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ORIGINAL ARTICLE

Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery

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Abstract

Purpose We tested the hypothesis that elevated postoperative interleukin-6 (IL-6) and C-reactive protein (CRP) concentrations are associated with short- and medium-term impairment of cognitive functions in patients after coronary artery surgery using cardiopulmonary bypass.

Methods Eighty-six age- and education-balanced patients $\geq$55 years of age undergoing elective coronary artery bypass surgery with cardiopulmonary bypass and 28 nonsurgical controls with coronary artery disease were enrolled. Recent verbal and nonverbal memory and executive functions were assessed before surgery and at 1 week and 3 months after surgery using a cognitive test battery. IL-6 concentrations were measured before surgery and 4 h after cardiopulmonary bypass, and CRP concentrations were measured before surgery and at 24 and 72 h after anesthetic induction. Overall cognitive function between high and low biomarker concentration groups was analyzed by the Wilcoxon rank-sum test.

Results Recent memory was at least 1 standard deviation (SD) impaired at 1 week and 3 months in the high-CRP compared with low-CRP and in the high-IL-6 compared with low-IL-6 concentration groups. Overall cognitive function was significantly ($P = 0.04$ and $P = 0.01$, respectively) different between the high- and low-CRP concentration groups (CRP assayed 24 h after anesthetic induction) at both 1 week and 3 months. Overall cognitive function was also significantly ($P = 0.04$) different between the high- and low-IL-6 concentration groups at 1 week after surgery.

Conclusion The results suggest that elevated postoperative IL-6 and CRP concentrations are associated with the subsequent development of short- and medium-term impairment of cognitive functions after coronary artery surgery.

Keywords C-reactive protein · Interleukin-6 · Coronary artery bypass graft · Cardiopulmonary bypass · Postoperative cognitive dysfunction

Introduction

Postoperative cognitive dysfunction (POCD) after cardiac surgery affects as many as 80% of patients, may persist for several months [1, 2], and may become a permanent disability with profound consequences for quality of life [3, 4]. POCD is characterized by impairments in recent memory, concentration, language comprehension, and social integration [5, 6]. Patients with POCD may experience delayed transfer from the intensive care unit after surgery, prolonged hospitalization, and a longer recovery before returning to work [7–9]. These patients may also experience impaired self-care, increased dependency, increased attrition from rehabilitation, and higher rates of hospital readmission. Advanced age, low educational level, preexisting cognitive impairment, alcohol abuse, and severity of coexisting illness are risk factors for POCD [6, 10, 11].

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A systemic inflammatory response occurs during cardiac surgery as a result of surgical trauma, blood contact with the cardiopulmonary bypass (CPB) circuit, and lung reperfusion injury [12–14]. Inflammation also occurs in the brain after off-pump coronary artery bypass graft surgery [15] or after nonneurological, noncardiac surgery, as indicated by increased concentrations of proinflammatory cytokines in the cerebrospinal fluid [16]. Irrespective of the underlying cause, these inflammatory changes may adversely affect learning, memory, and other cognitive domains by altering hippocampal function [17]. Indeed, an increase in inflammatory markers predicts cognitive decline. Multiple elevated inflammatory markers are especially indicative of systemic inflammation and are predictive of subsequent cognitive dysfunction [18]. Elevated serum interleukin (IL)-6 [19] and C-reactive protein (CRP) [19, 20] concentrations are associated with reduced cognition and contribute to accelerated functional decline in the elderly. An association between CRP concentration during middle age and subsequent risk of dementia has also been demonstrated [20, 21]. The current investigation tested the hypothesis that elevated postoperative IL-6 and CRP concentrations are associated with short- and medium-term impairment of cognitive functions in older patients after coronary artery surgery using CPB.

Materials and methods

The protocol was approved by the Institutional Review Board of the Zablocki Veterans Administration Medical Center, Milwaukee, WI, USA. All subjects provided written informed consent.

Participants

One hundred and fourteen patients (86 surgical and 28 nonsurgical) were recruited. Inclusion criteria included 55 years of age or older, providing written informed consent, and being scheduled for elective coronary artery bypass surgery with CPB. Nonsurgical patients also had coronary artery disease; inclusion of this group was important to account for practice effects of repeated cognitive testing [22]. Exclusion criteria included a history of a cerebrovascular accident, permanent ventricular pacing, previously documented cognitive deficits, or vascular dementia (Hachinski score [23] >4). Patients with hepatic impairment (aspartate aminotransferase or alanine aminotransferase more than twice the upper normal limit) and chronic renal insufficiency (creatinine > 2 mg/dl) were also excluded.

Protocol

Within 1 week before surgery, cognitive functions were assessed with a neuropsychometric battery including recent verbal and nonverbal memory and executive functions. Cognitive functions were reassessed at 1 week or at hospital discharge (whichever occurred first) and 3 months after surgery, or 1 week and 3 months after the first testing in patients in the nonsurgical group. Three parallel forms of the tests were used except for Stroop and Digit Span; the latter tests are not vulnerable to practice effects. The internal consistency of the parallel test forms has been previously demonstrated [24–27]. Story Memory (subtest of the Rivermead Behavioral Memory Test [25]) and Word List Memory (Hopkins Verbal Learning Test-Revised [24]) were used to test recent verbal memory. *Story Memory* measures the ability to learn and recall a narrative story immediately and after a brief delay (maximum score, 21). *Word List Memory* assesses the ability to learn and remember a list of 12 unrelated words across three sequential learning trials, delayed free recall, and a recognition task (maximum score, 36). In the delayed free recall phase, the 12 words are recalled 20–25 min after initial presentation (maximum score, 12). The Brief Visual Memory Test Revised [27] was used to test recent nonverbal memory. This test provides a measure of nonverbal recent memory over three sequential acquisition trials (maximum score, 12 points/trial). The obtained scores are Figure Construction, Immediate Recall and Delayed Figure Reproduction. Backward Digit Span [28], Semantic Fluency [29], Phonemic Fluency [30], and the Color-Word Stroop Test, third part [31] were used to test executive functions. Semantic and Phonemic Fluency are subtests of the Delis–Kaplan Executive Function System [26] that examine executive functions related to language. *Semantic Fluency* measures speed of word generation using semantic cues such as identifying all the “fruits and vegetables” (form A), “animals in the zoo” (form B), or “items of clothing” (form C) that the patient is able to produce in 1 min (score: the number of appropriate words generated within the time interval). *Phonemic Fluency* measures speed of word generation using phonetic cues such as identifying all the words that start with the letter “S” (form A), “P” (form B), or “B” (form C) that the patient is able to produce in 1 min (score: the number of appropriate words identified within the specified time interval.) *Digit Span* is a subtest of the Wechsler Adult Intelligence Scale-Third Edition [28] that measures attention span, concentration, and working memory (score: number of correct digits repeated forward and backward). *The Color-Word Stroop Test, third part* [31] assesses executive functions of inhibition, selective attention, mental speed, and interference susceptibility. This test presents a list of color words printed in an incongruous color and requires that the examinee name the correct color while ignoring the word (score: number of colors correctly identified in 1 min). The *Geriatric Depression Scale 15-item version* assesses the presence of depression in older adults. The obtained score is the number of items endorsed (maximum score, 15).

Serum IL-6 and CRP concentrations were measured before induction and at their expected peak concentration times (IL-6 at 4 h after CPB and CRP at 24 (first postoperative day) and 72 h (third postoperative day) after anesthetic induction) [32–34]. IL-6 concentrations were assayed by enzyme-linked immunoassay (Wood Dale, IL, USA; normal values: 0.31–5 pg/ml). High-sensitivity CRP concentrations were assayed by immunonephelometry (normal values: 0–3 mg/l).

Midazolam, fentanyl, and etomidate were used for anesthetic induction and isoflurane and fentanyl were used for maintenance as previously described [35]. All coronary artery surgery patients underwent a standard median sternotomy. Myocardial protection during CPB consisted of antegrade and retrograde cold blood cardioplegia administered at regular intervals (15 min), topical hypothermia (slushed 0.9% saline), and systemic hypothermia (30–32°C). A dose of continuous warm blood cardioplegia was administered during rewarming before removal of the aortic cross-clamp. CPB flows were maintained between 2.4 and 2.5 l/min/m^2. Mean arterial pressure was maintained between 55 and 70 mmHg during bypass. Heparin (400 U/kg) was used for systemic heparinization to maintain activated clotting time (ACT) >500 s.

Sample size calculation

Assuming 90% power and a two-sided alpha of 0.05, power analysis yielded $N = 35$ as the minimum estimated number of surgical subjects per group to detect a composite Z score difference 1 week after cardiac surgery (-1.65 ± 0.71 and -0.92 ± 1.11, respectively) between high and low CRP concentration groups. Patients were divided to high and low CRP concentration groups by splitting them at the median of the increase between baseline and the first postoperative day values. An attrition rate of 20% was estimated to account for those whose second neurocognitive testing could not be performed due to possible dropout; therefore, we recruited 1.2 times 35 surgical subjects per group, yielding a total of 84 surgical subjects.

Statistical analysis

Group comparisons were made using unpaired t tests for continuous variables, and chi-square or Fisher's exact test for dichotomous variables. Patients were divided to high and low CRP and IL-6 concentration groups by splitting them at the median CRP and IL-6 values (median increase between baseline and the first and third postoperative days, and median increase between baseline and 4 h after CPB, respectively). Differences between pre- and postoperative concentrations of IL-6 and CRP were analyzed using the Wilcoxon rank-sum test. Z scores were used to assess cognitive change from baseline to 1 week or discharge and to 3 months after surgery [6]. The Z score for the change in performance in each neuropsychological test was calculated by using the following formula: Z score = [(Change score) − (Mean change score$_{\text{control}}$)]/(SD change score$_{\text{control}}$). A suitable normative population was used to correct for practice effects and variability between sessions (nonsurgical patients) [22]. Average Z score for each test was calculated. Cognitive dysfunction was defined as a deterioration of $\geq$1 standard deviation (SD) from baseline, in at least two of a ten-test cognitive battery [36]. Overall cognitive function between high and low biomarker concentration groups was analyzed by the Wilcoxon rank-sum test. The null hypothesis was rejected at $P < 0.05$. All errors were reported as standard error of the mean. Statistical calculations were performed using NCSS 2001 (NCSS, Kaysville, UT, USA) and STATA/IC 10.0 (StataCorp LP, College Station, TX, USA) software.

Results

Baseline medical and demographic data including age and education were similar between groups (Table 1). Baseline cognitive scores were also similar between groups (Table 2).

Performance on two cognitive tests showed at least a 2 SD decrease from baseline (immediate word list recall and delayed word list recall), and performance on five additional tests demonstrated a 1 SD decrease (figure reconstruction, immediate story recall, delayed story recall, digit span, and Stroop) at 1 week after surgery. After 3 months, performance on six tests (figure reconstruction, immediate story recall, delayed story recall, immediate word list recall, delayed word list recall, and digit span) continued to show at least a 1 SD decrease from baseline. These data suggest slightly improved but still impaired cognitive functions at 3 months compared with 1 week after surgery (see Table 2).

Baseline, 24-h, and 72-h CRP concentrations were 5 ± 9, 69 ± 30, and 165 ± 66 (mg/l), respectively ($P < 0.0001$ vs. baseline). Baseline and 4 h after CPB, IL-6 concentrations were 4 ± 20 and 61 ± 35 (pg/ml), respectively ($P < 0.0001$). Patients were divided to high and low CRP and IL-6 concentration groups by splitting them at the median CRP and IL-6 values (median increase between baseline and the first and third postoperative days, and median increase between baseline and 4 h after CPB, respectively). Recent nonverbal and verbal memory performance was at least 1 SD different between the high and low CRP and IL-6 concentration groups at both 1 week and 3 months (Figs. 1, 2, 3, 4, 5, 6). Overall cognitive function (all tests in battery) was significantly ($P = 0.04$ and $P = 0.01$, respectively) different between the high and low CRP concentration groups (when CRP assayed at baseline and on the first postoperative day) at both 1 week and 3 months (Wilcoxon rank-sum test) (see Figs. 1, 3). Overall cognitive function (all tests in battery) was also significantly ($P = 0.04$) different between the high and low IL-6 concentration groups at 1 week after surgery (Wilcoxon rank-sum test) (see Fig. 5).

Table 1 Demographics and medical data in two patient groups

	(+) CABG $N = 86$	(−) CABG $N = 28$	P
Age (years)	68 ± 0.9	69 ± 1.5	0.40
Education (years)	13 ± 0.2	13 ± 0.4	0.54
Caucasian (%)	78 (91)	23 (82)	0.21
Married (%)	54 (63)	17 (61)	0.84
History of smoking (%)	26 (30)	23 (82)	0.19
Current smoker (%)	20 (23)	2 (7)	0.10
Right-handedness (%)	76 (88)	26 (93)	0.73
Hypertension (%)	78 (91)	22 (79)	0.09
Hypercholesterolemia (%)	78 (91)	26 (93)	1.00
Angina (%)	34 (40)	6 (21)	0.08
Arrhythmia (%)	17 (20)	5 (18)	0.82
Myocardial infarction (%)	14 (16)	9 (32)	0.07
Peripheral vascular disease (%)	9 (10)	2 (7)	1.00
Diabetes (%)	49 (57)	15 (54)	0.75
Congestive heart failure (%)	12 (14)	2 (7)	0.51
Anxiety disorder (%)	6 (7)	1 (4)	1.00
Stroke (%)	5 (6)	1 (4)	1.00
Sleep disorder (%)	31 (36)	15 (54)	0.10
Depression (%)	21 (24)	8 (29)	0.66
Geriatric depression score (GDS-15)	3 ± 0.2	4 ± 0.8	0.16
Antihypertensive drug (%)	83 (97)	25 (89)	0.16
Diuretic drug (%)	33 (38)	6 (21)	1.00
Lipid-lowering drug (%)	72 (84)	25 (89)	0.56
Hachinski score ≥4, baseline (%)	0 (0)	0 (0)	

Data are expressed as number (%) or mean ± SEM. P values are from t test for continuous variables and chi-square or Fisher's exact test for dichotomous variables

CABG, coronary artery bypass graft

Discussion

The current results demonstrate that elevated postoperative IL-6 and CRP concentrations are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. The current findings support the hypothesis that an inflammatory response plays a role in the development of neurological injury after CPB [37] through the elevation of proinflammatory cytokines [38] to produce POCD [38, 39]. The current investigation was conducted in older patients (55–84 years) undergoing cardiac surgery who are known to be at a greater risk for POCD. (1) In human and animal models of the systemic inflammatory response syndrome, four cytokines (tumor necrosis factor-α, IL-1, IL-6, and IL-8) are sequentially released, resulting in an "inflammatory cascade." Serum IL-6 concentration appears to be a particularly sensitive indicator of inflammatory cascade activation and a predictor of subsequent organ dysfunction and death [40–42]. We also evaluated CRP as a measure of systemic inflammation. This protein is synthesized in the liver in response to IL-6 stimulation, may be an integrated marker of total body inflammation, and has been correlated with cognitive decline in elderly patients [20, 43]. Indeed, the related increases in IL-6 and CRP were observed after coronary artery surgery using CPB in the current investigation, confirming well-known observations that cardiac surgery is associated with a robust inflammatory response [12–14].

Table 2 Baseline cognitive raw scores and Z scores at 1 week and 3 months after surgery

	(+) CABG $N = 86$	Z 1 wk	Z 3 mo	(−) CABG $N = 28$	P
Figure reconstruction	20 ± 0.09	−1.9	−1.3	20 ± 0.26	0.93
Delayed figure reproduction	8 ± 0.03	−0.6	−0.2	7 ± 0.09	0.73
Immediate story recall	18 ± 0.05	−1.1	−1.4	17 ± 0.15	0.82
Delayed story recall	9 ± 0.03	−1.5	−1.3	8 ± 0.09	0.31
Immediate word list recall	26 ± 0.08	−2.1	−1.5	23 ± 0.25	0.09
Delayed word list recall	6 ± 0.03	−2.4	−1.7	5 ± 0.09	0.10
Digit span	8 ± 0.02	−1.2	−1.4	8 ± 0.08	0.32
Semantic fluency	16 ± 0.04	−0.5	−0.2	16 ± 0.15	0.80
Phonemic fluency	12 ± 0.05	−0.6	−0.2	13 ± 0.17	0.21
Stroop	38 ± 1.14	−1.3	−0.8	38 ± 0.43	0.99

Data are expressed as mean ± SEM. Z 1 wk, Z scores at 1 week; Z 3 mo, Z scores at 3 months. P values between surgical and nonsurgical groups at baseline are from t tests

Fig. 1 Comparison of cognitive *Z* scores (±SEM) at 1 week between high and low C-reactive protein (CRP) groups on postoperative day (POD) 1. *Asterisk*, ≥1 SD between groups; $P = 0.04$, Wilcoxon rank-sum test

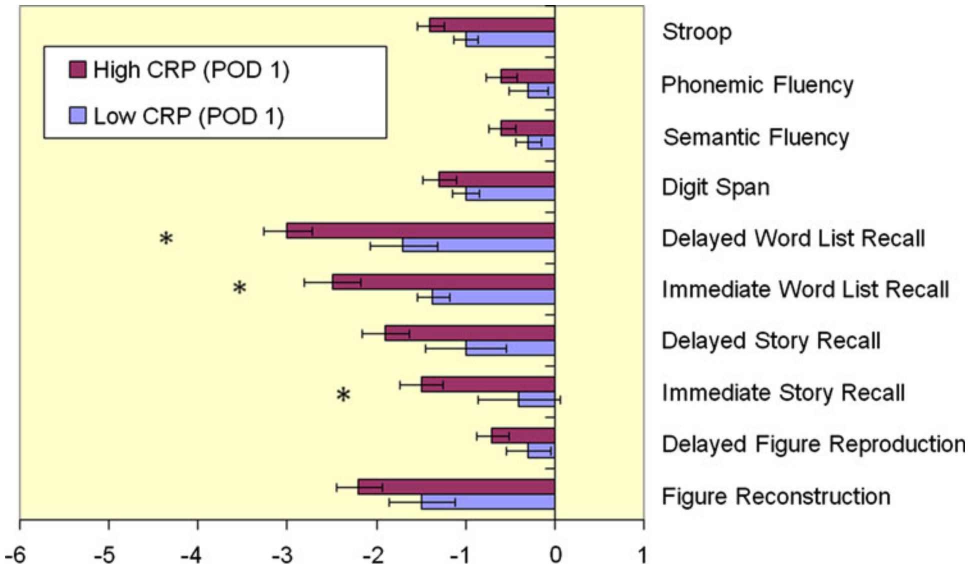
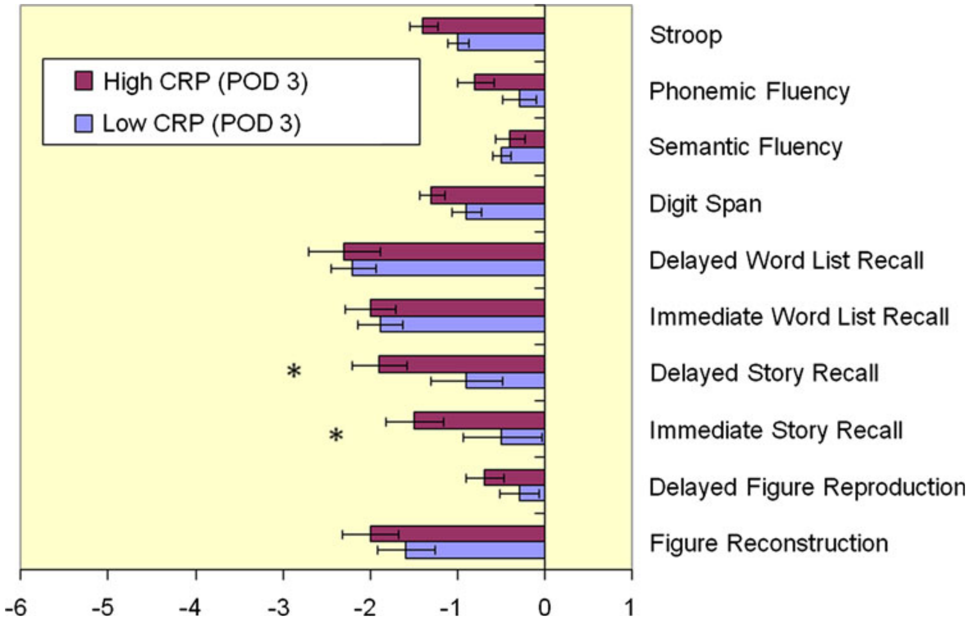


Fig. 2 Comparison of cognitive *Z* scores (±SEM) at 1 week between high- and low-CRP groups on POD 3. *Asterisk*, ≥1 SD between groups; $P > 0.05$, Wilcoxon rank-sum test



The cognitive tests used in this investigation were designed to measure performance in recent verbal and nonverbal memory and executive functions. Previous studies suggested that cognitive impairments may develop in these domains after surgery [44, 45]. Dysfunction in recent memory may be caused by impairments in hippocampi, entorhinal cortices, thalami, and basal forebrain [46]. Executive functions depend on prefrontal cortices including dorsolateral white matter tracts [47]. Difficulty in completing executive function tasks suggests an impairment in the frontal lobe functions of POCD patients [47], and such deficits predict difficulty with postoperative rehabilitation [48]. Differences in the degree of impairments on various cognitive tests as observed in different individuals may reflect site-specific variability in cognitive reserve. Because associations between inflammatory biomarkers and cognitive decline in specific cognitive domains were observed, it appears likely the systemic inflammatory response differentially but concurrently impairs the function of several individual brain structures. It appears that recent nonverbal and verbal memory was most affected at 1 week and 3 months after surgery, implying that the hippocampi are the most sensitive areas for postoperative cognitive impairment.

Longitudinal population-based studies have shown an association between the inflammatory markers IL-6 and CRP and cognitive decline in older adults [19, 20, 49]. For

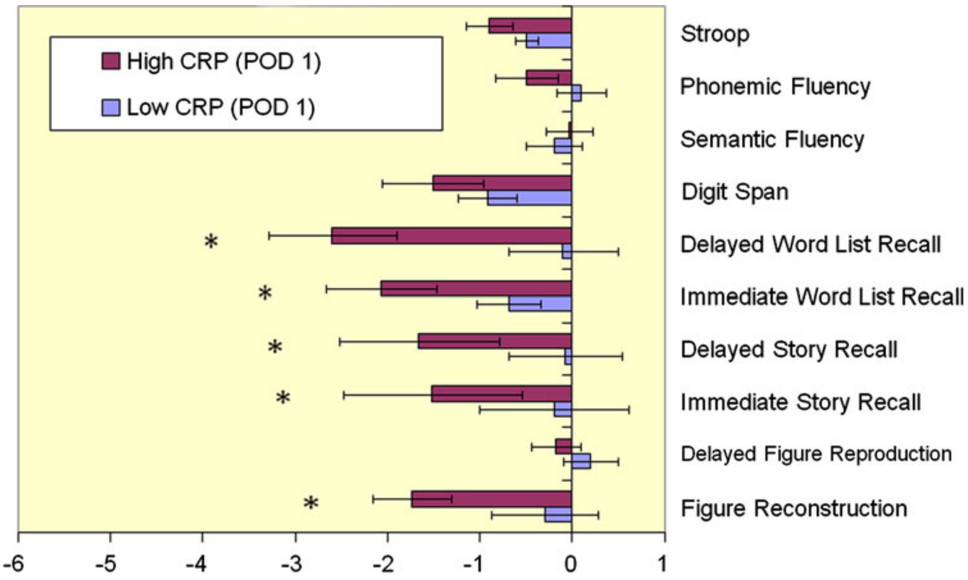


Fig. 3 Comparison of cognitive *Z* scores (±SEM) at 3 months between high- and low-CRP groups on POD 1. *Asterisk*, ≥1 SD between groups; $P = 0.01$, Wilcoxon rank-sum test

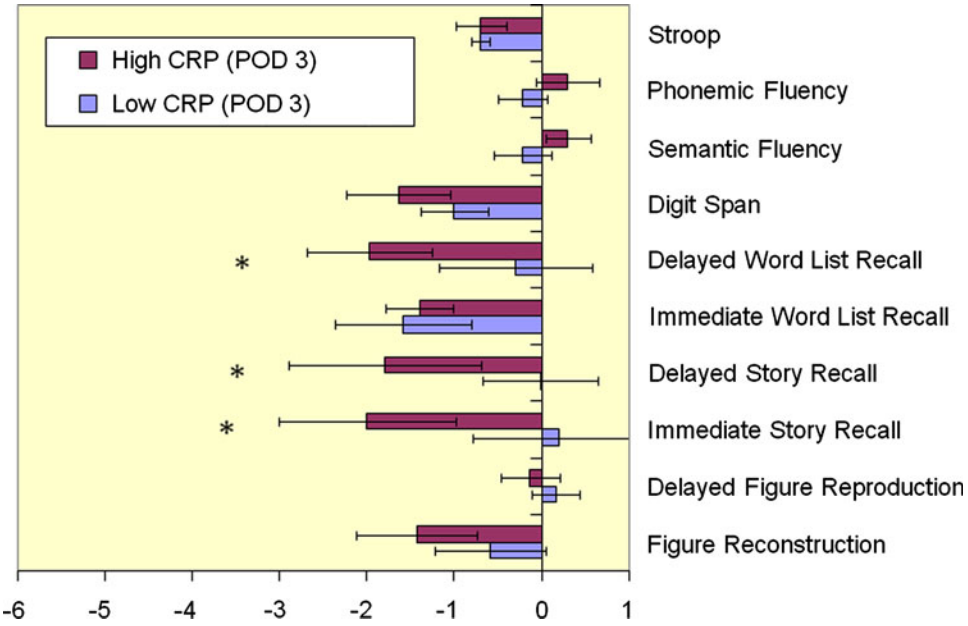


Fig. 4 Comparison of cognitive *Z* scores (±SEM) at 3 months between high-CRP and low-CRP groups on POD 3. *Asterisk*, ≥1 SD between groups; $P > 0.05$, Wilcoxon rank-sum test

example, increased CRP levels may precede the diagnosis of dementia by as much as 25 years, suggesting that a chronic inflammatory process may be present before clinical symptoms appear [21]. Most of the patients undergoing coronary artery surgery were taking lipid-lowering drugs (e.g., statins) that are known to produce antiinflammatory effects including a reduction in CRP concentration [50]. However, considering that total cholesterol exceeds 200 mg/dl in nearly half of all adults, it is likely that many patients enrolled in previous studies were also prescribed statins for the treatment of hypercholesterolemia [51]. Notably, there was no difference in statin use between patients undergoing coronary artery surgery and nonsurgical controls, and as a result, the current results cannot be attributed to a selective antiinflammatory effect of these lipid-lowering drugs.

The current results should be interpreted within the constraints of several potential limitations. We measured CRP and IL-6 concentrations but did not examine other inflammatory biomarkers. Nevertheless, marked increases in CRP and IL-6 were observed consistent with a well-known systemic inflammatory response to cardiac surgery. Thus, we believe that inclusion of measurement of other biomarkers would most likely provide only confirmatory data and would not provide unique information.

Cognitive performance was reassessed 3 months after cardiac surgery, which may be considered as “medium-term” follow-up. Whether similar results would be obtained

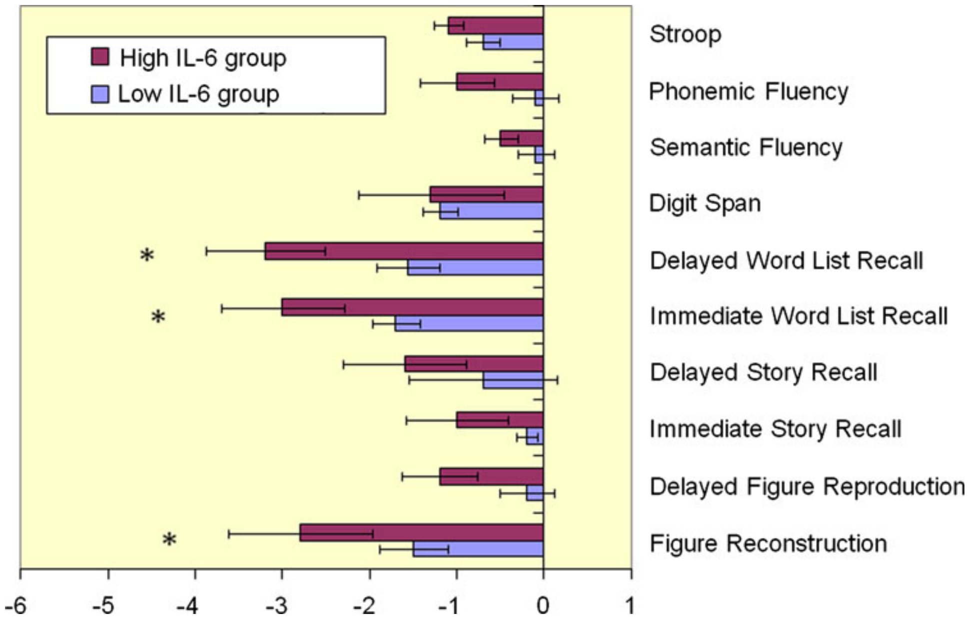


Fig. 5 Comparison of cognitive *Z* scores (±SEM) at 1 week between high- and low-interleukin-6 (IL-6) groups 4 h after cardiopulmonary bypass (CPB). *Asterisk*, ≥1 SD between groups; $P = 0.04$, Wilcoxon rank-sum test

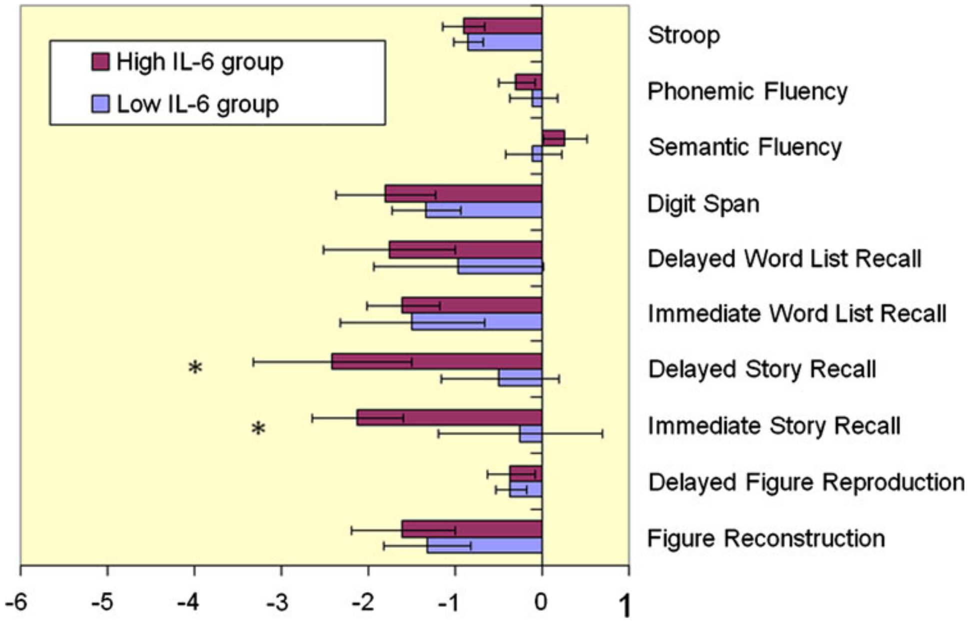


Fig. 6 Comparison of cognitive *Z* scores (±SEM) at 3 months between high- and low-IL-6 groups 4 h after CPB. *Asterisk*, ≥1 SD between groups; $P > 0.05$, Wilcoxon rank-sum test

if patients were evaluated after a more prolonged period of time after surgery is unknown. The current investigation included only male veterans, and whether similar results occur in women undergoing heart surgery is unknown.

In summary, the results suggest that elevated postoperative IL-6 and CRP concentrations are associated with the subsequent development of short- and medium-term impairment of cognitive functions after coronary artery surgery, and that the most affected cognitive modality is recent memory.

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Conflict of interest The authors have no conflicts of interest pursuant to this work.

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