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LONGITUDINAL ASSESSMENT OF NEUROCOGNITIVE FUNCTION AFTER CORONARY-ARTERY BYPASS SURGERY

MARK F. NEWMAN, M.D., JERRY L. KIRCHNER, B.S., BARBARA PHILLIPS-BUTE, PH.D., VINCENT GAVER, B.S., HILARY GROCOTT, M.D., ROBERT H. JONES, M.D., DANIEL B. MARK, M.D., JOSEPH G. REVES, M.D., AND JAMES A. BLUMENTHAL, PH.D., FOR THE NEUROLOGICAL OUTCOME RESEARCH GROUP AND THE CARDIOTHORACIC ANESTHESIOLOGY RESEARCH ENDEAVORS INVESTIGATORS*

ABSTRACT

Background Cognitive decline complicates early recovery after coronary-artery bypass grafting (CABG) and may be evident in as many as three quarters of patients at the time of discharge from the hospital and a third of patients after six months. We sought to determine the course of cognitive change during the five years after CABG and the effect of perioperative decline on long-term cognitive function.

Methods In 261 patients who underwent CABG, neurocognitive tests were performed preoperatively (at base line), before discharge, and six weeks, six months, and five years after CABG surgery. Decline in postoperative function was defined as a drop of 1 SD or more in the scores on tests of any one of four domains of cognitive function. (A reduction of 1 SD represents a decline in function of approximately 20 percent.) Overall neurocognitive status was assessed with a composite cognitive index score representing the sum of the scores for the individual domains. Factors predicting long-term cognitive decline were determined by multivariable logistic and linear regression.

Results Among the patients studied, the incidence of cognitive decline was 53 percent at discharge, 36 percent at six weeks, 24 percent at six months, and 42 percent at five years. We investigated predictors of cognitive decline at five years and found that cognitive function at discharge was a significant predictor of long-term function ($P<0.001$).

Conclusions These results confirm the relatively high prevalence and persistence of cognitive decline after CABG and suggest a pattern of early improvement followed by a later decline that is predicted by the presence of early postoperative cognitive decline. Interventions to prevent or reduce short- and long-term cognitive decline after cardiac surgery are warranted. (N Engl J Med 2001;344:395-402.)

COGNITIVE decline has increasingly been recognized as a complication after cardiac surgery. Although important advances in techniques for perioperative anesthesia, surgery, and the protection of organs have resulted in substantial reductions in age-adjusted and risk-adjusted mortality,[1] the incidence of cognitive decline has changed little over the past 15 years. Elderly patients with multiple health problems, who are at higher risk than other groups of patients for neurologic and neurocognitive problems, are now able to undergo surgical procedures relatively late in life without serious concern about loss of life. However, they are at substantially increased risk for central nervous system dysfunction and, in particular, cognitive decline after surgery.[2-5] The clinical and financial implications of these problems can be profound, since prolonged hospitalization and an increased use of resources are associated with major and even minor neurobehavioral declines.[6,7]

Many clinicians have minimized the importance of perioperative cognitive decline, because the decline appears to be transient in a substantial number of patients. The incidence of impairment is related to the time that has elapsed between cardiac surgery and the assessment of cognitive function. The incidence of decline is highest at discharge (when it is approximately 50 to 80 percent); it is 20 to 50 percent at six weeks and 10 to 30 percent at six months.[5,8-10] Despite this substantial rate of persistent decline, many have questioned the importance of cognitive deterioration with regard to long-term outcome for patients.

From the Department of Anesthesiology (M.F.N., J.L.K., B.P.-B., V.G., H.G., J.G.R.), the Department of Surgery (R.H.J.), the Division of Cardiology (D.B.M.), and the Department of Psychiatry and Behavioral Science (J.A.B.), Duke University Medical Center, Durham, N.C. Address reprint requests to Dr. Newman at the Division of Cardiothoracic Anesthesia, Box 3094, Duke University Medical Center, Durham, NC 27710, or at newma005@mc.duke.edu.

*The members of the study groups are listed in the Appendix.

We undertook a prospective investigation to determine the effect of perioperative cognitive deterioration on longer-term cognitive function by following cognitive function longitudinally for five years after cardiac surgery.

METHODS

Enrollment of Patients

After approval was obtained from the institutional review board, 261 patients undergoing elective coronary-artery bypass grafting (CABG) gave their written informed consent and were enrolled in the study. Patients who had a history of symptomatic cerebrovascular disease (with residual deficit), psychiatric illness, renal disease (indicated by a serum creatinine concentration higher than 2.0 mg per deciliter [177 μmol per liter]), or active liver disease, who had less than a seventh-grade education, or who could not read were excluded.

Measurement of Neurocognitive Function

A brief battery of neurocognitive tests was administered before surgery (at base line), on the day before discharge (approximately seven days after CABG), and six weeks, six months, and five years after CABG (Fig. 1). Assessments were performed individually by experienced psychometricians using a well-validated battery that included five tests. The short-story module of the Randt Memory Test requires subjects to recall the details of a short story immediately after it is read to them and after a 30-minute delay. Scoring is based on both the ability of the subject to recall the story verbatim and the ability to capture its gist on immediate and delayed testing (resulting in four variable scores ranging from 0 to 10 or 0 to 20, with higher scores indicating better function).[11] The Digit Span subtest of the Wechsler Adult Intelligence Scale–Revised requires subjects, first, to repeat in numerical order a series of digits that has been presented to them orally and then, in an independent test, to repeat the digits in reverse order (resulting in two variable scores ranging from 0 to 14, with higher scores indicating better function).[12] The Benton Revised Visual Retention Test requires subjects to reproduce from memory a series of geometric shapes after a 10-second exposure (resulting in one variable score ranging from 0 to 10, with a higher score indicating better function).[13] The Digit Symbol subtest of the Wechsler Adult Intelligence Scale–Revised is a task that requires subjects to reproduce on paper, within 90 seconds, as many coded symbols as possible in blank boxes beneath randomly generated digits, according to a coding scheme for pairing digits with symbols (for one variable score ranging from 0 to 90, with a higher score indicating better function).[12] The Trail Making Test (Part B) requires subjects to connect with a line, as quickly as possible, a series of numbers and letters in sequence (e.g., 1–A–2–B) (for one variable score ranging from 1 to 300, with a lower score indicating better function).[14]

Treatment of Patients during Cardiac Surgery

Anesthetic management with midazolam, fentanyl, vecuronium, and a perfusion apparatus has been previously described.[2] Nonpulsatile perfusion of 2 to 2.4 liters per minute per square meter of body-surface area was maintained throughout cardiopulmonary bypass. The pump was primed with crystalloid solution designed to achieve a hematocrit of 18 percent or higher during extracorporeal circulation. Packed red cells were added when necessary to achieve the desired hematocrit. Cardiopulmonary bypass was instituted through cannulation of the ascending aorta in all patients. Arterial carbon dioxide tension was maintained at 35 to 40 mm Hg (uncorrected for temperature) throughout the cardiopulmonary-bypass procedure, and the partial pressure of oxygen was maintained at 150 to 250 mm Hg.

Statistical Analysis

To assess neurocognitive function over time while minimizing the potential for redundancy in the neurocognitive measures, a factor analysis with orthogonal rotation (a linear transformation used to make the results of the factor analysis easier to interpret) was first performed on the base-line scores on the nine individual neurocognitive tests. This analysis included all 261 enrolled patients. Factor analysis was used to reduce the larger number of correlated dependent variables to a smaller number of uncorrelated outcome variables to be used in the final analysis. The factor loadings (weights) of each test on each factor were used to construct comparable domain scores at each of the follow-up evaluations, on the basis of the patients' test scores at that time. Thus, the domains (areas tested) were identified at base line and remained consistent throughout follow-up. Because the factors were not correlated with each other, type I errors due to multiple comparisons were minimized. The use of factors instead of the individual scores as the outcomes in subsequent analyses also eliminated concern about the redundancy of tests and the possibility of overrepresenting a single domain of cognitive functioning.

Factor analysis of the base-line scores on the nine neuropsychological tests suggests that four factors accounted for 86 percent of the variance among patients' base-line results on our battery of tests. The four factors represent the cognitive domains of verbal memory and language comprehension (short-term and delayed); abstraction and visuospatial orientation; attention, psychomotor proc-

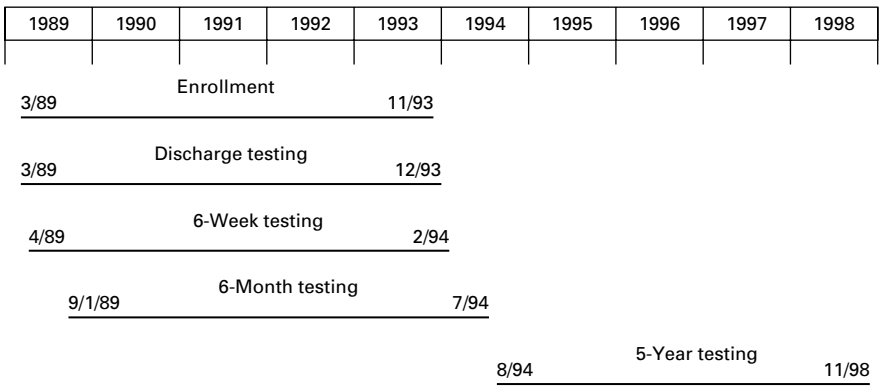

Figure 1. Time Line of the Study.

Patient enrollment began in March 1989 and ended in November 1993. Discharge testing was conducted between 5 and 15 days after surgery, 6-week testing 4 to 6 weeks after surgery, 6-month testing 5 to 8 months after surgery, and 5-year testing 4.4 to 5.4 years after surgery.

essing speed, and concentration; and visual memory. We calculated the change in score for each of the factors by subtracting the base-line scores for that factor from the follow-up scores for that factor. Cognitive decline was defined as a decline of 1 SD in performance in any one of the four domains (the standard deviation was equal to the cross-sectional standard deviation of the base-line scores for the relevant factor).

To assess overall cognitive function and the degree of learning (improvement due to practice, reflecting repeated exposure to the testing procedures) or cognitive decline across all domains, we calculated a composite cognitive index by adding the four domain scores to yield a single, continuous measure of cognitive function. This summary measure was used to control for base-line function in multivariable models and included improvement as well as decline.

Predictors of the presence or absence of cognitive decline (as a dichotomous outcome) were investigated by means of logistic-regression analysis. Predictors of change in the composite cognitive index were investigated by means of a linear regression model. When patients were unable to complete one or two of the nine tests or subtests at base line or at follow-up, we included data in the analysis for the tests they did not complete by imputing values on the basis of a regression equation incorporating the available values. Data for patients with more than two missing scores were not included in the analysis. However, to ensure that the exclusion of data for patients who were unable to complete the five-year follow-up evaluation because they had died or had had a stroke did not bias our results with respect to the effect of early decline on long-term function, we repeated our analysis after imputing worst-case scores for these patients.

RESULTS

A total of 261 patients were enrolled in the study at the Duke Heart Center from March 1989 through November 1993, and final five-year follow-up was completed in November 1998. Characteristics of the patients, including age, sex, race, years of education, duration of cardiopulmonary bypass, duration of aortic cross-clamping, and medical conditions are listed in Table 1. Of the original 261 patients, 172 were available for follow-up at five years and completed the postoperative testing at the earlier times. Comparison of the demographic and clinical characteristics of the patients who completed follow-up with the characteristics of those who did not indicated that the latter were more likely to have American Society of Anesthesiologists (ASA) class IV risk, to have had a previous myocardial infarction, and to have a history of symptomatic neurologic events (Table 1). The reasons for loss to follow-up (in 89 patients) were our inability to contact the patient (30 patients [34 percent]), death (23 patients [26 percent]), health problems (14 patients [16 percent]), lack of interest (8 patients [9 percent]), lack of transportation (5 patients [6 percent]), and other reasons (9 patients [10 percent]).

The mean scores on the neurocognitive tests at base line and at the four follow-up evaluations are presented in Table 2. Cognitive decline was evident in 53 percent of the patients at discharge; the incidence decreased to 36 percent at six weeks and 24 percent at six months. Five years after surgery, the incidence of cognitive decline was 42 percent. The in-

TABLE 1. CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	ALL ENROLLED PATIENTS (N=261)	PATIENTS WHO COMPLETED FOLLOW-UP (N=172)	PATIENTS WHO DID NOT COMPLETE FOLLOW-UP (N=89)	PATIENTS WHO COMPLETED FOLLOW-UP, HAD A STROKE, OR DIED (N=197)†
Age (yr)	60.9±10.6	61.0±10.4	61.6±10.8	61.9±10.5
Education (yr)	12.2±3.8	12.1±3.8	13.0±3.8	12.1±3.8
Male sex (%)	74.7	71.6	84.4	73.1
White race (%)	91.2	89.7	92.2	89.3
Duration of cardiopulmonary bypass (min)	111.6±34.5	113.2±34.0	112.8±42.1	112.8±34.3
Duration of aortic cross-clamping (min)	47.8±18.3	48.5±18.1	46.4±16.3	48.9±18.9
Left ventricular ejection fraction	0.517±0.119	0.522±0.113	0.512±0.128	0.511±0.117
History of hypertension (%)	51.2	51.8	50.0	50.3
ASA class IV risk (%)	57.4	52.5	67.1‡	54.6
CCS class IV angina (%)	43.0	43.0	43.1	42.6
Diabetes (%)	14.0	13.2	15.7	13.3
Previous myocardial infarction (%)	47.3	42.2	47.1‡	43.6
Previous symptomatic neurologic event (%)	7.6	4.8	13.3§	6.4

*Plus–minus values are means ±SD. ASA denotes American Society of Anesthesiologists, and CCS Canadian Cardiovascular Society.

†Worst-case scores were imputed for patients who had died.

‡P=0.03 for the comparison with patients who completed follow-up.

§P=0.02 for the comparison with patients who completed follow-up.

TABLE 2. SCORES ON TESTS OF NEUROCOGNITIVE FUNCTION AT THE FIVE TESTING POINTS.*

MEASURE	RANGE OF POSSIBLE SCORES†	BASE LINE (N=261)	DISCHARGE (N=252)	6 WEEKS (N=222)	6 MONTHS (N=210)	5 YEARS (N=172)
Test						
Digit Symbol subtest‡	0–90	38.78±13.71	33.44±13.60	45.28±14.24	46.46±14.02	38.00±14.94
Benton Visual Retention subtest	0–10	5.14±2.25	4.53±2.37	6.55±2.21	6.29±2.39	5.02±2.17
Randt Short-Story Memory Test						
Delayed						
Gist	0–10	5.01±2.14	4.63±2.30	5.48±2.22	6.04±2.08	5.63±2.31
Verbatim	0–20	6.23±3.26	5.70±3.43	7.10±3.69	8.09±3.58	7.30±3.51
Immediate						
Gist	0–10	5.73±1.83	5.80±1.91	6.37±2.05	6.61±1.74	6.49±1.90
Verbatim	0–20	7.88±3.25	8.09±3.32	9.17±3.72	9.90±3.49	9.21±3.34
Digit Span subtest‡						
Forward	0–14	7.25±2.29	6.99±2.33	7.73±2.25	7.91±2.57	7.00±2.29
Backward	0–14	5.43±2.26	4.71±2.21	6.10±2.28	6.43±2.38	5.30±2.19
Trail Making Test (Part B)	1–300	142.24±73.56	158.77±81.81	109.93±62.64	106.77±64.27	184.54±146.69
Factor						
Verbal memory and language comprehension	—	0±1	0.048±1.04	0.28±1.13	0.48±1.03	0.58±0.95
Abstraction and visuospatial orientation	—	0±1	−0.3±1.02	0.41±0.93	0.38±0.9	−0.53±1.53
Attention, psychomotor processing speed, and concentration	—	0±1	−0.18±1.00	0.18±0.98	0.29±1.1	−0.07±0.93
Visual memory	—	0±1	0.08±1.17	0.18±1.08	0.22±1.23	−0.11±0.46
Composite cognitive index	—	0±2	−0.36±2.05	0.99±2.03	1.37±2.11	−1.45±4.09

*For each point, data are given for the patients who were still participating in the trial (i.e., those who withdrew, were lost to follow-up, or died are excluded). Plus–minus values are means ±SD.

†Higher scores indicate better function, with the exception of scores on the Trail Making Test, for which lower values indicate better function.

‡This test is a subtest of the Wechsler Adult Intelligence Scale–Revised.

clusion of worst-case scores for patients who were unable to complete testing as a result of death or debilitating stroke changed the incidence of decline only minimally.

The composite cognitive index showed a similar gradual improvement up to six months, both in patients who had early postoperative cognitive decline and in those who did not (Fig. 2). In patients without evidence of early postoperative decline, the composite cognitive index score at five years returned to a value near its base-line level after having shown a learning effect between six weeks and six months. In contrast, the composite cognitive index score of patients who had early postoperative cognitive impairment declined below base-line levels to a level similar to that assessed at discharge (Fig. 2). Data on the patients who died or had strokes are not included in Figure 2.

Predictors of Cognitive Decline at Five Years

To determine which demographic and perioperative factors were associated with cognitive decline at five years, suspected univariable predictors of cognitive decline were assessed by means of logistic regression (Table 3). Significant univariable predictors included older age, lower level of education, and evidence of cognitive decline at discharge. Predictors found to be significant in the univariable analysis were included in a multivariable analysis assessing predictors of cognitive decline. All three univariable predictors, including cognitive decline measured at discharge ($P=0.03$), remained significant in the multivariable analysis predicting long-term cognitive decline at five years. The inclusion of data for the patients who died or had strokes did not appreciably change the predictors or their significance.

Predictors of the Composite Cognitive Index

In addition to predictors of the incidence of cognitive decline, we also assessed the factors predicting the level of function (composite cognitive index) at five years, using univariable linear regression followed by multivariable linear regression (Table 3). Independent predictors of the decline in the composite cognitive index at five years included older age, lower level of education, higher base-line score for cognitive function, and presence of cognitive decline at discharge. Lower base-line scores are constrained by a "basement" effect: they leave a smaller range for decline than do higher scores. A comparison of patients' composite cognitive index according to the presence or absence of impairment at discharge (Fig. 2) showed a gradual improvement in overall cognitive function in both the patients with cognitive impairment and those without impairment, with function returning to or near the base-line level at six months. However, whereas the function of patients without cognitive impairment at discharge remained above the base-line level five years after surgery, that of patients who had impairment at discharge

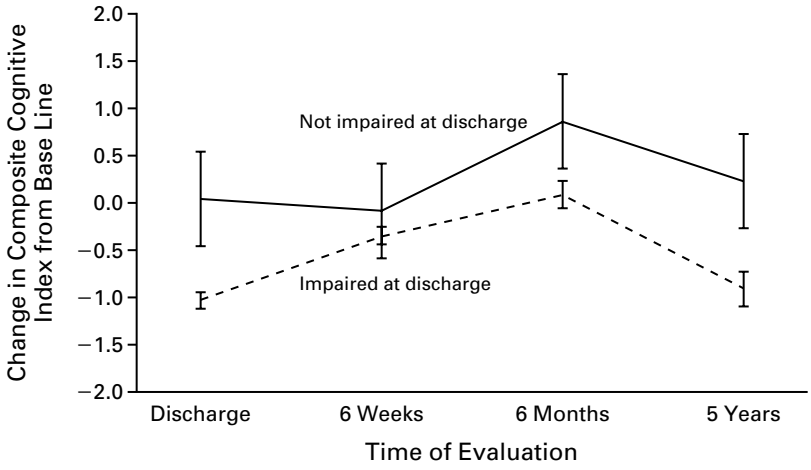

Figure 2. Composite Cognitive Index as a Function of Cognitive Impairment at Discharge.
The composite cognitive index is the sum of the scores for the four domains and includes cognitive decline as well as increases in scores as a result of learning. Positive change represents an overall improvement (learning), whereas negative values indicate overall decline. The I bars represent the standard error.

TABLE 3. UNIVARIABLE AND MULTIVARIABLE PREDICTORS OF COGNITIVE DECLINE AND CHANGE IN THE COMPOSITE COGNITIVE INDEX AT FIVE YEARS.*

VARIABLE	PREDICTORS OF DICHOTOMOUS OUTCOME		PREDICTORS OF CHANGE IN THE COMPOSITE INDEX	
	UNIVARIABLE P VALUE	MULTIVARIABLE P VALUE	UNIVARIABLE P VALUE	MULTIVARIABLE P VALUE
Cognitive decline at discharge	0.006	0.03	0.002	<0.001
Lower left ventricular ejection fraction	0.97	—	0.03	—
Longer duration of aortic cross-clamping	0.82	—	0.85	—
History of hypertension	0.18	—	0.95	—
Longer duration of cardiopulmonary bypass	0.97	—	0.49	—
Female sex	0.28	—	0.67	—
CCS class IV angina	0.17	—	0.50	—
Previous symptomatic neurologic event	0.12	—	0.44	—
Previous myocardial infarction	0.31	—	0.04	—
Diabetes	0.38	—	0.83	—
Higher composite base-line neurocognitive score	0.74	0.07	<0.001	<0.001
Older age	0.02	0.01	<0.001	<0.001
Fewer years of education	0.02	0.003	<0.001	0.003

*The predictors of cognitive decline as a dichotomous outcome were determined by means of logistic regression, and the predictors of change in the composite cognitive index were determined by means of linear regression. Univariable P values indicate the significance of the variable as a factor predicting cognitive decline, defined as a decline of 1 SD in any of the four domains of cognitive function or in the composite cognitive index (the sum of the changes in the four domains). Multivariable P values were derived either from multivariable logistic-regression analysis of predictors of cognitive decline (including those that were significant in the univariable model) or from multivariable linear regression analysis of predictors of change in the composite cognitive index from base line to five years. CCS denotes Canadian Classification System.

showed a marked decline from base-line function five years later. This association between perioperative cognitive decline and long-term cognitive decline remained significant even after we controlled for factors such as age, educational level, and base-line score in the multivariable model ($P<0.001$) (Table 3).

DISCUSSION

The results of this investigation further define the effect of perioperative cognitive decline on long-term cognitive function. Patients whose cognitive function declines immediately after surgery (approximately 50 percent of patients who undergo CABG) are at increased risk for long-term cognitive decline and a reduced level of overall cognitive functioning. Our work in assessing the longitudinal effects of cardiac surgery on cognitive functioning extends that of Sotaniemi et al.[15] and Murkin et al.[10] by using a larger sample and a longer period of follow-up. The change that occurred between base line and five years after surgery in the patients in our study who showed a cognitive decline at discharge was more than two to three times that demonstrated in a longitudinal assessment of cognitive function in 5888 Medicare patients who were followed for five years.[16] Adjectives such as "subtle," "transient," and "subclinical" have been used to describe the cognitive decline that occurs after CABG, but such descriptions minimize the importance of these changes to clinicians, patients, and their families. The results of our study indicate that early cognitive impairment is clinically significant and is a harbinger of later cognitive impairment.

The methods we used to define cognitive decline were chosen on the basis of our previous studies and recommendations from consensus statements on the assessment of neurobehavioral outcome after cardiac surgery.[17,18] We used factor analysis to minimize the redundancy of tests and potential type I errors. The factor loadings represented four recognized domains of cognitive function, and these domains were identified and defined at base line and remained consistent at the follow-up time points. This model allowed us to compare the change from base line in the cognitive function of different patients by determining whether there was a change of 1 SD or more in any of the domains at any of the times, as recommended by the consensus statement on cognitive dysfunction after surgery.[17,18] It also allowed us to assess learning by means of the composite cognitive index, the sum of the four domain scores. A downward change of 1 SD in a domain of cognition indicates a reduction of approximately 20 percent in cognitive function in that domain. To put this in context, on a test such as the Digit Symbol subtest, for which good age-related normative data exist, a 20 percent decline is similar to the difference in function between 40- and 60-year-old subjects. More information is needed to determine the importance of these changes to real-world behavior.

To understand better the demographic and perioperative factors associated with cognitive change, we assessed a number of factors that we and others have identified as significant predictors of cognitive decline after surgery.[9] Multivariable analysis identified older age, higher base-line neurocognitive function, lower educational level, and cognitive decline at discharge as predictors of long-term (five-year) cognitive decline. A number of demographic and perioperative variables were not significant predictors of long-term decline; these included sex, duration of cardiopulmonary bypass, and duration of aortic cross-clamping. The left ventricular ejection fraction did approach significance in the multivariable assessment of predictors of the composite cognitive index, indicating that patients with cardiac dysfunction may be at increased risk for overall cognitive decline after cardiac surgery. With a larger sample, left ventricular ejection fraction might have been a significant factor affecting long-term decline. The inclusion of patients who died or had strokes before the scheduled testing at five years did not substantially change the predictors of cognitive decline or their significance.

The consistency of the predictors of cognitive decline and the composite cognitive index indicates the stability of our model, in which age, educational level, and the presence or absence of perioperative cognitive decline consistently predicted the level of long-term cognitive function. The degree of protection provided by higher levels of education is similar to that found previously.[2] Given that higher levels of education also "protect" patients from the progression of Alzheimer's disease,[19] the mechanism of this protection may be an ability to compensate for acquired cognitive difficulties, or it may be some more complex central mechanism.

Our study is limited by the loss to follow-up that is inevitable in a longitudinal study in which patients are followed for five years. Statistical comparisons were made between the patients who completed follow-up and those who did not; these data are shown in Table 1. Patients who did not complete follow-up were more likely to have ASA class IV risk (indicating a high level of coexisting conditions), to have had a previous myocardial infarction, and to have a history of symptomatic neurologic disease. The addition of data for the patients who died before the five-year follow-up assessment narrowed this difference but did not change the results of the trial. This selective attrition of high-risk patients suggests that the overall incidence of cognitive decline may underestimate the persistent decline demonstrated at each of the follow-up visits. In order to include as much data as possible, we gave patients who were unable to complete the testing at five years because of death or stroke a worst-case score for cognitive function, and we then analyzed the data with and without these patients included. The inclusion of these patients produced only

minimal changes in the calculated incidence of dysfunction and no difference in the predictors of long-term cognitive decline.

Our data demonstrate a significant association between cognitive decline immediately after CABG surgery and both the incidence and the severity of cognitive decline five years later. This association indicates that because of perioperative injury, increased susceptibility to such injury, or decreased ability to recover from it, patients with perioperative decline are at increased risk for long-term cognitive decline. Determining how this decline compares with any changes in cognitive function that occur in a population of similar age and state of health who have not undergone CABG would require a prospective longitudinal study that included the latter group. Studies of elderly subjects have demonstrated a gradual decline in neurocognitive function with age.[15,20-22] In most investigations, genetic and environmental factors have been shown to interact to affect the progression of cognitive decline related to aging. Our data indicate that cardiac surgery with cardiopulmonary bypass is an additional factor that can alter this progression.

Further investigation of the effects of cognitive change on the quality of life of patients who have undergone CABG surgery is essential. The effect of short- and long-term neurocognitive decline on the quality of life after cardiac surgery is the subject of an ongoing debate. In the context of a number of medical situations, including chronic obstructive pulmonary disease,[23] repair of abdominal aortic aneurysm,[24] neurosurgery,[25] and cardiac rehabilitation,[26] substantial change in cognitive function is associated with changes in the quality of life. These findings are consistent with our earlier results, which showed a significant correlation between cognitive function and quality of life after cardiac surgery.[27] This analysis is preliminary, but if our findings hold true after further scrutiny, they underscore the importance of preventing or reducing perioperative cognitive decline in order to preserve long-term cognitive function and the quality of life in the growing population of elderly patients undergoing cardiac surgery. Patients in whom early postoperative cognitive decline is identified may be candidates for aggressive intervention strategies to prevent the late cognitive deterioration we have documented.

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APPENDIX

The members of the Neurologic Outcome Research Group and the Cardiothoracic Anesthesiology Research Endeavors Investigators of the Duke Heart Center were as follows: *Director:* M. Newman; *Codirector:* J. Blumenthal; *Anesthesiology:* F. Clements, N. de Bruijn, K. Grichnik, H. Grocott, S. Hill, A. Hilton, J. Mathew, J. Reves, D. Schwinn, M. Stafford Smith, A. Grigore, M. Gamoso, G. Mackensen, R. Panten, T. Stanley, L. Ti, J. Kirchner, A. Butler, V. Gaver, W. Cohen, B. Funk, M. Tirronen, W. White, and B. Phillips-Bute; *Behavioral Medicine:* J. Blumenthal, M. Babyak, and P. Khatri; *Neurology:* C. Graffagnino, D. Laskowitz, A. Saunders, and W. Strittmatter; *Surgery:* R. Anderson, T. D'Amico, R. Davis, D. Glower, R. Harpole, J. Jaggers, R. Jones, K. Landolfo, C. Milano, P. Smith, and W. Wolfe; *Cardiology:* D. Mark, E. Peterson, M. Sketch, and R. Califf.

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