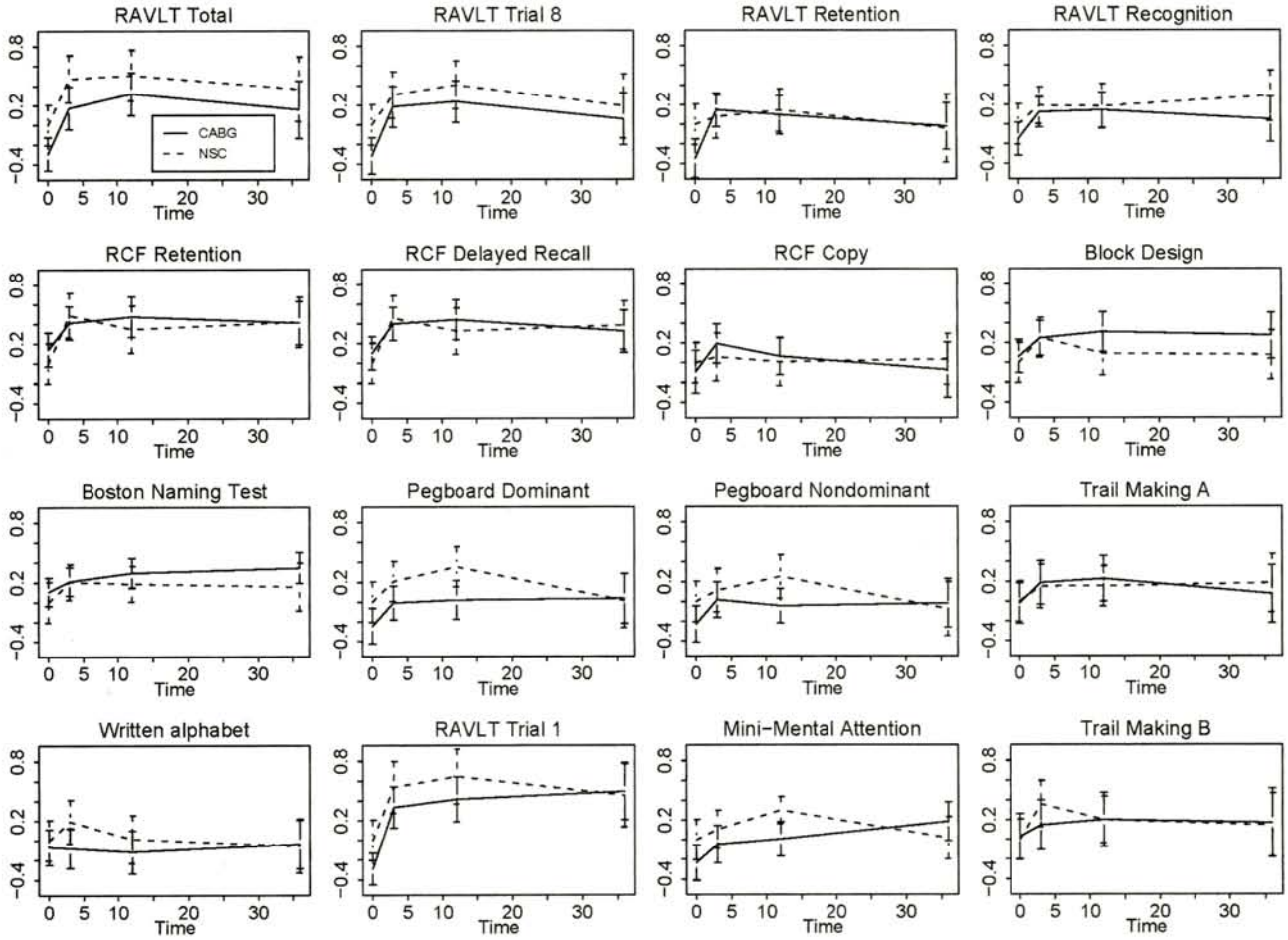

*Fig 1. Mean z-scores for each neuropsychological measure adjusted for age, education, sex, and Center for Epidemiological Studies Depression Scale score for both study groups at baseline and at 3-, 12-, and 36-month follow-up. Scores on timed tests have been inverted to reflect speed of performance, so that positive represents improved performance for all tests. (*CABG = *coronary artery bypass graft surgery;* NSC = *non-surgical control group;* RAVLT = *Rey Auditory Verbal Learning Test;* RCF = *Rey Complex Figure.)*

and (8) executive function: Trail Making Test B, a timed test of psychomotor speed that requires the participant to connect numbered and lettered circles alternately in sequential (numerical and alphabetical) order. Patients were also administered the Mini-Mental State Examination (MMSE). The Center for Epidemiological Studies Depression scale (CES-D) [8] and Functional Status Questionnaire (FSQ) were also administered at baseline and follow-up [9].

Operative Technique

All patients underwent median sternotomy and received at least one arterial graft. A standard anesthetic technique was used consisting of low to intermediate dose narcotics, inhalation agents, and paralytics. Cardiopulmonary bypass was performed with use of a Sarns roller head pump, nonpulsatile flow, membrane oxygenator, α-stat pH blood gas management, antegrade crystalloid cardioplegia and topical hypothermia, moderate systemic hypothermia (28°C to 32°C), and pump flow rates to achieve a mean arterial pressure of 60 to 80 mm Hg. Intraoperative ultrasound aortic scanning was not used. Cardiotomy suction was returned to the cardiopulmonary bypass circuit for all patients. The double-clamp technique was used by all surgeons with one exception. The aortic cross-clamp was applied and distal anastomoses were made, after which the aortic cross-clamp was released and a sidebiting clamp was applied as needed; the proximal anastomoses were then made.

Statistical Methods

The primary data analyses examined within-patient changes in neuropsychological test scores from baseline to 3, 12, and 36 months. This approach allows both improvement and decline relative to a person's baseline performance to be quantified. All analyses were performed using z-scores based on the mean and standard deviation of the baseline performance of the nonsurgical control patients. For timed tests, the z-score was inverted

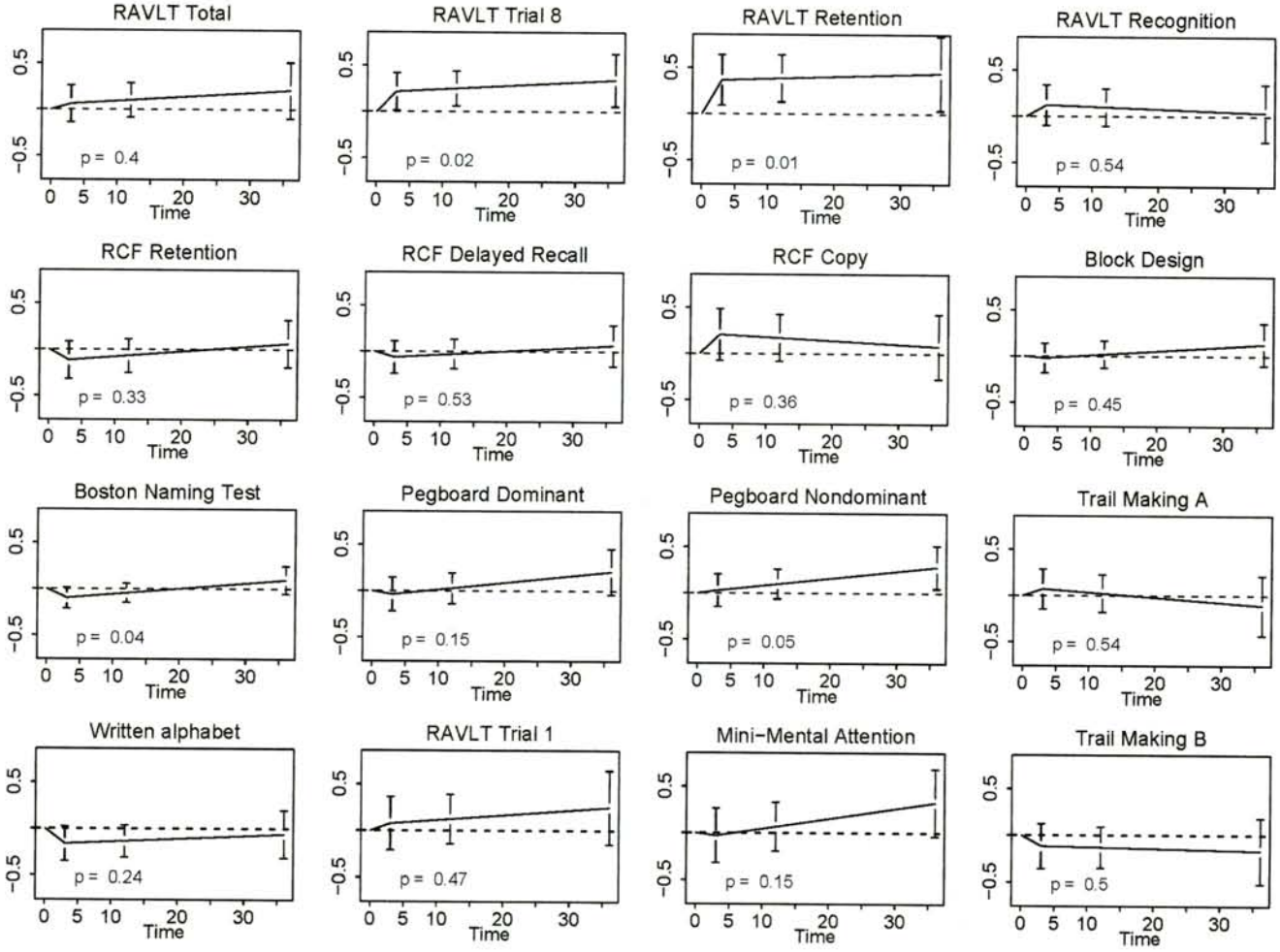

Fig 2. Model estimates of group differences in change in z-scores for each neuropsychological measure from baseline that adjusts for missing data. Scores on timed tests have been inverted to reflect speed of performance. A positive increase in the solid line *indicates a greater improvement from baseline in the coronary artery bypass graft surgery group than in the nonsurgical group. The* dashed line *at 0 represents no difference between the two groups.* (RAVLT = *Rey Auditory Verbal Learning Test;* RCF = *Rey Complex Figure.*)

so that improved performance resulted in a higher score for all variables. For cognitive domains with more than one test, each patient received a composite score consisting of the mean of the z-scores for the individual tests. These were then renormalized so that the nonsurgical control group had a mean of zero and standard deviation of 1 at baseline.

To examine how the changes in neuropsychological test z-scores over time might be related to subject-specific covariates, we used a separate linear mixed effects model for the z-scores from each test. The response variable was the individual subject's test scores on each of the occasions. The model allows for a separate random intercept and time trend for each subject to account for within-person autocorrelation. The model assumes that the average trend can differ between the two study groups. To account for a learning effect from baseline to 3 months, we included an indicator variable to distinguish second and subsequent measurements from the baseline measures. To calculate the treatment effects in the eight cognitive domains, we pooled the estimates from the separate tests in each domain and used bootstrapping to quantify the statistical uncertainty of these estimates (see the accompanying statistical paper by Barry and associates for more details). This analysis protects against biases that can arise if the rate of loss to follow-up differs between the two groups. It does so by internally imputing the missing data by using available observations for that subject before their loss to follow-up.

Our original power calculations were based on a sample size of 100 CABG patients and 100 nonsurgical controls at 1 year, and a range of estimates of the probability of cognitive change in the CABG group. For the estimated probability of cognitive change of 0.30 in the CABG group, and on the assumption that this represents a threefold increase above the probability of that outcome in the nonsurgical controls, the power to detect such a difference would be in the range of 0.80 to 0.94 with our current 3-, 12-, and 36-month sample sizes. (For additional details regarding the statistical methods,

Ann Thorac Surg
2005;79:1201–9

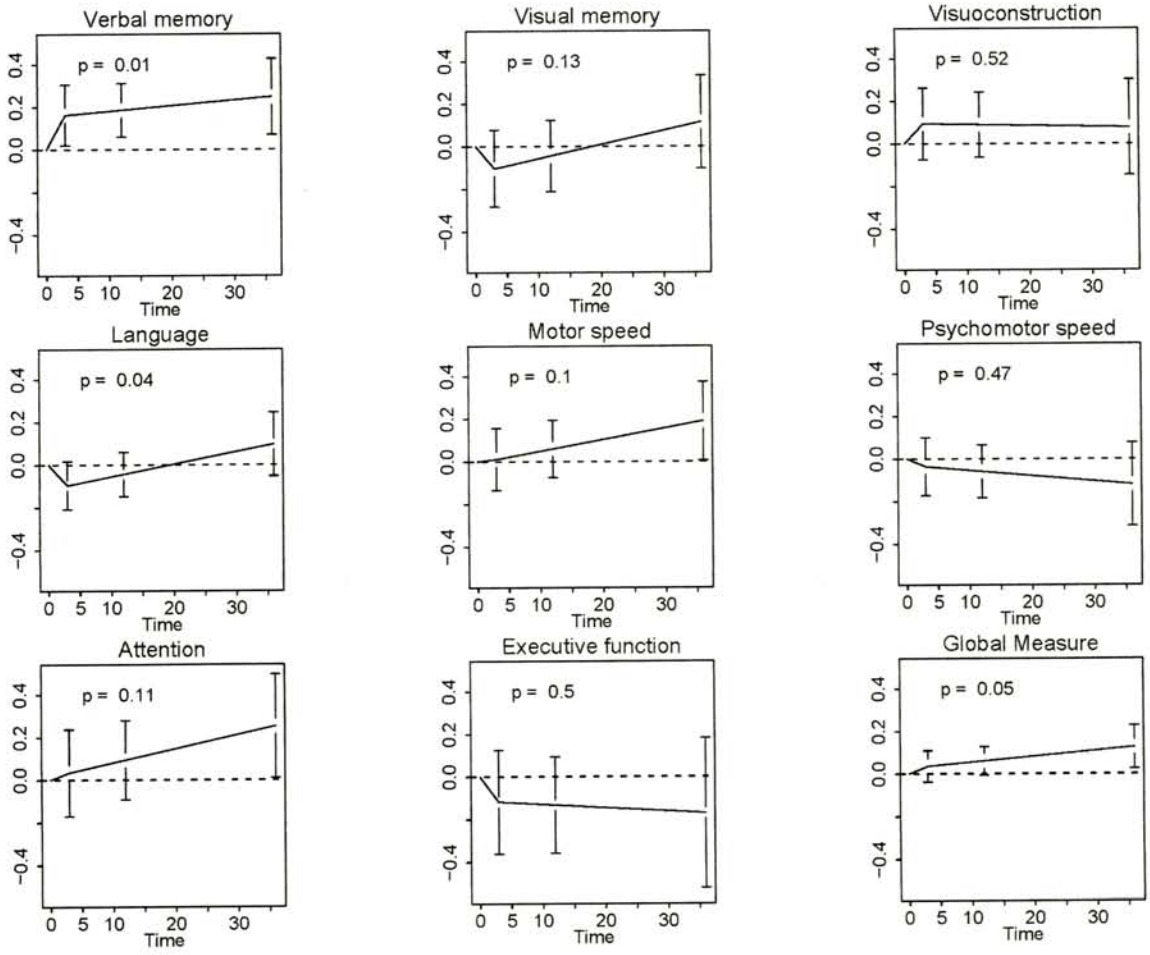

Fig 3. Model estimates of the difference in cognitive performance relative to baseline between the coronary artery bypass graft surgery group and the nonsurgical group over time for eight cognitive domains and one global summary measure that adjusts for missing observations. A positive increase in the solid line *indicates a greater improvement from baseline in the coronary artery bypass graft surgery group than in the nonsurgical group (*dashed line*). In the two domains where there is only one test (Language; Executive Function), the estimate for that particular test is used instead of bootstrapping. (See also accompanying paper by Barry and colleagues for more details [Barry et al., Ann Thorac Surg 2005;79:1104–9].)*

please see the accompanying paper by Barry and coworkers in this issue of *The Annals*.)

Results

Demographic characteristics for the CABG patients and the nonsurgical controls have been previously described [5]. Of the 140 CABG patients recruited into the study, 70 completed the follow-up testing at 36 months, 47 refused further testing, 10 died, and 13 were lost to follow-up. Of the 92 nonsurgical controls, 57 completed 36-month testing, 15 refused further testing, 7 died, and 13 were lost to follow-up. The follow-up rate (excluding deaths) was thus somewhat higher among the nonsurgical controls (67%) than for the CABG group (54%). The average interval between baseline and the 3-year follow-up was similar for the CABG group (3.4 years) and the nonsurgical controls (3.3 years). Approximately one third of each group was tested at their homes.

Interim Medical Events

Mortality, CES-D scores, and interim medical events, including some with a potential for influencing cognitive changes over time, are summarized in Table 1. At 3 years, the number of participants reporting chest pain/angina was significantly higher among the nonsurgical controls. The frequency of other events, including the number of rehospitalizations, noncardiac surgery with general anesthesia, or repeat catheterization, did not differ between the two groups.

Cross-Sectional Results

Mean baseline neuropsychological test scores for the two study groups have been previously described [5]. Baseline scores for patients who did not complete 36-month follow-up testing were generally lower than the scores of those patients who did complete. The only statistically significant difference among the CABG patients who did

not complete the 36-month follow-up was a lower mean score on a test of language (Boston Naming). The nonsurgical controls who did not complete follow-up testing had significantly lower mean scores on measures of visual memory, language, and motor speed (Table 2). Mean unadjusted scores for both groups for the 12- and 36-month follow-up points are also shown in Table 2. After adjusting for demographic factors, education, and CES-D score, the only statistically significant cross-sectional difference between the two study groups at 1 year was higher performance by the CABG group on two measures of memory. At 36 months, the CABG patients continued to have higher performance on the two measures of memory and also on one measure of motor speed (Table 2).

Change From Baseline to 12 and 36 Months

We have previously reported the changes in neuropsychological test performance from baseline to 3 and 12 months for the two groups. Both the CABG and nonsurgical subjects showed significant improvement, with the majority of the change taking place between baseline and 3 months. Similarly, both groups show improved performance from baseline to 12 and 36 months. Where there was some decline, it was very minor for both groups. The one exception to this was a 0.31 standard deviation decline in motor speed (nondominant hand) for the NSC group. Comparing the degree of change from baseline for the two groups, the results are consistent with the cross-sectional comparisons. The CABG group showed statistically significant greater improvement on two measures of memory (delayed recall and percent retention score) at both the 12- and 36-month follow-up. Additionally, greater improvement in one measure of motor speed (Grooved Pegboard, nondominant hand) was observed for the CABG group between baseline and 36 months.

Change From 12 to 36 Months

With only a few exceptions, both groups had marginally lower scores at 36 months than at 12 months. Comparing the degree of change between the two groups, the NSC group had significantly greater decline for two measures of motor speed as well as the overall MMSE score.

Overall Longitudinal Trends

The overall trends in the change in neuropsychological test performance for the CABG and NSC groups over time are shown in Figure 1. The graphs show group mean z-scores that are adjusted for age, education, sex, and CES-D score for each of the neuropsychological measures. The overall performance of the two groups over time is strikingly similar for the majority of the neuropsychological tests and subtests. For most of the measures, the performance of the two groups over time appears relatively stable, with no evidence of significant decline relative to baseline performance.

We performed additional analyses using a mixed linear model, which allowed missing observations for a given subject to be taken into account by using available observations for that subject before their loss to follow-up. The graphs illustrating the adjusted longitudinal course of the two study groups are shown in Figure 2. There were only four subtests (RAVLT Trial 8, RAVLT Retention, Boston Naming Test, and Pegboard, nondominant hand) for which the overall differences between the two groups reached statistical significance. In all cases, the scores of the CABG were slightly higher than those of the NSC group; thus, we observed no evidence of a disproportionate late decline associated with the surgery. Although there was a nonsignificant trend in the direction of lower scores at 36 months for the CABG group for some measures (RAVLT Recognition, Rey Complex Figure Copy, and Trail Making Test A and B), relative to the performance of the nonsurgical control group, there was no evidence of statistically significant late decline in the CABG group for any of the neuropsychological tests and subtests.

We also combined the results of the individual neuropsychological subtests into eight cognitive domains, and one global measure representing the average of the z-scores for all of the individual neuropsychological measures. The longitudinal trends in the differences between the CABG and NSC in changes from baseline for these summary measures are shown in Figure 3. Relative to the performance of the nonsurgical controls, the CABG patients had statistically significantly greater improvement over time in the domain of verbal memory ($p = 0.001$) and in the global summary measure ($p = 0.05$). There were nonsignificant trends for greater improvement in the CABG group relative to the nonsurgical control group for visual memory, language, motor speed, and attention. For the domains of psychomotor speed and executive functions, there were nonsignificant trends for a decrease in performance over time in the CABG group relative to the nonsurgical controls.

Comment

Coronary artery bypass grafting (CABG) can provide significant improvement in survival and quality of life for patients with CAD, but the possibility of delayed or late cognitive decline up to 5 years after CABG with CPB has been reported by several recent studies [1, 2, 10]. None of the previous long-term outcome studies included a control group, and it is therefore not possible to determine if these late cognitive changes were due to delayed effects of the use of CPB, nonspecific effects of major surgery with general anesthesia, interim central nervous system events, or normal aging. In this prospective study of late cognitive changes after CABG, we compared the cognitive test performance of CABG patients with that of a group of nonsurgical control patients with diagnosed CAD.

The principal finding of this continued follow-up of our study groups was that the overall long-term neuropsychological test performance of CABG patients did not differ from that of the nonsurgical control patients with CAD. After statistical adjustments for loss to follow-up, the only statistically significant differences between the longitudinal performance of the two groups were in favor

Ann Thorac Surg
2005;79:1201–9

of the CABG group, which showed higher test performance for some of the cognitive measures. Both groups showed mild, but statistically nonsignificant decline between 12 and 36 months. These findings suggest that the degree of long-term change up to 3 years after CABG does not appear to be different from that observed among patients with CAD but no surgery. Thus, we have no evidence that the changes observed between 12 and 36 months are specifically due to the use of CPB. Whether this decline will become significant at 5 years remains to be determined through additional follow-up. Moreover, whether this decline is associated with normal aging, cerebrovascular disease, or other factors can only be determined by comparison with a control group without risk factors for cerebrovascular disease.

Short-term changes in cognitive test performance during the first days to weeks after surgery are well documented [11, 12], and typically involve multiple cognitive domains such as attention, memory, and psychomotor speed. Although the etiologies of these acute cognitive changes are still incompletely understood, recent studies with a control group demonstrate that the early cognitive decline is largely reversible by 3 months or sooner after surgery [5, 13, 14].

For obvious reasons, long-term, or progressive decline in cognition years after surgery is of greater concern than transient, acute postoperative changes. Several studies have concluded that there is greater than expected decline in cognitive test performance 5 years after CABG [2, 10], with one of these reporting that up to 42% of their patients had late cognitive decline [1]. These previous studies, however, focused only on the CABG group, and did not include a control group with similar demographic and medical risk factors. There is only one contemporary long-term follow-up study of cognition after CABG that has included a control group. Hlatky and colleagues [15] compared cognitive functioning in two groups that had been randomly assigned 5 years earlier to receive either CABG (n = 61) or angioplasty (n = 64) and concluded that there were no cross-sectional differences in cognitive test performance between the two groups at 5 years. This study did not include a baseline cognitive assessment, however, and differences between the two groups in the degree of change over time could not be compared.

Surprisingly, in two of the previous studies reporting late cognitive decline at 5 years after surgery, the greatest decline was not in the area of memory, but rather in measures of speed and executive type functioning (Trail Making Test B) [1, 2]. Indeed, in both of these studies there appeared to be improvement in the memory scores at 5 years when compared with the baseline scores. This may be significant for two reasons. First, the improvement in the overall memory scores over time would argue against the onset of a dementing illness such as Alzheimer's disease as the explanation for the late decline. Second, the disproportionate decline on a test such as the Trail Making Test that measures speed of performance would be consistent with normal aging or progression of subcortical microvascular disease. In a recent large community-based study of cognitive changes over time in neurologically normal elderly persons, the only subtest to show significant decline over time was the Trail Making Test B [16], suggesting that longitudinal decline on this particular measure is also seen in otherwise healthy persons. Decline in motor and psychomotor speed has also been reported as part of the cognitive profile of patients with subcortical microvascular disease [17, 18].

The only previous prospective long-term follow-up study of cognitive outcomes that has not found evidence of late decline after CABG was reported recently by Mullges and colleagues [19]. They found no decline in cognitive test performance (1 standard deviation decline in two or more of seven tests) among the 52 patients available for follow-up 5 years after baseline testing. The authors suggested that strict medical management of risk factors for cerebrovascular disease (including blood pressure, cholesterol, and diabetes), after the surgery, may explain the lack of any late cognitive decline in their study group. While this remains an interesting possibility, it has not yet been tested in any longitudinal follow-up study of cognition after CABG. In our current study, a high proportion of patients in both the CABG and nonsurgical control groups were taking lipid-lowering medications at all follow-up time points. The importance of optimal medical therapy after CABG has been emphasized by the American Heart Association, but several studies report underutilization of postoperative strategies for reducing the risk of cerebrovascular disease [20].

Previous longitudinal studies have generally not reported the frequency of interim medical events that might adversely influence cognitive performance over time [1, 2, 10]. In the current study, we recorded several interim events that may have resulted in worse cognitive performance over time, including a history of new stroke, surgery with general anesthesia, repeat cardiac catheterization, and others. With the exception of a greater frequency of angina in the nonsurgical control group at 3 years, we found a comparable rate of interim medical events in the two study groups.

Limitations

Loss to follow-up is always a major concern in longitudinal studies, and in our study, the loss to follow-up at 36 months was slightly higher among the CABG patients than the nonsurgical controls. In previous long-term studies of cognition after CABG, follow-up rates ranged from 57% to 66%. The mixed linear model used for our analyses gives valid inferences when the probability of dropping out does not differ between the two study groups. It cannot, nor can any method, protect against a scenario in which the probability of dropping out depends on different factors for the two study groups. Baseline cognitive scores for the CABG subjects who did not complete the 36-month follow-up were statistically significantly lower for only one of 16 tests, suggesting that their loss to follow-up may not have been specifically related to lower cognitive test performance.

Our study is also limited because to date we have

followed up the study participants for only 3 years after baseline. Previous long-term follow-up studies have generally observed their patients out to 5 years, and it is therefore possible that additional follow-up of our cohort will demonstrate decline in cognition. One advantage of having our 3-year follow-up time point is that it will allow us to determine if any changes between 1 and 5 years are linear or whether most of the changes take place beyond 3 years.

For multiple logistical and ethical reasons, our study was not a prospective randomized trial, and therefore we cannot rule out that the study participants who had CABG differed in important ways from the otherwise comparable nonsurgical participants. For example, it is possible that the CABG patients had more extensive CAD than the controls. Nevertheless, in the absence of any differences between the two groups in their long-term cognitive outcomes, this does not appear to be a significant limitation.

Continued follow-up of our cohort to 5 years after surgery will help determine if one or both groups show significant decline between 3 and 5 years. It is also our intention to compare these two groups with two additional groups that are being studied prospectively: a coronary artery group undergoing "off-pump" surgery (to control for possible effects of anesthesia) and a healthy control group consisting of persons without known risk factors for cardiovascular and cerebrovascular disease.

Based on our data available to date, we conclude that patients undergoing CABG are no more likely to develop cognitive decline between 1 and 3 years after surgery than are control patients with CAD but no surgery.

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