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The influence of cognitive reserve on neuropsychological functioning following coronary artery bypass grafting (CABG)☆

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Abstract

Neuropsychological impairment is common, yet variable, after coronary artery bypass grafting (CABG). Similar variability has been observed in other CNS-related diseases. Empirical findings in Alzheimer's disease and HIV, among other areas, suggest cognitive reserve (CR) may mediate the cognitive impact of these diseases. The present study examined whether CR mediates neuropsychological outcome after CABG. Participants were 42 ($N = 42$) individuals who underwent elective, normothermic CABG. Each was placed in high ($n = 22$) or low ($n = 20$) CR groups based on estimated premorbid intelligence and occupational attainment. All were administered neuropsychological tests preoperatively and at discharge. The total incidence of neuropsychological decline (66.7%) was not significantly different between CR groups. However, on working memory and executive function tests, specifically, the high CR group demonstrated greater post-operative decline compared to the low CR group. These data are considered in the context of a threshold model of CR theory.

Keywords: Cognitive reserve; Neuropsychological; Coronary artery bypass grafting; CABG

Neuropsychological impairment has been increasingly recognized as a complication after cardiac surgery, in general, and coronary artery bypass grafting (CABG), in particular. Despite important advances in surgical techniques and clinical management of patients, neuropsychological impairment remains a problematic side effect for many of those who undergo CABG. Empirical investigations have reported variable rates of neuropsychological impairment among study participants, with the incidence, according to a review by Van Dijk et al. (2000) ranging between 4 and 47% 2 months after surgery. A subsequent review (Royter, Bornstein, & Russell, 2005) indicates the incidence of neuropsychological impairment specifically in the early post-operative period is higher, ranging from 33 to 83%. In those who experience post-CABG neuropsychological impairment, declines are observed most commonly in attention, verbal fluency, verbal

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learning and recall, visual learning and recall, and psychomotor speed (e.g., Chernov, Efimova, Efimova, Akhmedov, & Lishmanov, 2006; Hall et al., 1999; Lund et al., 2005; Newman et al., 2001; Rankin, Kochamba, Boone, Petitti, & Buckwalter, 2003; Taggart, Browne, Halligan, & Wade, 1999; Van Dijk et al., 2004; Walzer, Herrmann, & Wallesch, 1997; Weinstein, Woodard, & DeSilva, 1998; Wimmer-Greinecker et al., 1998).

The etiology of neuropsychological impairment after CABG remains unclear, though it is likely multifactorial. Historically, cerebral injury after CABG has been attributed to the use of cardiopulmonary bypass (CPB; Roach et al., 1996), though results of studies have been mixed. Kilo et al. (2001), for example, found that use of CPB predicted post-operative neuropsychological impairment, and results of a study by Van Dijk et al. (2002) revealed that patients who underwent CABG without CPB versus with CPB had improved neuropsychological outcomes 3 months after surgery. Other investigators have demonstrated that CPB is not a major cause of neuropsychological impairment after cardiac surgery (Lund et al., 2005; Rankin et al., 2003; Selnes et al., 2003; Taggart et al., 1999; Van Dijk et al., 2004).

The impact of CPB *duration* on neuropsychological outcome has been considered as well, with some studies suggesting that longer CPB results in more extensive neuropsychological difficulties (e.g., Chernov et al., 2006; Murkin, 1995), and others finding that it does not (e.g., Selnes, Goldsborough, Borowicz, & McKhann, 1999; Vingerhoets, Van Nooten, Vermassen, De Soete, & Jannes, 1997). Inadequate or fluctuating cerebral perfusion during CPB may also impact post-operative neuropsychological functioning (Chernov et al., 2006; Degirmenci et al., 1998; Hall et al., 1999; Mills, 1993; Nussmeier, 1994; Pugsley et al., 1990). For instance, Chernov et al. (2006) studied neuropsychological functions and regional cerebral blood flow (rCBF) in 65 patients undergoing CABG. A decrease in rCBF in the right posterior parietal regions in the early post-operative period was correlated with deterioration of delayed visual memory. Six months post-operatively, immediate verbal memory correlated with an increase in rCBF in the right inferior frontal region. Similarly, Hall et al. (1999) studied 35 neurologically normal patients and found that those individuals who showed post-operative neuropsychological decline had significantly poorer cerebral perfusion (as measured by SPECT) both before and during surgery.

Normothermic and hypothermic CPB have been directly compared to determine if there is differential impact on neurological and neuropsychological outcome after CABG. In a randomized, controlled study of normothermic versus hypothermic CPB, Nathan, Wells, Munson, and Wozny (2001) found that mild hypothermia was associated with less neuropsychological decline. Other investigators, however, have found that normothermic CPB is associated with less neuropsychological impairment (e.g., Arrowsmith & Dunning, 2001; Grimm et al., 2000), while yet other studies have failed to reveal an effect of systemic temperature on post-operative neuropsychological functioning (Grigore et al., 2001; Plourde et al., 1997).

Despite procedural changes that lower the incidence of microemboli, increase cerebral perfusion, and regulate potentially damaging temperature changes, post-operative neuropsychological dysfunction clearly remains a problematic side effect for a number of CABG patients. This suggests that some other mechanism(s) may be contributory.

Findings from other fields may provide direction for empirical investigation of factors yet to be explored in CABG. In Alzheimer's disease and other neurodegenerative disorders (e.g., Andel, Vigen, Mack, Clark, & Gatz, 2006; Le Carret et al., 2005; Qiu, Backman, Winblad, Aguero-Torres, & Fratiglioni, 2001; Scarmeas et al., 2003; Stern, Albert, Tang, & Tsai, 1999), HIV/AIDS (Satz et al., 1993; Stern, Silva, Chaisson, & Evans, 1996), and electroconvulsive therapy (Legendre, Stern, Solomon, Furman, & Smith, 2003) one factor that has been examined and found to impact outcome is "cognitive reserve." Cognitive reserve (CR) is a heuristic model for explaining observed differences in clinical presentation between people with relatively similar brain pathology or degree of brain damage (for review, see Stern, 2002). CR theory purports that an individual's cognitive reserve determines his or her threshold for clinical manifestation of the event or evolving disease process. A greater CR is hypothesized to be a protective factor that raises the threshold for the clinical manifestation of symptoms, while a lower CR is hypothesized to be a vulnerability factor that lowers the threshold for clinical presentation (Satz, 1993).

Kliegl, Smith, and Baltes (1989), along with others such as Satz (1993), sought to explain why individuals with the same *biological* markers of disease progression could have such different clinical presentations. They posited that individual differences in CR, or brain reserve capacity, might account for differences in symptom threshold, and might thus explain varying clinical courses and presentations. As Satz (1993) explains, the threshold effect rests on the assumption that the amount of brain tissue or neuronal loss is the same across individuals. However, individual differences probably exist in terms of brain reserve that might alter the symptom threshold.

Educational attainment, occupational level, and premorbid intelligence are factors that have been examined as markers of an individual's CR. Educational attainment has been conceptualized as an indirect measure of CR, given findings that more educated individuals have higher intelligence, heavier brains, more dendrites, and more nerve cells with more synaptic connections than less educated people (Jacobs, Schall, & Scheibel, 1993; Mortimer, 1997). It has also been proposed that education increases synaptic density in the neocortical association cortex, thus increasing CR (Katzman et al., 1998). More educated individuals may also have more CR because of the effect of education on neurochemical activity in the brain (Stern, Alexander, Prohovnik, & Mayeux, 1992). This assumption was supported in a longitudinal study of nearly 600 nondemented elderly persons in which the risk for developing Alzheimer's disease was reduced in those with greater educational (as well as occupational) attainment (Stern et al., 1994).

Occupation may also be an indirect marker of CR, as one's life work may provide particular cognitive strengths or certain skills that, like education, infer some sort of protection against clinical symptoms or provide the individual with greater compensatory strategies for coping with neuropsychological decline. In fact, a higher incidence of dementia was found among those who had either low educational or low occupational attainment; the risk was even greater for those who had both low educational and occupational attainment (Stern et al., 1994). In a later investigation, Stern, Albert, et al., 1999) found that education and occupation were related to the rate of memory decline in Alzheimer's disease. That is, those with higher education and occupational attainment experienced a slower rate of neuropsychological decline over the course of the disease than those with low education and occupational attainment.

In addition to education and occupation, premorbid intelligence may be an indirect marker of CR. Some have suggested that intelligence may be a more sensitive marker of CR than education level alone (Alexander et al., 1997; Schmand, Smit, Geerlings, & Lindeboom, 1997). As Satz (1993) explained, intelligence might represent a more robust indirect measure of brain reserve capacity than education because the latter is determined by other factors besides the innate capacities of the individuals. For example, unfavorable socioeconomic circumstances may limit the individual's opportunities to receive an appropriate education. Support for this idea is provided by studies revealing a relationship between early intellectual abilities and incident dementia. For example, it was found that lower intellectual ability measured as early as childhood may be associated with higher rates of late-onset dementia (Whalley et al., 2000). Using data from a 1932 survey measuring the mental ability of the 1921 Scottish birth cohort, the authors determined that the mental ability scores of children who eventually developed late-onset dementia were significantly lower than those of other Scottish children who were tested that year. Additionally, Snowdon et al. (1996) found a negative correlation between the grammatical complexity of autobiographies written in early life and the incidence of Alzheimer's disease in late life among a large group of nuns. Indeed, a study with healthy young adults revealed that neural activity during a nonverbal recognition task is correlated with intelligence as estimated by a reading test (Stern et al., 2003). Among studies of premorbid intelligence estimated in later life, Geerlings et al. (1999) also found that the effect of premorbid intelligence on mortality in demented patients was stronger than that of education alone.

CR, per se, has yet to be explored as a potential mediating factor in differential neuropsychological outcome after CABG. However, previous studies on CR in Alzheimer's disease, HIV, and ECT have all suggested that it may account for some of the observed differential response to treatment, just as it has in these other diseases and CNS-challenging events. Certainly, the observed relationship between education and post-CABG neuropsychological functioning supports this hypothesis. Newman et al. (1994) found that higher educational attainment was associated with less neuropsychological decline on eight of the nine neuropsychological measures administered to CABG patients. In a later study by Newman et al. (2001), poorer neuropsychological function at discharge, fewer years of education, and older age were significant predictors of long-term functioning. Similarly, independent predictors of neuropsychological decline 5 years post-operatively included presence of neuropsychological decline at discharge, fewer years of education, and older age. Hall et al. (1999) examined whether education was correlated with post-surgical neuropsychological functioning. Patients with higher educational levels had less deterioration on test scores of psychomotor speed, verbal fluency, and attention. The authors suggested that patients who are most vulnerable to the deleterious effects of CABG may be those with preexisting vulnerability, as reflected in low education. Contradictory results, however, were revealed by investigators, including Selnes, Goldsborough, Borowicz, Enger, et al. (1999), who did not find that years of education was a predictor of neuropsychological change after CABG. The authors acknowledged, however, that this lack of association may have been attributable to the relatively lower proportion of subjects (22%) with fewer than 12 years of education.

The relationship between education and outcome after CABG, albeit somewhat inconsistent, suggests that CR, perhaps as a more robust measure of education, is worth further consideration as a factor contributing to the differential neuropsychological outcome. No studies to date have examined CR directly in CABG patients before and after surgery. The purpose of the present investigation was to examine whether CR contributes to differential neuropsychological profiles after CABG. The construct of CR was operationalized by a combination of factors that, based on previous literature, potentially contribute to CR, including an estimate of premorbid intelligence that incorporates educational attainment and vocabulary knowledge, as well as occupational attainment. It was hypothesized that CR would mediate the extent of neuropsychological impairment after CABG surgery. Specifically, it was predicted that individuals with a higher CR would experience less post-operative neuropsychological impairment compared to those with a lower CR.

1. Method

1.1. Participants

Approval for this study was obtained from the Institutional Review Boards of the University of Rhode Island and Rhode Island Hospital. All participants gave their informed, written consent to be enrolled in the study. Enrolled participants were 51 ($N=51$) consecutive men and women scheduled to undergo elective CABG. In order to control for differences in surgical techniques and CPB temperature, only patients treated by one surgeon who only performed normothermic CPB were recruited for this study. Data from enrolled patients who refused post-operative testing ($n=3$), were discharged and could not be contacted to schedule post-operative testing ($n=2$), or experienced adverse preoperative, intraoperative, or post-operative events (e.g., stroke [$n=1$], myocardial infarction [$n=2$], renal insufficiency [$n=1$]) were not included in analyses. As a result, data from 42 ($N=42$) participants were included in the analyses. Four patients were inpatients at the time of enrollment, all of whom had been admitted with symptoms of angina. Participants were enrolled in this study between November 2001 and June 2002. Only patients between 18 and 90 years old were included and all subjects were required to have at least 6 years of education and speak English as their primary language (to assure the appropriate use of the standardized neuropsychological tests). Exclusion criteria included a history of head injury, neurodegenerative disease, history of drug or alcohol abuse, significant psychiatric disorder, renal disease, active liver disease, previous cardiac surgery, or severe left ventricular dysfunction (i.e., ejection fraction <20%).

1.2. Materials

Neuropsychological tests were selected to sample a broad range of cognitive abilities (e.g., attention, concentration, learning and memory, psychomotor speed). In addition, tests were selected using suggestions from a published consensus statement on assessment of neurobehavioral outcomes after cardiac surgery (see Murkin, Newman, Stump, & Blumenthal, 1995; Stump, 1995). Finally, tests with alternate versions were utilized, when available, to reduce test–retest effects to the extent possible. Measures included several subtests of the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997a) (Digit Span, Digit Symbol-Coding, Letter–Number Sequencing, and Vocabulary); FAS test (verbal fluency; Benton, 1967; Spreen & Benton, 1969) and category fluency (i.e., animals); Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict, Schretler, Groninger, & Brandt, 1998); Mental Control subtest of the Wechsler Memory Scale-III (WMS-III; Wechsler, 1997b); Short Story subtest of the Randt Memory Test (Randt & Brown, 1983); Rey–Osterrieth Complex Figure test (Spreen & Strauss, 1998) scored with the Boston Qualitative Scoring System (BQSS; Stern, Javorsky, et al., 1999); and the Trail Making Test, parts A and B (Reitan & Wolfson, 1985).

1.3. Procedure

1.3.1. Testing schedule

Participants were approached to participate in this study when they presented to their surgeon for a routine, presurgery medical examination in the hospital (for inpatients) or in the surgeon's office (for outpatients). Participants were tested on two occasions: before the CABG surgery and again before discharge from the hospital. For inpatients, the first session took place 1–3 days before surgery, on the hospital unit in a private or semi-private patient room. For outpatients, the first session took place 1–7 days before surgery (on the day the participant presented for his or her routine, pre-surgical medical examination) in a private, designated room in the pre-admission testing suite. The second session took place 1–2 days before discharge from the hospital, on the hospital unit. On occasion, when a participant was discharged before testing could be performed ($n=3$), the final test session was conducted at the patient's home 1–2 days following discharge. All patients were alert and medically and pharmaceutically stable at the time of the neuropsychological examinations, as deemed by the team of cardio-thoracic surgeons, anesthesiologists, and research nurses collaborating on this investigation.

The testing schedule was chosen based on several considerations. Specifically, baseline preoperative assessment was conducted on each participant for comparison against his or her post-operative performance. This allowed each participant to serve as his or her own control. The second testing time point (post-test) was chosen based on findings by Newman et al. (2001) and Bruggemans, Van Dijk, and Huysmans (1995), which have shown that neuropsychological functioning in the early post-operative period (i.e., 3–7 days) is the best predictor of long-term neuropsychological outcome after CABG.

Each of the two testing sessions lasted approximately 60 min. All neuropsychological measures were administered to each participant at the first testing session. All measures except the Vocabulary subtest of the WAIS-III were re-administered at the second testing session with alternative forms used if available and randomly counterbalanced across subjects. At the conclusion of the second testing session, participants were asked a series of questions pertaining to their educational and occupational history. The total length of participation (from recruitment to post-test) ranged from 2 to 6 weeks.

1.3.2. CR scores

For the present study, the construct of CR was operationalized by a combination of estimated full-scale IQ (FSIQ) and occupational attainment. This combination of estimated premorbid intelligence and occupation was chosen as a more robust measure of CR given that education alone may be confounded by socioeconomic status, availability of educational opportunities, or other cultural, social, or economic limitations. This combination of factors also allowed for comparisons to other studies on CR that have examined the influence of various markers of CR, including years of education, premorbid intelligence, and occupational attainment (alone and in combination) on neuropsychological functioning. Premorbid FSIQ was estimated using the Oklahoma Premorbid Intelligence Estimate (OPIE-3V; Schoenberg, Scott, Duff, & Adams, 2002), a combined demographic- and performance-based method of estimation that incorporates several indirect markers of CR into one regression formula. The variables combined in the regression equation include the WAIS-III Vocabulary subtest raw score, years of education, ethnicity, region of the country, and gender (see Appendix A). Research suggests that vocabulary knowledge is resistant to the effects of brain insult (see Lezak, 2004). Lezak (2004) added the argument that using only demographic characteristics, such as years of education, to estimate patient functioning before the onset of an illness such as dementia may not fully reflect the degree of intellectual ability achieved during the life span. Additional empirical evidence indicates that the OPIE-3V is a good measure for use with clinical samples because it yields estimated IQ scores that most closely approximate a mean of 100 and standard deviation of 15, as well as the least restricted range of estimated FSIQ scores as compared to other IQ estimates (Schoenberg et al., 2002).

Occupational attainment was classified based on seven United States census occupation categories as described by Stern et al. (1994): student; housewife; unskilled/semi-skilled; skilled trade or craft; clerical/office worker; manager of business/government; professional/technical. Occupational ratings for retired subjects was determined based on the individuals' primary occupation while working or based on the job the individual held for the longest period of time.

A CR score (CRS) was calculated for each subject by summing the rank values of the z-scores for OPIE-3V and occupation rating. Using a median split, the sample was then divided into two groups, with a low CR (low CR) group comprised of those participants with a CRS below the median for the entire group ($n = 20$), and a high CR (high CR) group comprised of those participants with a CRS at or above the median for the entire group ($n = 22$).

1.3.3. Surgical and anesthesia procedures

Anesthesia management was standardized with the use of midazolam, fentanyl, and pancuronium for induction, and additional narcotic with inhalational agents for maintenance of general anesthesia. Ketamine and barbiturates for induction were avoided. Surgical technique included median sternotomy with cannulation of the ascending aorta and atrial venous cannulae. Non-pulsatile systemic perfusion at a flow rate of 2.5 L/min/m^2 was maintained during normothermic cardiopulmonary bypass (CPB). All extracorporeal circuits included a membrane oxygenator and arterial filter (40 μm), and were primed with the standard crystalloid solution. Normothermic CPB (35.5–36.5 °C) was maintained by control of arterial inflow blood temperature. Inflow temperature was not allowed to exceed 38 °C in any patient. During CPB, systemic pressure was maintained between a mean arterial pressure of 50–90 mmHg, PaO_2 between 150 and 300 mmHg, $PaCO_2$ between 30 and 40 mmHg, and hematocrit was maintained between 20 and 27%.

Myocardial preservation was accomplished with cold antegrade blood cardioplegia and topical cooling with saline slush in the pericardial sac. No retrograde cardioplegia was used. There was a single period of aortic cross-clamping for construction of proximal and distal anastomoses. The attending anesthesiologist utilized those medications that were necessary to wean the patient from CPB as required.

1.4. Statistical analyses

Analyses were carried out using the SPSS (Version 12.0.1) statistical software package (SPSS, Inc., Chicago, IL). An alpha level of .05 was considered statistically significant. As described below, care was taken to diminish type I error by way of several statistical techniques.

1.4.1. Demographics and intraoperative measures

Group differences on demographics were examined with independent samples *t*-tests for continuous data; Mann–Whitney *U*-tests for ordinal data; and chi-square (χ^2) tests for categorical data. Group differences on intraoperative variables were evaluated using independent samples *t*-tests for continuous data and χ^2 tests for categorical data.

1.4.2. Factor analysis

An exploratory factor analysis was conducted for the purpose of guiding subsequent multivariate analyses. Specifically, a principal components factor analysis with varimax rotation and the Kaiser normalization method was conduced using raw test scores obtained at baseline testing. Because factor analysis is sensitive to the effects of multicollinearity, only dependent variable(s) deemed robust and theoretically meaningful were chosen for entry into the factor analysis (e.g., the forgetting score on the Randt Short Story subtest was chosen for analysis in lieu of the four recall variables of this subtest, because the forgetting score is a single score which is calculated from two highly correlated variables, immediate verbatim recall score and the delayed verbatim recall score).

1.4.3. Incidence of neuropsychological impairment

A change score from preoperative (baseline) testing to post-operative discharge testing (post-test) was also calculated for each subject for each outcome measure. A significant decline on a measure was defined as a change in raw score of 1 or more standard deviations below the mean raw score for that measure for the entire sample. An individual was considered "neuropsychologically impaired" if there was a significant decline on at least 20% of the outcome measures (two or more out of nine measures). This method of defining neuropsychological impairment and significant decline has been used previously in studies of neuropsychological functioning in CABG patients (e.g., Kneebone, Andrew, Baker, & Knight, 1998). Group differences in the number of subjects demonstrating neuropsychological decline were examined with chi-square analyses. Group differences in the number of subjects demonstrating neuropsychological decline on at least 20% of the measures comprising each of the factors identified by factor analysis were examined with chi-square analyses.

1.4.4. Repeated measures MANOVAs

To examine the interaction of group membership and change in test performance over time, a mixed within-between subjects (repeated measures) multivariate analysis of variance (MANOVA) was completed using those variables that comprised each factor. For these analyses, CR group (high versus low CR) served as the between-subjects variable, and time (baseline and post-test) served as the within-subjects (repeated measures) variable. All models were checked for violations of assumptions of heterogeneity of variance and outlying cases. Significant interactions (i.e., those involving the combined effects of CR group and time of testing) were examined further with follow-up univariate analyses (ANOVAs) for group effects and time effects.

2. Results

2.1. Demographics and intraoperative measures

Demographics for each CR group, as well as clinical characteristics, are presented in Table 1. The groups were comparable with regard to demographic and clinical characteristics including age, gender, and medical history. As expected,

Table 1
Demographics and clinical history by cognitive reserve (CR) group

	Low CR, mean (S.D.)	High CR, mean (S.D.)
Age (years)	65.9 (9.7)	61.6 (5.9)
Education (years)	11.5 (2.5)	14.1 (2.1)*
Cognitive Reserve Score (CRS) (mean)	15.1 (6.7)	37.7 (6.6)*
OPIE-3V (mean)	91.8 (8.2)	110.6 (5.6)*
Male sex (%)	70.0	86.4
Caucasian (%)	90.0	100.0
Occupational rank (mean)	15.6	26.9
Occupational level (%)		
Student	0	0
Homemaker	10.0	0
Unskilled/semi-skilled	40.0	0
Skilled trade or craft	10.0	27.3
Clerical/office worker	5.0	22.7
Manager business/government	35.0	13.6
Professional/technical	0	36.4
Living situation		
With spouse/significant other	80.0	77.3
Alone	15.0	22.7
With family/friends	5.0	0
Northeast Geographic Region (%)	95.0	86.4
COPD (%)	5.0	9.1
Diabetes (%)	30.0	31.8
History of high cholesterol (%)	75.0	85.0
History of hypertension (%)	85.0	77.3
Smoking history (%)	70.7	72.7
PVD (%)	15.0	4.5
Previous MI (%)	30.0	40.9
LVEF	50.8 (8.9)	53.4 (9.4)
Length of stay (surgery to discharge)	5.3 (1.2)	6.5 (6.8)

Note: OPIE: Oklahoma Premorbid Intelligence Estimate; COPD: chronic obstructive pulmonary disease; PVD: peripheral vascular disease; MI: myocardial infarction; LVEF: left ventricle ejection fraction.
* $p < .01$.

there was a significant difference between groups on the CRS [$t(41) = 11.0$, $p < .01$], OPIE-3V scores [$t(41) = 8.8$, $p < .01$], occupational rank [$U(1,41) = 102.0$, $p < .01$], and years of education [$t(41) = 3.7$, $p < .01$], given that each of these measures was a factor upon which group membership was based.

There were no group differences on any of the intraoperative measures, including duration of cardiopulmonary bypass, cross-clamp time, and the number of bypassed vessels (see Table 2). There was also no significant group difference in the mean number of post-operative hospital days, suggesting similar recovery rates and comparable testing intervals for participants in each group.

2.2. Factor analysis

Factor analysis yielded a theoretically meaningful solution with four components/factors, accounting for 74% of the variance among patients' baseline results on this test battery (see Table 3 for factor structure table). Only those measures that loaded highly (i.e., ±.40) on each component were included; those measures that loaded on more than one factor were grouped with conceptually related measures. Two measures, Mental Control and category fluency (animals) did not load onto any factors. On the basis of scale content, the four factors were given the following labels: (1) psychomotor speed; (2) working memory and executive functions; (3) verbal learning and memory; and (4) visual learning and memory. The psychomotor speed factor was comprised of total time to completion on the Trail Making Test (part A), and the raw score on the Digit Symbol subtest. The working memory and executive functions factor was

Table 2
Intraoperative comparisons by CR group

	Low CR, mean (S.D.)	High CR, mean (S.D.)
CPB time (min)	83.0 (24.2)	79.6 (21.4)
Anesthesia time (min)	284.5 (56.1)	270.6 (55.6)
Surgery time (min)	219.0 (58.2)	221.8 (44.0)
Cross-clamp time (min)	68.3 (20.3)	66.8 (20.0)
Extubation time (h)	9.5 (4.5)	9.8 (7.8)
Grafts (*n*)	3.0 (0.8)	3.0 (1.0)
Total BPU	1.5 (1.7)	1.0 (1.4)
Water temperature (°C)	38.0 (0.5)	37.9 (0.6)
Tympanic temperature (°C)	36.8 (0.5)	37.0 (0.5)
Bladder temperature (°C)	36.5 (0.4)	36.6 (0.4)

Note: CPB: cardiopulmonary bypass; total BPU: total blood product units. No significant differences were observed between any variables.

comprised of total words generated on the FAS verbal fluency test, total raw score on the Digit Span subtest, total time to completion on the Trail Making Test (part B), and the raw score on the Letter–Number Sequencing subtest. The verbal learning and memory factor included the percentage of information forgotten on the Short Story subtest of the Randt Memory Test and the percentage of information forgotten on the HVLT-R. The visual memory factor consisted of the delayed retention score from the BQSS for the Rey–Osterrieth Complex Figure test.

2.3. Incidence of neuropsychological impairment

Overall, 66.7% of subjects demonstrated significant post-operative neuropsychological decline. In the low CR group, 11 subjects showed neuropsychological decline (55.5% of the low CR group) and in the high CR group, 17 subjects exhibited neuropsychological decline (77.3% of the high CR group). This did not represent a significant group difference in overall incidence of neuropsychological decline.

A total of 47.6% of all CABG patients demonstrated significant decline on measures of psychomotor speed, 45.2% had significant decline on working memory and executive function measures, 57.1% declined significantly on verbal memory measures and 16.7% showed significant decline on a test of visual memory. There were no significant differences in the incidence of decline on any factors by CR group.

2.4. Repeated measures MANOVAs

Four repeated measures MANOVAs were performed using the raw scores of those measures that comprised each of the four factors described above. Results of the MANOVA with the psychomotor speed variables did not reveal a significant interaction effect. A main effect was not found for group membership. However, there was a main

Table 3
Factor structure table (rotated component matrix)

	Component			
	1	2	3	4
Digit-symbol coding	−.876			
Trails A	.791			
Verbal fluency (F,A,S)		.629		
Digit span		.870		
Letter–Number Sequencing		.750		
Trails B		−.468		
HVLT-R % forgotten			.413	
Randt % forgotten			.925	
BQSS delayed retention (%)				.904

Note: Extraction method: principal component analysis. Rotation method: varimax rotation with Kaiser normalization. Rotation converged in five iterations.

effect of time [$F(2,39) = 18.98$, $p < .001$)], indicating that performance on these measures declined significantly from baseline to post-test for both CR groups. Univariate analysis revealed that scores on both the Trail Making Test part A [$F(1,40) = 9.79$, $p < .01$) and Digit Symbol subtest [$F(1,40) = 31.26$, $p < .001$] decreased significantly from baseline to post-test for both groups. Results of the MANOVA with the working memory and executive functions variables revealed a significant interaction effect [$F(4,37) = 3.50$, $p = .016$]. Analysis of main effects did not reveal a group effect. There was a significant effect of time [$F(4,37) = 4.02$, $p < .01$), indicating that both CR groups declined on these measures from baseline to post-test. Univariate tests of each of the four working memory and executive functions measures revealed an interaction effect on the Digit Span subtest [$F(1,37) = 11.1$, $p < .01$] and the Trail Making Test part B [$F(1,37) = 5.37$, $p = .026$], such that the high CR group declined significantly more on these measures from baseline to post-test compared to the low CR group. A main effect of time was revealed for the Digit Span subtest [$F(1,40) = 14.69$, $p < .001$] and Trail Making Test part B [$F(1,40) = 4.84$, $p = .034$]. A main effect of group was shown on the FAS [$F(1,40) = 7.58$, $p < .01$], Digit Span subtest [$F(1,40) = 4.99$, $p = .03$], and Letter–Number Sequencing subtest [$F(1,40) = 6.43$, $p = .015$]. The third MANOVA performed on the verbal memory measures did not reveal a significant interaction effect or a main effect of group. There was a significant main effect of time [$F(2,39) = 4.92$, $p = .01$], indicating that both groups declined significantly from baseline to post-test on these verbal memory measures. Univariate tests showed that patients experienced a significant decline over time on the HVLT-R [$F(1,40) = 7.59$, $p < .01$] but not on the Randt Memory Test Short Story subtest. A fourth MANOVA performed using the delayed retention score from the BQSS for the Rey–Osterrieth Complex Figure test did not reveal a significant interaction effect nor significant main effects.

3. Discussion

A total of 66.7% of subjects in the present study demonstrated significant post-operative neuropsychological decline. This rate is consistent with other studies examining the rates of neuropsychological impairment in the first few weeks after CABG surgery (Newman et al., 2001; Stroobant, Van Nooten, Belleghem, & Vingerhoets, 2002; Van Dijk et al., 2004). A total of 47.6% demonstrated significant decline on measures of psychomotor speed, 45.2% had significant decline on working memory and executive function measures, 57.1% declined significantly on verbal memory measures and 16.7% showed significant decline on a test of visual memory. These findings are consistent with past research demonstrating that patients undergoing CABG most frequently experience post-operative deficits in attention, working memory, verbal fluency, verbal memory, and psychomotor speed (e.g., Chernov et al., 2006; Hall et al., 1999; Lund et al., 2005; Newman et al., 2001; Taggart et al., 1999; Walzer et al., 1997; Weinstein et al., 1998; Wimmer-Greinecker et al., 1998). Significant declines in visual memory functioning were not observed in a majority of patients, though this may have been due to the reliance on a single test of visual memory in this study. There were no significant differences by CR group in the overall incidence of neuropsychological decline, nor in the incidence of decline on measures of psychomotor speed, working memory and executive functions, verbal memory, or visual memory specifically.

Nearly half of all those undergoing CABG, regardless of CR group membership, experienced significant post-operative decline on measures of psychomotor speed, working memory and executive functions, and verbal memory. These results do not support the main hypothesis that high CR would provide a more general protection against neuropsychological decline after CABG. Rather, CR mediated the amount of decline only on working memory and executive function measures. Moreover, contrary to our hypotheses, it was the *high* CR group that experienced more significant decline on these tests.

One possible explanation for these findings is that each group may have met threshold for clinical expression of neuropsychological impairment at different time points. That is, the low CR group may have already met threshold for the clinical expression of cerebrovascular disease and thus did not demonstrate a rapid decline in performance beyond their already compromised performance. The high CR group, in contrast, may not have met threshold by the time of initial assessment, and thus threshold would have been met at a later time point, perhaps once the additional challenge of CABG was initiated. Research on the rate of neuropsychological decline in Alzheimer's disease, Parkinson's disease, and other dementias (e.g., Andel et al., 2006; Satz, 1993; Stern, Albert, et al., 1999; Wilson et al., 2004) found that once individuals met a threshold for expression of the disease, neuropsychological functioning declined at a more rapid rate. In the case of individuals with low CR, that decline could have occurred as possible cerebrovascular disease progressed prior to surgery, and thus would not have been observed in the context of the short testing period of this study. In the case of individuals with high CR, that decline would have occurred when the surgery put them over threshold, yielding observable decline. This position cannot, however, be substantiated in the present study because of the lack of information on the presence or severity of cerebrovascular disease in these subjects. Future investigations should address, using MRI or SPECT ideally, the potential differences in the severity of any cerebrovascular disease in individuals with varying levels of CR and their subsequent influence on post-operative neuropsychological functioning.

Conversely, these results also raise the possibility that individuals with higher CR (or those with more education) merely perform better than those with low CR on neuropsychological measures and that observed differences are not due to the interaction of CR and CABG. Indeed, the high CR group performed significantly better than the low CR group on each of the factor domains preoperatively. However, if only CR or education level was accounting for these differences, then we would also expect to see similar discrepancies in scores post-operatively. No significant differences on these factors remained between CR groups post-operatively. In a study examining the influence of initial test scores on detection of change in neuropsychological functioning conducted by Temkin, Heaton, Grant, and Dikmen (1999), the authors found that initial test scores accounted for 67–88% of the variance for scores at follow-up, compared with a maximum of 8% for a number of demographic variables. Furthermore, if neuropsychological functioning was influenced by education or CR alone, an improvement in performance rather than a decline in the higher educated individuals would have been observed as a result of the known practice effects typically demonstrated by more educated individuals who are administered the same or similar tests over short intervals of time, as they were in the present study (see Dikmen, Heaton, Grant, & Temkin, 1999 for discussion of practice effects on neuropsychological tests).

The convergence of scores post-operatively may also be argued to reflect regression to the mean. Dikmen et al. (1999) describe the typical pattern observed because of regression to the mean involves a large positive change for people initially scoring poorly and a much smaller improvement or even deterioration for those initially scoring well with the end result being that each gets closer to the overall group mean. The low CR group generally failed to demonstrate an improvement in scores. Furthermore, analysis of published age-corrected scores for the measures used in the present study shows that the high CR group was initially performing within 1 standard deviation of the mean on each primary outcome measure, and therefore their subsequent decline in scores represented a further deviation from the mean rather than a regression toward the mean. At the same time, the lack of movement toward the mean in the low CR group was not observed; this was not due to poor initial performance by the low CR group. In fact, the low CR group, though they performed significantly below the high CR group on nearly all measures at baseline, were also performing within 1–1.5 standard deviations of age-corrected normative scores on all outcome measures and showed significant decline post-operatively.

A limitation of the current study, as with many neuropsychological studies with CABG patients, is that a separate control group is lacking. As such, the effects of other factors such as general anesthesia or medications, normal test variability, and practice effects could not be determined. However, such nonexperimental effects were distributed across all subjects and do not preclude detecting valid trends, or the association between demographic variables, such as CR, and neuropsychological impairment. Defining "significant neuropsychological decline" also proved problematic. Other authors, faced with the same limitations, have used a variety of techniques to identify which patients suffered meaningful neuropsychological decline after CABG. In this study, patients who suffered short-term neuropsychological decline were identified as those whose change score was 1 or more standard deviations below the mean. Patients could thus be considered impaired after CABG if there was at least a minimal general trend to do worse across most tests or significant impairment on two tests out of nine (20% of tests). While imperfect, this was considered a conservative measure of impairment.

Overall, the findings from the present study have implications for the understanding of CR theory, CABG surgery and its neuropsychological consequences, and study design for future investigations of CR. Continued study of the factors that impact neuropsychological functioning is essential, given that adverse central nervous system outcome after CABG has an impact on post-operative recovery and quality of life. Previous studies have shown that more significant long-term neurologic and neuropsychologic impairment is associated with longer intensive care treatment and hospital stays and more time on assistance devices (Mills, 1993). These consequences have tremendous social and economic implications for the practice of surgery, the identification of populations at risk for poorer outcome, and development of post-operative treatments and interventions. Furthermore, future research should also investigate preoperative differences in existing cerebrovascular disease (by way of imaging studies) and any interaction between cerebrovascular disease and CR. Future studies should also aim to obtain a larger sample with greater differentiation between CR groups. Dividing such a sample into thirds and comparing the neuropsychological performance of the highest and lowest groups may illustrate additional or more marked variations in neuropsychological performance as a function of CR. Finally, potential preoperative treatments and interventions should be investigated, given that individuals with lower CR may be more vulnerable to the neuropsychological consequences of progressing cerebrovascular disease than the CABG procedure itself.

Appendix A. OPIE-3V: Estimation of Full Scale IQ using Vocabulary subtest score and demographic variables

Formula for Estimating Full Scale IQ:

$$\text{FSIQ} = 57.338 + 0.871(\text{Voc.Raw score}) + 1.770(\text{Education}) + 1.066(\text{Ethnicity}) + 0.682(\text{Region of Country}) - 1.493(\text{Gender})$$

Coding Variables	
Ethnicity:	1 = African American, 2 = Hispanic, 3 = Other, 4 = Caucasian
Education:	1 = 0–8 years, 2 = 9–11 years, 3 = 12 years, 4 = 13–15 years, 5 = 16+years
Gender:	1 = male, 2 = female
Region of Country:	1 = South, 2 = North Central, 3 = North East, 4 = West

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