Report of the Substudy Assessing the Impact of Neurocognitive Function on Quality of Life 5 Years After Cardiac Surgery

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Background and Purpose—The importance of perioperative cognitive decline has long been debated. We recently demonstrated a significant correlation between perioperative cognitive decline and long-term cognitive dysfunction. Despite this association, some still question the importance of these changes in cognitive function to the quality of life of patients and their families. The purpose of our investigation was to determine the association between cognitive dysfunction and long-term quality of life after cardiac surgery.

Methods—After institutional review board approval and patient informed consent, 261 patients undergoing cardiac surgery with cardiopulmonary bypass were enrolled and followed for 5 years. Cognitive function was measured with a battery of tests at baseline, discharge, and 6 weeks and 5 years postoperatively. Quality of life was assessed with well-validated, standardized assessments at the 5-year end point.

Results—Our results demonstrate significant correlations between cognitive function and quality of life in patients after cardiac surgery. Lower 5-year overall cognitive function scores were associated with lower general health and a less productive working status. Multivariable logistic and linear regression controlling for age, sex, education, and diabetes confirmed this strong association in the majority of areas of quality of life.

Conclusions—Five years after cardiac surgery, there is a strong relationship between neurocognitive functioning and quality of life. This has important social and financial implications for preoperative evaluation and postoperative care of patients undergoing cardiac surgery. (Stroke. 2001;32:2874-2881.)

Key Words: cardiac surgical procedures — cognitive disorders — quality of life

Neurocognitive decline after cardiac surgery is a common complication occurring in up to three quarters of patients at hospital discharge and persisting in a third of patients up to 6 months after surgery. However, the importance of postoperative cognitive decline is still debated. Descriptions such as “subtle,” “transient,” and “subclinical” have been used to minimize the importance of these changes to clinicians, patients, and their families. In a 5-year prospective study, we found a significant association between cognitive decline immediately after cardiac surgery and both the incidence and severity of cognitive dysfunction at 5 years. This linkage between perioperative injury and long-term cognitive function suggests that perioperative dysfunction may serve either as a marker of brain injury, increased susceptibility to brain injury, decreased reserve capacity, or inability to recover or tolerate similar injury (plasticity).

Changes in cognitive function have been associated with reduced quality of life in a number of different disease processes and perioperative settings. However, despite the evidence in some patients of poor outcome (eg, increase in depression, anxiety, cognitive decline), most studies have demonstrated that cardiac surgery has beneficial effects on psychological functioning and quality of life for the majority of patients. Within 6 months after surgery, most patients report a reduction in depressive and anxiety symptoms. Patients also experience marked improvements in physical (eg, fewer restrictions on activity, decreased fatigue, fewer...
sleep problems), sexual (eg, decreased pain and worry, increased desire and energy), social (eg, increased participation in social activities and hobbies), and work activity (return to work, increased job performance).12–14 Furthermore, 1 year after surgery, patients report increased life satisfaction and improvements in emotional well-being and family life.15 However, these studies have not included detailed serial psychometric testing to assess the role of cognitive function.

To determine the clinical importance of cognitive dysfunction after cardiac surgery, we examined these changes in the context of other aspects of quality of life in patients with cardiovascular disease undergoing treatment. The purpose of our investigation was to determine the impact of neuropsychological dysfunction on quality of life after cardiac surgery.

Subjects and Methods

Patient Enrollment
After institutional review board approval and written informed consent were obtained, 261 patients undergoing elective cardiac surgery were enrolled in this investigation. Patients with a history of symptomatic cerebrovascular disease (with residual deficit), psychiatric illness, renal disease (serum creatinine concentration $>2.0$ mg/dL), active liver disease, less than a seventh-grade education, or an inability to read were excluded from enrollment.

Measurement of Neurocognitive Function
A brief neurocognitive test battery was administered before surgery (baseline), the day before discharge (approximately 7 days after coronary artery bypass grafting [CABG]), and at 6 weeks, 6 months, and 5 years postoperatively (results of neurocognitive outcome were previously reported).16 Assessments were performed individually by experienced psychometricians using a well-validated battery that included the following: (1) The Short Story module of the Randt Memory Test requires subjects to recall the details of a short story immediately after it was read to them (immediate) and after a 30-minute delay (delay). Scoring is based on both the “verbatim” and “gist” of the response on immediate and delayed testing (4 variable scores).16 (2) The Digit Span subtest of the Wechsler Adult Intelligence Scale–Revised (WAIS-R) requires subjects to repeat a series of digits that have been orally presented to them both forward and, 30-minute delay (delay). Scoring is based on both the “verbatim” and “gist” of the response on immediate and delayed testing (4 variable scores).16 (3) The Benton Revised Visual Retention Test requires subjects to reproduce a series of geometric shapes after a 10-second exposure (1 variable score).16 (4) The Digit Symbol subtest of the WAIS-R is a paper-and-pencil task that requires subjects to reproduce, 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 (1 variable score).17 (5) The Trail-Making Test (Trails B) requires subjects to connect, by drawing a line, a series of numbers and letters in sequence (ie, 1-A-2-B) as quickly as possible (1 variable score).16

Measurement of Quality of Life
Quality of life instruments were administered individually by a trained psychometrician who was blinded to the patient’s neurocognitive test results at the 5-year end point. Most of the questionnaires were self-administered; however, the measures were read to the patient if he or she was feeling ill or was unable to read. The following quality of life measures were used:

(1) The Duke Activity Status Index (DASI).20 The DASI is a 12-item scale of functional capacity that has been found to correlate well with objective measures of maximal exercise capacity. Items reflect activities of personal care, ambulation, household tasks, sexual function, and recreational activities. Activities reported to be done “with no difficulty” receive scores weighted higher for more taxing activities, which are summed for a quantitative measure of functional status (minimum 0, maximum 58.2). A higher weighted score is better.

(2) The Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).21,22 The SF-36 was designed to measure general health status. The results are expressed in terms of 8 subscores and 2 summary scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). SF-36 items and scales are scored so that a high score indicates a better health state. Summary scores have been standardized to the US general population (mean score of 50±10) to allow easier norm-based interpretation.

(3) Center for Epidemiological Studies Depression Scale (CES-D).23 The CES-D is a 20-item self-report measure designed to measure symptoms of depression. Subjects rate the degree to which they have experienced a range of symptoms of depression on items such as “I had crying spells” and “I felt lonely.” Scores range from 0 to 60, with higher scores indicating greater depressive symptoms. Scores >16 are typically considered indicative of clinically significant depression.

(4) Spielberger State and Trait Anxiety Inventory (STAI).24 The STAI consists of two 20-item scales that measure state (current) and trait (chronic) anxiety. Representative items include statements such as “I feel nervous” and “I feel worried.” These items are rated on a 4-point scale of how well they describe the patient’s current or typical mood from “not at all” to “very much so.” Scores range from 20 to 80, with higher scores indicating greater anxiety.

(5) Mini-Mental State Examination (MMSE).25,26 This test is designed to grossly assess executive cognitive functioning. It assesses orientation, memory, calculations, reading and writing capacity, visuospatial ability, and language. Patients are quantitatively measured on those functions; a perfect score is 30 points, a score of $<25$ suggests impairment, and a score of $<20$ indicates definite impairment.25,26

(6) Perceived Social Support Scale.27 Twelve items include how strongly subjects agree there is “a special person who is around when I am in need” and “my family really tries to help me.” Choices range from “very strongly disagree” to “very strongly agree.” Items are summed for a range of 12 to 84, with a high score indicating a better status.

(7) Working Status. This is a single-item instrument with 9 possible choices: 1, full time; 2, part time; 3, homemaker; 4, long-term sick leave; 5, short-term sick leave; 6, retired; 7, disabled; 8, unemployed; 9, other.

Patient Management
Anesthetic management with midazolam, fentanyl, isoflurane, and vecuronium has been previously described.28 The perfusion apparatus consisted of a Cobe CML oxygenator (COBÉ Chem Labs), a Sarns 7000 max pump (Sarns Inc), and a Pall SP 3840 arterial line filter (Biomedical Co). Nongenetic technique of oxygen (PaO$_2$) was maintained at 50 to 250 mm Hg.

Statistical Methods
All assessment instruments were scored according to the specific validated algorithms described by the test developers. In particular, the DASI uses a weighted sum, and the SF-36 uses weights and transformations to arrive at its 8 scales and 2 summary components.21 To assess neurocognitive decline over time while minimizing the potential for redundancy in the neurocognitive measures, a factor analysis with orthogonal rotation was first performed on the 9 individual baseline neurocognitive test scores. This analysis included scores from the entire baseline population of 261 patients. Factor analysis was used as a variable reduction technique to reduce the larger number of correlated scores to a smaller number of uncorre-
labeled 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 the 5-year follow-up time periods on the basis of patients’ test scores for that time period. In this manner, the domains were identified at baseline and remained consistent at follow-up.

Factor analysis on 9 baseline neuropsychological test scores suggests that 4 factors account for 86% of the variance present in our test battery at baseline. The 4 factors coherently represent the cognitive domains of (1) verbal memory and language comprehension (short-term and delayed); (2) abstraction and visuospatial orientation; (3) attention, psychomotor processing speed, and concentration; and (4) visual memory.

A change score for each of the factors was calculated by subtracting baseline factor scores from the follow-up factor scores. Categorically, a cognitive deficit was defined as a decline of 1 SD or more in performance on any 1 of the 4 domains. To quantify overall cognitive function and the degree of learning (practice from repeated exposure to the testing procedures) or cognitive decline across all domains, a composite cognitive index was calculated as the sum of the 4 domain scores to yield a single, continuous measure of cognitive function. This summary measure, accounting for improvement as well as decline, was used to represent overall cognitive functioning as the predictor of interest in our models.

The association between quality of life and long-term cognitive dysfunction was investigated univariately with each of the measures of quality of life with the use of our continuous measure of overall cognitive function. Continuous quality of life outcome measures were constructed using our continuous measure of overall cognitive function. In the multivariate models, the best predictive model without cognitive function was developed first, starting with all covariates listed and removing nonsignificant terms iteratively until only significant terms remained. The effect of cognitive function was then added to this “best” model to test whether it would demonstrate a significant relationship over and above the effects of covariates. Because there was no single way to bring together our multiple assessment of quality of life, we have presented all of the univariate and multivariate probability values for comparison.

Results

Two hundred sixty-one patients initially enrolled in the study and underwent baseline neurocognitive testing. Of these, a total of 172 patients were available for 5-year follow-up and completed both neurocognitive functioning and quality of life assessments (reasons for withdrawal of the 89 patients were previously described).3 The demographics and background clinical information of this patient population are listed in Table 1. Demographic parameters of the entire population (baseline) and those available for 5-year follow-up were similar, with exceptions as noted.

### TABLE 2. Neurocognitive Function Scores at Baseline and 5 Years

<table>
<thead>
<tr>
<th>Test/Score</th>
<th>Baseline (n=261)</th>
<th>5 Years (n=172)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit Symbol†</td>
<td>38.78±13.71</td>
<td>38.00±14.94</td>
</tr>
<tr>
<td>Benton Revised Visual Retention</td>
<td>5.14±2.25</td>
<td>5.02±2.17</td>
</tr>
<tr>
<td>Randt Delayed Gist‡</td>
<td>5.01±2.14</td>
<td>5.63±2.31</td>
</tr>
<tr>
<td>Randt Delayed Verbatim‡</td>
<td>6.23±3.26</td>
<td>7.30±3.51</td>
</tr>
<tr>
<td>Randt Immediate Gist‡</td>
<td>5.73±1.83</td>
<td>6.49±1.90</td>
</tr>
<tr>
<td>Randt Immediate Verbatim‡</td>
<td>7.88±3.25</td>
<td>9.21±3.34</td>
</tr>
<tr>
<td>Digit Span†</td>
<td>5.43±2.26</td>
<td>5.30±2.19</td>
</tr>
<tr>
<td>Repeat Forward</td>
<td>7.25±2.29</td>
<td>7.00±2.29</td>
</tr>
<tr>
<td>Trail Making Test (Trails B)</td>
<td>142.24±73.56</td>
<td>184.54±146.69</td>
</tr>
<tr>
<td>Composite cognitive index</td>
<td>0.183±1.944</td>
<td>−0.133±2.321</td>
</tr>
</tbody>
</table>

Values are mean±SD.

*Number of patients still participating in trial (excludes withdrawals and patients lost to follow-up and death).

†Subtest of WAIS-R.

‡Short Story module of Randt Memory Test.
Cognitive Function

The mean values for the raw neurocognitive function test battery and composite cognitive index scores at baseline and at 5-year follow-up are shown in Table 2. The raw scores represent the actual obtained scores from the test battery before factor analysis. Seventy-three patients (42.4%) experienced a decline of at least 1 SD in at least 1 domain of cognitive function at 5 years. Patients who showed a deficit also declined significantly on the composite cognitive index (average change = $-0.91; P<0.0001$), while patients with no deficit improved significantly over the 5 years on the composite cognitive index (average change = $0.03; P=0.006$, t test of no change).

Quality of Life Results

Quality of life results for all measures are reported in Table 3. Patients’ general health and working status self-ratings 5 years after cardiac surgery are illustrated in Figures 1 and 2. Participants reported their general health status at 5-year follow-up to be either excellent, very good, good, fair, or poor (see Figure 1 for distribution). Only 5.2% of patients reported a poor general health status.

Association of Quality of Life and Working Status With Cognitive Function

Univariate associations were assessed between dichotomous cognitive deficit status, baseline composite cognitive index, cognitive impairment status, change in composite cognitive index, 5-year composite cognitive index, and the independent measures of quality of life. In many areas, significant correlations existed between the cognitive indices and the assessments of quality of life. Univariate associations were demonstrated between baseline cognitive index, change in cognitive index, 5-year cognitive index, and quality of life assessed at 5 years. The association between 5-year composite cognitive index and 5-year quality of life was more robust than the association of quality of life with baseline cognitive function or change in function. Two of the associations between 5-year cognitive index and 5-year quality of life are demonstrated graphically in Figures 1 and 2. Figure 1 demonstrates the correlation between absolute level of cognitive function and the individual’s perception of better general health. Figure 2 demonstrates significant association between composite cognitive function score and the individual work status 5 years after CABG.

Multivariate Association of Quality of Life With Cognitive Function

Table 3 demonstrates the multivariable associations of 5-year cognitive function level (total score), defined by the composite cognitive index, and the various measures of quality of life outcome. Significant covariables in the models are listed as well as the total $R^2$ for the individual models. Substantial
correlation persisted between 5-year cognitive function and quality of life in the majority of domains assessed. Additional variables assessed included age, sex, diabetes, left ventricular ejection fraction, and education. Where multiple cognitive indices were placed in the model, 5-year cognition eliminated other cognitive variables.

**Discussion**

It is well established that cardiac surgery affects neurocognitive functioning. The results from this investigation further define a consistent and broad-based association between neurocognitive function and quality of life 5 years after cardiac surgery, independent of the recognized effects of age, sex, diabetes, and education.3,29 The results indicate that patients’ perception of general health correlates directly with neurocognitive functioning (Figure 1). In addition, patients with higher cognitive function scores were more likely to be working productively 5 years after cardiac surgery, independent of age. While some studies have investigated the longitudinal effects of cardiac surgery on neurocognitive functioning, there are very few studies that have included neurocognitive functioning and quality of life in this particular patient population (Table 3).2,3,8,29–35 The strengths of our methodology include the longitudinal nature of the study and our ability to maintain follow-up. Our results are unique because they provide an overall weighted cognitive function score (factor sum) instead of individual scores from neurocognitive measures. Although these factors limit the direct comparisons to other studies, they enhance the inferential integrity of the statistical results.

Cohen et al8 assessed neurocognitive functioning and improvement in quality of life at baseline and after 12 weeks of cardiac rehabilitation. The study included a small subset of patients who had undergone cardiac surgery. Cohen noted that cardiac surgery patients performed significantly worse in measures of neurocognitive function than the other patients undergoing cardiac rehabilitation at baseline. Baseline quality of life scores of the PCS and MCS of the SF-36 were also found to be lower than average in all patients but improved after cardiac rehabilitation and were statistically significant for PCS rather than MCS measures. He suggested that because neurocognitive performance was strongly associated with changes in SF-36 scores, cognitive abilities might be an important determinant of cardiac rehabilitation outcome.8 Such an observation could also be applied to the current study such that neurocognitive function could be a determinant of “cardiac surgery outcome.”

Quality of life is important in the assessment of any invasive surgical procedure, particularly when performed on a patient population considered by many to have a limited life expectancy. The primary limitation of our study is the lack of baseline quality-of-life data in order to measure change over time. Another limitation is loss to follow-up that is inevitable in the longitudinal study we have accomplished. The lack of baseline quality-of-life data limits our ability to compare cognitive change with quality of life change or to fully understand or compare the associations with our different cognitive indices and quality of life. With no well-defined mechanism to compile our multiple quality-of-life data in order to measure change over time. We encourage readers to assess for themselves the possible role of multiple comparisons in our analysis.

**Implications**

The association between neurocognitive functioning and quality of life has considerable financial and social implications. With older individuals presenting for cardiac surgery in ever-increasing numbers, cognitive dysfunction must be reduced if patients are to be given the same extension in the quality as well as the quantity of life that can be offered by undergoing cardiac surgery. These results further emphasize the need for aggressive strategies to monitor and improve both the neurocognitive function and quality of life of patients after cardiac surgery, a practice that is currently uncommon.8 Assessment of strategies to provide CABG without cardiopulmonary bypass should be assessed to determine whether cardiopulmonary bypass produces cognitive dysfunction and quality of life change. The same attention must go into improvement in brain protection and quality of life that has gone into myocardial protection. Methods must be developed to minimize the adverse affects of CABG on cognitive function since deterioration in cognitive function has adverse societal consequences.
Appendix 1

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Appendix 2

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References

Cognitive dysfunction after major surgery is not uncommon. Cognitive dysfunction is not the same as delirium, encephalopathy, or an altered state of consciousness. Rather, it refers to a condition in which memory and intellectual abilities seem impaired when the patient appears to have otherwise recovered from the immediate effects of surgery. It is a major concern for the patient, family, and physician when a patient is found not to be intellectually the same on awakening after surgery as before.

The precise pathophysiological mechanisms for postoperative cognitive decline are unknown, but are probably multifactorial. Elderly patients undergoing major cardiac surgery (eg, coronary artery bypass grafting [CABG] and thoracic vascular surgery) and noncardiac surgery (eg, orthopedic and abdominal) are at the greatest risk for postoperative cognitive decline. Other individual patient features that increase the risk of postoperative cognitive dysfunction include previous cerebrovascular disease, undetected cognitive impairment or dementia, and cardiovascular risk factors such as hypertension, diabetes, and peripheral vascular disease. Intraoperative risk factors include surgical technique (eg, duration of cardiopulmonary bypass and duration of aortic cross-clamping), hypotension, manipulation of the diseased aorta, and the effects of general anesthesia and hypothermia. Atherothromboembolic phenomena (microemboli) and hypoxia with watershed area injury secondary to hypoperfusion are also possible etiological mechanisms.

Cognitive changes may be obvious when there are gross deficits in learning, memory, attention, or concentration. The decline can also be subtle, with problems in initiative and planning. These changes can persist well beyond the immediate postoperative period, when the effects of anesthesia and analgesia directly affecting cognitive functions have clearly worn off. Most mental status changes improve but can persist for months and years.

In a recent report, Newman and colleagues found the incidence of cognitive decline after CABG to be 53% at discharge, 36% at 6 weeks, 24% at 6 months, and 42% at 5 years. Cognitive decline was defined as a drop of 1 or more standard deviations from baseline scores on tests in at least 1 of 4 domains of cognitive function identified by factor analysis. Older age, lower level of education, and evidence of cognitive decline at discharge were found to be significant predictors of long-term cognitive dysfunction. This suggests that injury during surgery caused in some way cognitive deficits 5 years later. In their accompanying editorial, Selnes and McKhann offer alternative explanations including the possibility that patients who undergo CABG are not cognitively normal because of comorbid cerebrovascular disease.

In the preceding article, Newman and colleagues have expanded their earlier study to investigate the relationship between cognitive function and quality of life 5 years after CABG. Self-perceived health status/quality of life indices are useful as broad outcome measures of the impact of disease and interventions, and associations have been found between cognitive function and quality of life. The study by Newman et al represents an important addition to this literature by demonstrating significant correlations between quality of life and cognitive function 5 years after CABG.

Lower cognitive status was associated with lower perceived general health and less-productive work status. Unfortunately, however, the conclusions are limited by the lack of baseline quality of life data, which makes comparisons with postsurgical values impossible. Without this comparison, it is not possible to evaluate whether there has been a change in quality of life after CABG.

In this study, 5-year quality of life measures (16 continuous variables) were correlated with 5 cognitive indices, including the baseline cognitive index score (sum of 4 cognitive domain scores), change in composite cognitive index at 5 years, and an absolute 5-year cognitive index score. All 3 composite indices correlated with the 5-year quality of life measures. The association between the 5-year cognitive index and quality of life at 5 years was reported to be more robust than the association of quality of life with baseline cognitive function or change in function in the univariate analyses.

It is surprising that baseline cognitive status would correlate with 5-year quality of life measures. This raises the possibility that some of the patients did not have normal cognitive abilities before the surgery. It is also possible that the correlations represent spuriously significant results given the number of comparisons made. The latter explanation is likely because when the multiple cognitive indices were placed in the multivariate model, only the 5-year cognitive index was associated with quality of life.

CABG is a common surgical procedure in the United States. As with other major surgeries, there is a risk of cognitive changes that can persist for months and years. Newman and colleagues eloquently demonstrated this in a recent study. The intent of the current study to investigate quality of life in patients who have undergone CABG is important and laudable. However, due to the absence of baseline quality of life data, the conclusion should be limited to the association of 5-year cognitive status and 5-year quality of life.


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