Cognitive Changes 5 Years After Coronary Artery Bypass Grafting

Is There Evidence of Late Decline?

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Objective: To determine the long-term (preoperative to 5 years postoperative) and late (1-5 years postoperative) changes in cognitive test performance in patients after coronary artery bypass grafting.

Setting: The departments of surgery and neurology at The Johns Hopkins University School of Medicine, Baltimore, Md.

Patients: A group of 102 patients who completed preoperative and follow-up cognitive testing up to 5 years after coronary artery bypass grafting.

Main Outcome Measures: A battery of neuropsychological tests, assessing 8 cognitive domains (attention, language, verbal and visual memory, visuoconstruction, executive function, and psychomotor and motor speed), was administered preoperatively and at 1 month, 1 year, and 5 years postoperatively.

Results: Significant changes in neuropsychological test scores from baseline to 5 years were observed in only 3 of the 8 domains: there were declines in visuoconstruction and psychomotor speed and an improvement in executive function. When the period from baseline to 5 years was divided into 2 intervals, we found that cognitive test scores generally improved from baseline to 1 year. By contrast, between 1 and 5 years, there was significant decline in all cognitive domains except for attention and executive function. Some potential explanatory covariates (demographic, medical history, and surgery variables) were associated with changes from baseline to 5 years in some cognitive domains, but few covariates were statistically significant in more than 1 cognitive domain.

Conclusions: The change in cognitive test performance between baseline and 5 years is likely related to several factors, including low baseline performance and practice effects. The significant decline in performance between 1 and 5 years, however, raises the possibility that a late cognitive decline may be occurring in this population. Additional studies, with the use of a nonsurgical control group, are needed to determine if the observed cognitive decline is related to bypass surgery itself, normal aging in a population with cardiovascular risk factors, or some combination of these and other factors.

Arch Neurol. 2001;58:598-604

Cognitive change during the first several weeks after coronary artery bypass grafting (CABG) has been extensively investigated, but relatively few studies have examined longer-term outcomes. In one study in which patients were followed up for 2 years after surgery, the investigators concluded that there was no evidence of late cognitive decline. In 2 studies in which patients were followed up for up to 5 years after surgery, however, a decline in cognitive performance from 1 to 5 years was noted. Moreover, this delayed decline appeared to be more frequent in some cognitive domains than in others. Individual case studies of late cognitive decline have also been reported.

To explore this observation further, we obtained long-term follow-up on a cohort of patients enrolled in a prospective study of cognitive outcomes after CABG. Patients had been previously examined preoperatively, at 1 month, and at 1 year. In this report, we describe the longer-term cognitive outcomes in those patients from our original study who were available for follow-up testing 5 years after CABG. As before, individual neuropsychological test scores were combined to represent the major cognitive domains (attention, language, verbal and visual memory, visuoconstruction, executive function, and motor and psychomotor speed). The use of cognitive domains allowed us to relate changes in cognitive performance to possible underlying brain mechanisms.
PATIENTS AND METHODS

PATIENTS

Patients who underwent CABG between February 20, 1992, and April 1, 1993 (N=172), were contacted 4 to 5 years after surgery. These patients had been prospectively evaluated with neuropsychological tests before and up to 1 year after surgery, as described elsewhere. Patients who agreed to further cognitive testing completed informed consent forms and were interviewed in the clinic or in their homes.

NEUROPSYCHOLOGICAL TESTS

The cognitive test battery included the same tests that had been used in the earlier assessments, and in most instances, each patient was tested by the same interviewer (M.A.G. or L.M.B.) as previously. Details of the neuropsychological test battery and the rationale for use of composite cognitive domain scores were described previously. The following cognitive domains and tests were included: (1) verbal memory: Rey Auditory Verbal Learning Test; (2) visual memory: Rey Complex Figure (delayed recall) and Symbol Digit (paired recall); (3) language: Boston Naming Test; (4) attention: Digit Span (forward and backward); (5) visuoconstruction: Rey Complex Figure (copy); (6) psychomotor speed: Symbol Digit and written alphabet; (7) motor speed: Grooved Pegboard (dominant and nondominant hand); and (8) executive function: Stroop Test. Patients were also administered the Mini-Mental State Examination (MMSE). Additional information on the psychometric characteristics of these measures has been published elsewhere.

The Center for Epidemiological Studies Depression Scale, a 20-item self-report questionnaire, was administered as a screening instrument for depression.

GENETIC TESTING

For patients who completed their 5-year follow-up, a blood sample was collected for apolipoprotein E (ApoE) genotype analysis. To identify ApoE alleles, genomic DNA was amplified using polymerase chain reaction, as described previously. Apolipoprotein E status was examined because of a previous report of greater likelihood of cognitive decline after CABG in patients with the ApoE epsilon 4 allele.

STATISTICAL METHODS

All analyses were performed using z scores based on the mean and SD of the preoperative cognitive scores of patients (n=127) who completed the 1-month and 1-year follow-up evaluation. For cognitive domains with more than 1 test, each patient received a composite score consisting of his or her z scores on the individual tests. The statistical significance of changes from baseline to 1 year, from 1 to 5 years, and from baseline to 5 years was assessed by 1-sample t tests on the average of the within-subject z score differences (later score minus earlier score) for each cognitive domain.

REGRESSION ANALYSES

To examine how the changes in cognitive test z scores over time might be related to patient-specific covariates, we used linear regression analyses. The response variable was the difference in a patient’s test scores on 2 occasions. The covariates were of several types: demographic (eg, age and sex), medical history, and operative and postoperative variables, as described previously. Because many potentially important covariates were measured, they were divided into 2 groups: (1) preoperative covariates (including the demographic and medical history variables) and (2) variables associated with surgery and the postsurgical period. Separate multiple regression analyses were performed for each of these 2 groups of covariates.

RESULTS

We examined changes in mean cognitive test scores both in the period from baseline (before surgery) to 1 year after surgery and between 1 and 5 years after surgery, and compared them with the changes from baseline to 5 years after surgery. We also examined various patient characteristics (demographic, medical history, and surgical variables) as covariates that might help to explain how changes in individual patients’ scores vary within this group.

Of the original 172 patients seen before surgery, 102 completed cognitive testing at 3 years. Demographic characteristics for these patients are shown in Table 1. There were 22 deaths (13%) since surgery. In addition, 48 patients (28%) either refused or were unable to return for follow-up. For the 23 patients who were unable to continue participation in the study, demographic and medical data were collected by telephone. The patients who completed the 5-year follow-up testing were more highly educated than those who did not (P=.002), but did not differ significantly in other demographic characteristics. The actual interval between baseline and the last follow-up visit varied somewhat, with a range from 47 to 74 months (mean, 53.7 months; SD, 3.9 months). Group mean neuropsychological test scores at baseline, 1 year, and 5 years are shown in Table 2.

FROM BASELINE TO 1 YEAR

Between baseline (presurgery) and 1 year (postsurgery), cognitive test scores generally improved (Table 3). There were statistically significant gains in 5 of the 8 domains (verbal memory, visual memory, executive function, motor speed, and psychomotor speed), with nonsignificant gains in language and attention and virtually no change in visuoconstruction.

FROM 1 TO 5 YEARS

By contrast, between 1 and 5 years, test scores showed significant decline, on average, in 6 of the 8 domains (verbal memory, visuoconstruction, visual memory, language, motor speed, and psychomotor speed). In the remaining 2 domains (attention and executive function), changes were slight and nonsignificant.
When the 2 intervals, baseline to 1 year and 1 to 5 years, are combined, the changes in scores on cognitive tests (5 years minus baseline) showed mixed results, with statistically significant changes in group mean scores appearing in only 3 of the 8 domains. There were declines in visuoconstruction and psychomotor speed and a gain in executive function.

### FROM BASELINE TO 5 YEARS

None of the covariates was found to be statistically significant across many cognitive domains. This, together with the fact that many covariates were examined (n = 49), suggests that the instances of statistical significance should be interpreted cautiously. For this reason, we included in the summary of these results only the cases in which covariates had regression coefficients with P values of .001 or less (Table 4). Conversely, because there may not have been adequate power to detect an effect even if one existed in this population, caution should be used in concluding that there is no relation between the covariates and the outcome measures.

With this criterion (P ≤ .001), the only demographic variable that was associated with change in cognitive test performance was race, and the association appeared in only 1 cognitive domain. (Race had a significant positive coefficient in the regression for 5 years minus baseline differences in visuoconstruction, indicating a smaller average decline for nonwhites than for whites in our sample.) Among medical history variables, only 1 was associated with cognitive change. (Previous history of stroke was associated with decline in language scores, from baseline to 5 years and from 1 to 5 years.) Of the operative and postoperative variables included in this analysis, the lowest esophageal temperature was associated with worse performance in verbal memory, postoperative neurological event with worse performance in visual memory, and longer time to awaken after surgery with worse performance on tests of language.

Including the baseline neuropsychological test scores as a covariate did not change the basic pattern of results shown in Table 3. Patients with lower baseline scores tended to improve more between baseline and 1 year than those with higher baseline scores, consistent with possible regression toward the mean. However, this pattern was not observed between 1 and 5 years. For the domains of visuoconstruction, motor speed, and psychomotor speed, patients with lower scores at baseline tended to decline more between 1 and 5 years.

### INTERIM MEDICAL EVENTS

The interim medical events since surgery included stroke (8%), myocardial infarction (4%), percutaneous transluminal coronary angioplasty (14%), redo CABG (3%), surgery with the use of general anesthesia (24%), and head trauma with loss of consciousness for longer than one-half hour (3%). None of these interim events was statistically associated with cognitive decline at 5 years in any of the cognitive domains. Depressed mood, as measured by the Center for Epidemiological Studies Depression Scale scores at 5 years, was not associated with change in cognitive test scores from baseline to 5 years or from 1 to 5 years.

### DEMENTIA

Change in neuropsychological test performance between baseline and up to 5 years or between 1 and 5 years was not associated with specific ApoE subtypes. Only 2...
patients had an MMSE score in a range consistent with possible dementia (score, <24) at 5 years, but 1 of these patients also had an abnormal MMSE score at baseline. None of the patients had a family history or clinical diagnosis of dementia.

The results of our prospective long-term follow-up study show that cognitive test performance between baseline (preoperatively) and 5 years (postoperatively) has a 2-stage course. Except for visuoconstruction, performance from baseline to 1 year tended to improve for most cognitive domains. By contrast, from 1 to 5 years, performance declined for most cognitive domains. Thus, when comparing preoperative performance and 5-year follow-up, there was no significant change for most cognitive domains. The only domains for which performance at 5 years was significantly worse than that at baseline were visuoconstruction and psychomotor speed.

Although there were some medical and surgical factors that showed a statistically significant association with change in cognitive test performance, there was little consistency in these factors across cognitive domains or across follow-up intervals. For example, lowest esophageal temperature during surgery was strongly associated with worse performance in verbal memory at 5 years, but not in any other cognitive domains. Therefore, these associations were not particularly helpful in determining who is at risk for cognitive decline after CABG or for discerning preoperative performance and 5-year follow-up.
ing possible underlying pathophysiological mechanisms of late cognitive decline. Previous studies have also found it difficult to identify consistent demographic, surgical, or medical predictors of cognitive decline after CABG.

**BASELINE PERFORMANCE AND PRACTICE EFFECTS**

We believe that in interpreting these data it is important to distinguish between cognitive ability (or cognitive function) and neuropsychological test performance. For a given level of ability, a subject’s test performance can be influenced by several factors. For example, repeated testing can produce an improvement in test scores due to practice effects. The magnitude of the improvement due to practice depends on several factors, including interval between testing, type of test, age, and educational level. Another possibility is that preoperative test performance may have been adversely affected by stress, anxiety, depression, or other factors associated with impending surgery, so that an improvement in scores may simply have been the result of changes in testing conditions.

Alternatively, it has been suggested that in candidates for CABG, cognitive function at baseline might be impaired because of long-standing cardiac disease, so that postoperative improvement in test scores might reflect a true improvement in cognitive function, perhaps as a consequence of improved cardiovascular functioning. Patients with lower baseline scores tended to improve more between baseline and 1 year, but we cannot determine if this improvement reflects true improvement in cognitive function, as opposed to practice effects, regression toward the mean, or the absence of preoperative conditions that may have adversely affected test performance.

**AGING EFFECTS**

The cause of the decline in cognitive performance from 1 to 5 years is also likely to be multifactorial. Cognitive changes do occur with normal aging, and we, therefore, considered whether the observed decline from 1 to 5 years could be attributed to normal aging. In the absence of a suitable control group for our patients, we relied on previously published estimates of longitudinal changes in performance on specific cognitive tests. Whereas previous reports based on cross-sectional cohort studies reported substantial declines in cognitive performance in the later decades of life, more recent prospective longitudinal studies have provided a more optimistic picture. Most studies have concluded that although there may be mild decline in some cognitive domains with advancing age, the magnitude of this decline is small and generally counterbalanced by practice effects inherent in longitudinal testing. Cognitive domains reported to show decline have included verbal fluency and psychomotor speed. Thus, longitudinal follow-up testing for intervals from 1 to 5 years have demonstrated little or no cognitive decline in persons without clinical evidence of dementia.

Our population of patients who underwent CABG, with a history of cardiovascular disease and risk factors for cerebrovascular disease, may not be comparable to “normal” controls. We are not aware of any published studies, however, that have specifically examined the effects of aging on cognitive performance in a population with cardiovascular disease. Several studies, on the other hand, have reported an increased risk of dementia in patients with myocardial infarction, hypertension, and other cardiovascular risk factors. Therefore, we cannot rule out the possibility that the late cognitive decline observed in our population may simply be due to a combination of long-standing cerebrovascular disease and aging. Our finding that the patients with lower baseline scores in visuoconstruction and motor and psychomotor speed showed the greatest decline between 1 and 5 years may be consistent with this. Psychomotor slowing and visuospatial abnormalities have been reported with subcortical small-vessel ischemic disease, although the specificity of the neuropsychological profile of subcortical vascular dementia remains somewhat controversial.

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**Table 4. Summary of Multivariate Analysis**

<table>
<thead>
<tr>
<th>Cognitive Domain</th>
<th>1 Year – Baseline</th>
<th>5 Year – Baseline</th>
<th>5 Year – Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal memory</td>
<td>Lowerest temperature in the OR (0.11)**</td>
<td>Lowerest temperature in the OR (0.13)**</td>
<td>Nonwhite race (1.25)†</td>
</tr>
<tr>
<td>Visuoconstruction</td>
<td>Postoperative neurological event (-1.18)**</td>
<td>History of stroke (-1.45)$ and awake time (-0.10)**</td>
<td>History of stroke (-1.48)$ and awake time (-0.07)**</td>
</tr>
<tr>
<td>Visual memory</td>
<td>History of stroke (-1.45)$ and awake time (-0.10)**</td>
<td>History of stroke (-1.48)$ and awake time (-0.07)**</td>
<td>-</td>
</tr>
<tr>
<td>Language</td>
<td>History of stroke (-1.45)$ and awake time (-0.10)**</td>
<td>History of stroke (-1.48)$ and awake time (-0.07)**</td>
<td>-</td>
</tr>
<tr>
<td>Attention</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Executive function</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Motor speed</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Psychomotor speed</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Coefficients are given in parentheses. Only variables significant at P < .001 are included. OR indicates operating room; ellipses, Variables not significant at P < .001.
†The lowest esophageal temperature during surgery. The positive coefficient indicates that a higher minimal temperature was associated with less decline.
‡Any neurological event after surgery (eg, stroke, delirium, or confusion).
§Before coronary artery bypass grafting.
||Time to awaken after surgery.
Dementia

Our study population included many older subjects (>70 years), and it is thus possible that early Alzheimer disease or other forms of dementia may account for some of the observed cognitive decline. None of the patients in our sample had been diagnosed as having dementia at the 5-year follow-up. Only 3 patients had an MMSE score in the range consistent with possible dementia at 5 years, and only 1 of these patients had an annual decline in MMSE score greater than the 3 points reported as average for patients with dementia.33

Furthermore, Alzheimer disease is characterized by early changes in specific cognitive domains, including memory, delayed recall, and language.14 The cognitive domains showing the greatest decline relative to baseline in our study were psychomotor speed and visuoconstruction, which are not among the cognitive domains showing the earliest change in Alzheimer disease in most patients.

A previous report35 has suggested an increased risk of cognitive decline after CABG in patients with the ApoE epsilon 4 allele. The presence or absence of the ApoE epsilon 4 allele was one of the preoperative variables included in our regression analyses, but we found no evidence that this variable was associated with decline in cognitive performance in our population.

Relation to CABG

In the absence of an appropriate control group, which would allow us to adjust for the effect of nonsurgical variables on longitudinal changes in cognitive performance, a specific causal relation between CABG and late cognitive decline cannot be established. There is nevertheless some indirect evidence of a possible link between late cognitive decline and CABG.

First, when performance at 5 years was compared with performance at baseline, one of the cognitive domains with significant decline was visuoconstruction. There is some indication that the changes observed in visuoconstruction after CABG may not be coincidental. In a previous study7 that included measures to assess visuoconstructive abilities, a specific causal relation between CABG and late cognitive decline cannot be established. There is nevertheless some indirect evidence of a possible link between late cognitive decline and CABG.

Second, a common neuroanatomical correlate of visuoconstructive deficits includes the posterior parietal regions of the cerebral hemispheres.37 This is also an area of the brain that is believed to be particularly vulnerable during or after cardiac surgery. For example, Barbut and colleagues38 reported that 53% of patients who had strokes after cardiac surgery had posterior watershed area infarcts. Furthermore, blood flow studies39 have also documented parietal lobe hypoperfusion after CABG, and autopsy studies40,41 of patients with neurological complications after cardiac surgery have reported a high incidence of posterior watershed area infarcts.

The mechanism by which cardiopulmonary bypass surgery might cause brain injury is generally believed to be related to hypoperfusion, microemboli, or both, but there is no obvious link between any of these mechanisms and a progressive or delayed decline in specific cognitive domains. There is, however, accumulating evidence that certain cerebrovascular events, such as incomplete infarction, may result in delayed neuronal necrosis.42-44 Progressive dementia after stroke has also been reported.45 Some investigators46,47 have suggested that hypoperfusion followed by reperfusion during cardiopulmonary bypass surgery in some patients may initiate a cascade of events that eventually lead to the development of amyloid plaques and subsequent neuronal injury.

Interpretation of the findings from our study are limited by several factors, including the unavailability for follow-up of some patients during the 5-year study period. The educational level of subjects who did not complete follow-up testing was lower than that of subjects who completed the follow-up. Therefore, the results of our study may have been biased by selective attrition of subjects with the lowest cognitive performance at baseline. Our results are also limited by the lack of appropriate controls. Further longitudinal studies with appropriate nonsurgical controls are needed to determine whether the observed late changes in cognitive test scores are the result of normal aging in a population with cardiovascular risk factors, of the cardiopulmonary bypass operation itself, or of some combination of these and other factors. We have in progress a 3-arm prospective study that may help resolve these questions. In addition to a group undergoing standard CABG, the study also includes a nonsurgical control group of patients with cardiovascular risk factors to control for the effects of normal aging and a group of patients undergoing off-pump bypass surgery that will control for the possible effects of anesthesia.

Accepted for publication September 7, 2000.
This study was supported by grant 35610 from the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, Md; and by the Charles A. Dana Foundation, New York, NY.

We thank Pamela Talalay, PhD, and Marilyn Albert, PhD, for their help during the preparation of the manuscript.

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