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Elevated Biochemical Markers of Myocardial Injury are not Associated with Postoperative Cognitive Dysfunction after Coronary Artery Surgery

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Abstract

Background: The systemic inflammatory response to cardiopulmonary bypass (CPB) and organ hypoperfusion during CPB contribute to cerebral and myocardial dysfunction in patients undergoing cardiac surgery. We hypothesized that biochemical markers of myocardial injury [creatine kinase - myocardial band (CK-MB), troponin-I] may be independently associated with postoperative cognitive dysfunction (POCD; an indicator of cerebral dysfunction) in patients undergoing coronary artery bypass graft (CABG) surgery using CPB.

Methods: Eighty-eight age- and education-balanced patients ≥55 years of age undergoing elective CABG with CPB and 28 nonsurgical controls with coronary artery disease were enrolled. Recent verbal and nonverbal memory and executive functions were assessed before surgery, 1 week, and 3 months after surgery using a standard psychometric test battery. Plasma CK-MB and troponin-I concentrations were determined before and at the end of surgery. Plasma troponin-I concentrations were also measured 24 hours after surgery.

Results: Performance on two cognitive tests decreased at least two standard deviations (SD) from baseline and performance on five additional tests decreased 1 SD 1 week after surgery. After 3 months, performance on six tests was at least a 1 SD below baseline. CK-MB and troponin-I concentrations were significantly ($p<0.00001$) elevated after surgery. There was no correlation between overall cognitive function (measured by average z-score) and postoperative CK-MB or troponin-I concentrations 1 week or 3 months after surgery.

Conclusion: The results suggest that elevated postoperative CK-MB or troponin-I concentration alone is not associated with the subsequent development of short- and medium-term impairment of cognitive functions after CABG.

Keywords: Troponin-I; CK-MB; Coronary artery bypass graft; Cardiopulmonary bypass; Postoperative cognitive dysfunction

Abbreviations: CPB: Cardiopulmonary Bypass; CK-MB: Creatine Kinase – Myocardial Band; POCD: Postoperative Cognitive Dysfunction; CABG: Coronary Artery Bypass Graft

Introduction

Postoperative cognitive dysfunction (POCD) is a major cause of morbidity after cardiac surgery [1-4]. Memory deficits, reduced concentration, impaired language comprehension, and abnormal social integration are characteristic features of POCD [5,6]. Patients with this disorder may experience prolonged intensive care unit and hospital stays, impaired self care, inability to participate in rehabilitation, and more frequent hospital readmission [7-9]. The presence and severity of other co-morbid conditions, preexisting cognitive impairment, and advanced age have been identified as major risk factors for POCD [6,10]. The systemic inflammatory response to cardiopulmonary bypass (CPB) also plays an important role in the subsequent development of POCD. Indeed, we recently demonstrated that an increase in inflammatory markers, including C-reactive protein and interleukin-6, predicted cognitive decline in patients undergoing cardiac surgery using CPB [11]. Such inflammatory effects may adversely affect learning, memory, and other cognitive domains by altering hippocampal function [12]. Cerebral hypoperfusion during CPB has also been strongly implicated as a crucial factor for the development of postoperative neurological deficits, including those affecting cognition [13,14].

The mechanisms by which the myocardium sustains damage during cardiac surgery are multifactorial, but it is well known that the use of CPB is inherently associated with myocardial injury [15-17]. Clearly, the effects of the systemic inflammatory response to CPB and reduced coronary perfusion during CPB play important roles in the myocardial damage that occurs in this setting. The similarities in the possible causes of cerebral and myocardial dysfunction resulting from CPB lead us to speculate that elevations in the plasma concentrations of biochemical markers of myocardial necrosis [e.g., creatine kinase-myocardial band (CK-MB), troponin-I] that are commonly observed immediately after cardiac surgery may also be independently predictive of the subsequent development of POCD. Thus, we tested the hypothesis that biochemical markers of myocardial injury are correlated with short- and medium-term POCD in older male veterans undergoing coronary artery surgery.

Materials and Methods

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

Participants

One hundred and sixteen patients (88 surgical and 28 nonsurgical)

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were recruited. Inclusion criteria included ≥55 years of age, providing written informed consent, and scheduled elective coronary artery 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 [18]. Exclusion criteria included a history of a cerebrovascular accident in the last 3 years, permanent ventricular pacing, previously documented cognitive deficits, or vascular dementia (Hachinski score(19) >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

Baseline cognitive functions were assessed with a neuropsychometric battery, including recent verbal and nonverbal memory and executive functions, within 1 week before surgery. Cognitive functions were reassessed 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 [20-23]. Story Memory (subtest of the Rivermead Behavioral Memory Test [21]) and Word List Memory (Hopkins Verbal Learning Test-Revised [20]) 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 3 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 minutes after initial presentation (maximum score: 12). The Brief Visual Memory Test Revised [23] was used to test recent nonverbal memory. This test provides a measure of nonverbal recent memory over 3 sequential acquisition trials (maximum score: 12 points/trial). The obtained scores are Figure Construction Immediate Recall and Delayed Figure Reproduction. Backward Digit Span, [24] Semantic Fluency, [25] Phonemic Fluency [26], and the Color-Word Stroop Test, 3rd part [27] were used to test executive functions. Semantic and Phonemic Fluency are subtests of the Delis-Kaplan Executive Function System [22] 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(24) that measures attention span, concentration, and working memory. (Score: number of correct digits repeated forward and backward.) The Color-Word Stroop Test, 3rd part [27] 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).

Measurement of biochemical markers of myocardial necrosis

Plasma CK-MB concentrations (normal < 3.6 ng/ml) and plasma troponin-I concentrations (normal < 0.1 ng/ml) were determined before and at the end of surgery using immunoassays. Plasma troponin-I concentrations were also measured 24 hours after surgery. The immunoassay methods are based on homogenous sandwich chemiluminescent LOCI® (Siemens, Newark, DE) technology. Two synthetic bead reagents and a biotinylated anti-CK-MB isoenzyme or anti-cardiac troponin-I monoclonal antibody fragment compromise the LOCI® reagents. The bead reagents are coated with streptavidin with a photosensitive dye or a CK-MB or anti-cardiac troponin-I monoclonal antibody with a chemiluminescent dye. The blood sample is first incubated with the streptavidin-photosensitive dye bead and biotinylated antibody to create a CK-MB biotinylated antibody or a cardiac troponin-I-biotinylated antibody sandwich. The second bead reagent is then added, which binds to the biotin to create a bead-pair immunocomplex. Photoillumination at 680 nm generates singlet oxygen from the first bead reagent, thereby stimulating chemiluminescence of the dye contained on the second bead. The magnitude of the chemiluminescence (measured at 612 nm) indicates the CK-MB or cardiac troponin-I concentration.

Anesthetic technique and conduct of cardiopulmonary bypass

Midazolam, fentanyl, and etomidate were used for anesthetic induction and isoflurane and fentanyl were used for maintenance as previously described [28]. 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 to 32 degrees centigrade). 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 sec.

Sample size calculation

We previously demonstrated that elevated postoperative concentrations of C-reactive protein and interleukin-6 were significantly associated with the subsequent development of short- and medium-term impairment of cognitive functions after coronary artery surgery with a sample size of 84 surgical subjects [11]. Therefore, we planned to include a minimum of 84 surgical subjects in the current investigation.

Statistical analysis

Group comparisons were made using unpaired t tests for continuous variables, and chi-square or Fisher's exact test for dichotomous variables. 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 Scorecontrol)] / (SD Change Score$_{control}$). A suitable normative population was used to correct for practice effects and variability between sessions (nonsurgical patients) [18]. An average z-score for each test was calculated. Cognitive dysfunction was defined as a deterioration of ≥1 standard deviation from baseline, in at least 2 of a 10-test cognitive battery [29]. The association between overall cognitive function (average Z-score of the individual patients) and

cardiac biomarker concentrations were assessed by linear regression analysis. The null hypothesis was rejected when $p<0.05$. All errors were reported as standard deviations. Statistical calculations were performed using NCSS 2001 (NCSS, Kaysville, UT) software.

Results

Baseline medical and demographic data including age and education were similar between surgical and nonsurgical groups (Table 1). Baseline cognitive scores were also similar between surgical and nonsurgical groups (Table 2). 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 in patients undergoing coronary artery 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 improved, but still impaired, cognitive functions

	(+) CABG N=88	(-) CABG N=28	p
Age, yr	68±8	69±8	0.41
Education, yr	12±2	13±2	0.49
Caucasian (%)	80(91)	23(8)	0.30
Married (%)	55(63)	17(61)	0.87
Current smoker (%)	20(23)	2(7)	0.07
Hypertension (%)	80(91)	22(79)	0.08
Hypercholesterolemia (%)	79(90)	26(93)	1.00
Angina (%)	35(40)	6(21)	0.08
Arrhythmia (%)	8(9)	5(18)	0.21
Myocardial infarction (%)	14(16)	9(32)	0.06
Peripheral vascular disease (%)	10(11)	2(7)	0.73
Diabetes (%)	49(56)	15(54)	0.84
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 (%)	33(38)	15(54)	0.13
Depression (%)	17(19)	8(29)	0.30
Geriatric depression score (GDS-15)	3±3	4±4	0.17
Antihypertensive drug (%)	68(77)	25(89)	0.28
Diuretic drug (%)	33(38)	6(21)	0.12
Lipid lowering drug (%)	74(84)	25(89)	0.76
Hachinski score >=4, baseline (%)	0(0)	0(0)	

The *p* values are from *t*-test for continuous variables and Chi-square or Fisher's exact test for dichotomous variables, Data are expressed as number (%) or mean±SD, CABG: coronary artery bypass graft

Table 1: Demographics and medical data in two patient groups.

	(+) CABG			(-) CABG	
	N=88	z 1 wk	z 3 mo	N=28	p
Figure Reconstruction	20±7	-1.9	-1.4	20±7	0.96
Delayed Figure Reproduction	7±3	-0.5	-0.2	7±3	0.71
Immediate Story Recall	18±5	-1.2	-1.5	17±4	0.77
Delayed Story Recall	9±3	-1.5	-1.6	8±3	0.27
Immediate Word List Recall	26±7	-2.1	-1.6	23±5	0.09
Delayed Word List Recall	6±3	-2.5	-1.7	5±2	0.09
Digit Span	8±2	-1.2	-1.5	8±2	0.3
Semantic Fluency	16±4	-0.5	-0.2	16±4	0.69
Phonemic Fluency	12±5	-0.6	-0.2	13±5	0.2
Stroop	38±12	-1.3	-0.8	38±12	0.99

Data are expressed as mean±SD, 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

Table 2: Baseline cognitive raw scores and z-scores at 1 week and 3 months after surgery.

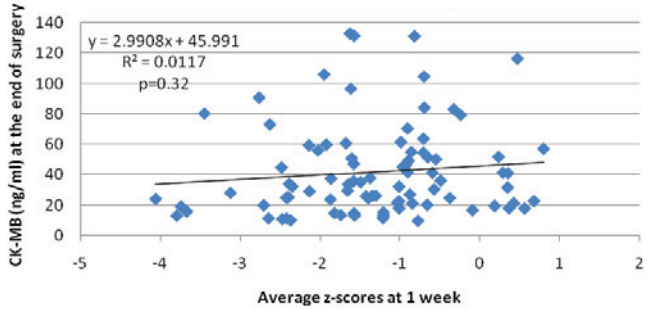

Figure 1: Association between average z-scores at 1 week and CK-MB at the end of surgery.

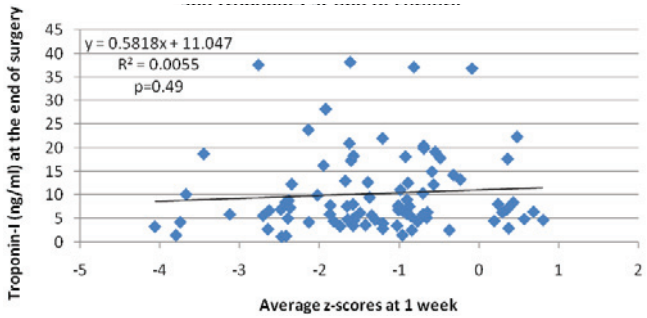

Figure 2: Association between average z-scores at 1 week and troponin-I at the end of surgery.

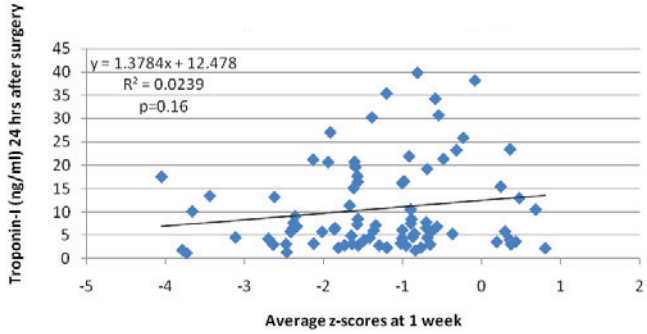

Figure 3: Association between average z-scores at 1 week and troponin-I 24 hours after surgery.

at 3 months compared with 1 week after surgery (Table 2). Significant increases in CK-MB [1.5±2.0 before to 44.2±39.0 (ng/ml) after surgery; $p<0.0001$] and troponin-I [0.1±0.6 before to 10.9±12.2 and 11.2±11.0 (ng/ml) at the end of and 24 h after surgery, respectively; $p<0.0001$] were observed. There was no correlation between overall cognitive function (patients' average z-score) and postoperative CK-MB or troponin-I concentrations 1 week (Figures 1-3) or 3 months after surgery. Similarly, no significant ($p>0.05$) correlations were observed between verbal, nonverbal memory or executive function tests and postoperative CK-MB or troponin-I concentrations 1 week or 3 months after surgery.

Discussion

The results of the current investigation indicate that elevated postoperative CK-MB and troponin-I concentrations are not associated

with short- and medium-term cognitive dysfunction in male veterans after coronary artery surgery using CPB. These findings are not entirely unanticipated because the causes of cardiac injury during CPB may be more complex than those responsible for neurological dysfunction that results in POCD, although these phenomena share some similarities. Cerebral hypoperfusion and exposure to the systemic inflammatory response to CPB have been linked to compromise of the blood-brain barrier and the subsequent development of cerebral edema [16]. These factors are certainly involved in the development of POCD associated with cardiac surgery, and it is reasonable to postulate that analogous mechanisms of injury may play contributing roles to postoperative myocardial damage as well. However, the heart, but not the brain, is exposed to a severe no-flow ischemic insult when the aortic cross-clamp is placed during CPB, the metabolic consequences of which cannot be completely obviated by the use of optimal myocardial protection strategies such as intermittent administration of substrate-enriched blood antegrate and retrograde cardioplegia, systemic and topical hypothermia, and administration of continuous warm cardioplegia before cross-clamp removal. The myocardial ischemia inherent in this process undoubtedly produces more substantial tissue damage than the factors responsible for cerebral injury that cause POCD. In addition, surgical incisions in the right atrium are required for placement of venous drainage and coronary sinus cannulae, and epicardial dissection is necessary for construction of distal coronary artery anastomoses during the procedure itself. This surgical trauma to the heart also contributes to the elevations in biochemical markers of myocardial injury that are typically observed after coronary artery surgery.

The current investigation was conducted in older men (55-84 years) undergoing cardiac surgery who are known to be at a greater risk for POCD [1]. The cognitive tests used 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 [30,31]. Dysfunction in recent memory may be due to impairments in hippocampi, entorhinal cortices, thalami, and basal forebrain [32]. Executive functions depend on prefrontal cortices including dorsolateral white matter tracts [33]. Difficulty in completing executive function tasks suggests an impairment in the frontal lobe functions of POCD patients, [33] and such deficits predict difficulty with postoperative rehabilitation [34]. Differences in the degree of impairments on various cognitive tests as observed in different individuals may reflect site-specific variability in cognitive reserve. In the current investigation, it appears that recent nonverbal and verbal memory was most affected at 1 week and 3 months after surgery, implying that the hippocampi may be the most sensitive areas for postoperative cognitive impairment. Nevertheless, we did not specifically examine functional activity in the hippocampi (using functional magnetic resonance imaging, for example) to verify this hypothesis. In addition, the degree of cognitive dysfunction observed may have been substantially less severe than the magnitude of cardiac injury.

The current results should be interpreted within the constraints of several potential limitations. We measured CK-MB and troponin-I concentrations, but did not examine other biomarkers of cardiac injury. However, marked increases in CK-MB and troponin-I were observed in response to cardiac surgery and, as a result, we feel that measurement of other indices of myocardial damage would most likely provide only confirmatory data and would not provide truly 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 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 CK-MB and troponin-I concentrations may not be used as surrogate indices of cerebral injury that predict the subsequent development of short- and medium-term impairment of cognitive functions after coronary artery surgery using CPB.

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References

1. Newman MF, Kirchner JL, Phillips-Bute B, Gaver V, Grocott H, et al.(2001) Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. N Engl J Med 344: 395-402.
2. Selnes OA, Goldsborough MA, Borowicz LM, McKhann GM (1999) Neurobehavioural sequelae of cardiopulmonary bypass. Lancet 353: 1601-1606.
3. Bedford PD (1955) Adverse cerebral effects of anaesthesia on old people. Lancet 269: 259-263.
4. Phillips-Bute B, Mathew JP, Blumenthal JA, Grocott HP, Laskowitz DT, et al.(2006) Association of neurocognitive function and quality of life 1 year after coronary artery bypass graft (CABG) surgery. Psychosom Med 68: 369-375.
5. Rasmussen LS, Christiansen M, Hansen PB, Moller JT (1999) Do blood levels of neuron-specific enolase and S-100 protein reflect cognitive dysfunction after coronary artery bypass? Acta Anaesthesiol Scand 43:495-500.
6. Moller JT, Cluitmans P, Rasmussen LS, Houx P, Rasmussen H, et al. (1998) Long-term postoperative cognitive dysfunction in the elderly ISPOCD1 study. ISPOCD investigators. International Study of Post-Operative Cognitive Dysfunction. Lancet 351: 857-861.
7. Wilmore DW, Kehlet H (2001) Management of patients in fast track surgery. BMJ 322: 473-476.
8. Marshall SI, Chung F (1999) Discharge criteria and complications after ambulatory surgery. Anesth Analg 88: 508-517.
9. Roach GW, Kanchuger M, Mangano CM, Newman M, Nussmeier N, et al. (1996) Adverse cerebral outcomes after coronary bypass surgery. Multicenter Study of Perioperative Ischemia Research Group and the Ischemia Research and Education Foundation Investigators. N Engl J Med 335: 1857-1863.
10. Ancelin ML, de Roquefeuil G, Ledesert B, Bonnel F, Cheminal JC, et al. (2001) Exposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. Br J Psychiatry 178: 360-366.
11. Hudetz JA, Gandhi SD, Iqbal Z, Patterson KM, Pagel PS (2010) Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. J Anesth 25: 1-9.
12. Dantzer R, Kelley KW (2007) Twenty years of research on cytokine-induced sickness behavior. Brain Behav Immun 21: 153-160.
13. Millar SM, Alston RP, Andrews PJ, Souter MJ (2001) Cerebral hypoperfusion in immediate postoperative period following coronary artery bypass grafting, heart valve, and abdominal aortic surgery. Br J Anaesth 87: 229-236.
14. Fearn SJ, Pole R, Wesnes K, Faragher EB, Hooper TL, McCollum CN (2001) Cerebral injury during cardiopulmonary bypass: emboli impair memory. J

Thorac Cardiovasc Surg 121: 1150-1160.

15. Schneider M, Valentine S, Hegde RM, Peacock J, March S, Dobb GJ (1999) The effect of different bypass flow rates and low-dose dopamine on gut mucosal perfusion and outcome in cardiac surgical patients. Anaesth Intensive Care 27: 13-19.
16. Taylor KM (1998) Central nervous system effects of cardiopulmonary bypass. Ann Thorac Surg 66(5 Suppl): S20-4; discussion S5-8.
17. Stump DA, Rogers AT, Hammon JW, Newman SP (1996) Cerebral emboli and cognitive outcome after cardiac surgery. J Cardiothorac Vasc Anesth 10:113-118; quiz 118-119.
18. Rasmussen LS, Larsen K, Houx P, Skovgaard LT, Hanning CD, et al. (2001) The assessment of postoperative cognitive function. Acta Anaesthesiol Scand 45: 275-289.
19. Hachinski V, Munoz D (2000) Vascular factors in cognitive impairment--where are we now? Ann N Y Acad of Sci 903: 1-5.
20. Benedict HB, Schretlen D, Groninger L, Brandt J (1998) Hopkins Verbal Learning Test - Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. The Clinical Neuropsychologist 12: 43-55.
21. Wilson B, Cockburn J, Baddeley A, Hiorns R (1989) The development and validation of a test battery for detecting and monitoring everyday memory problems. J Clin Exp Neuropsychol 11: 855-870.
22. Delis DC, Kaplan E, Kramer JH (2001) Delis-Kaplan Executive Function System (D-KEFS). San Antonio, TX: The Psychological Corporation.
23. Benedict RH, Schretlen D, Groninger L, Dobraski M, Shpritz B (1996) Revision of the Brief Visuospatial Memory Test: Studies of normal performance, reliability, and validity. Psychol Assess 8: 145-153.
24. Wechsler DA (1997) Wechsler Adult Intelligence Scale-Third Edition. San Antonio, TX: The Psychological Corporation.
25. Randolph C (1998) Repeatable Battery for the Assessment of Neurological Status. San Antonio, TX: Psychological Corporation.
26. Benton AL, Hamsher K (1989) Multilingual Aphasia Examination. Iowa City, Iowa: AJA Associates.
27. Bohnen N, Twijnstra A, Jolles J (1992) Performance in the Stroop color word test in relationship to the persistence of symptoms following mild head injury. Acta Neurol Scand 85: 116-121.
28. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, et al. (2009) Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery. Acta Anaesthesiol Scand 53: 864-872.
29. Newman SP (1995) Analysis and interpretation of neuropsychologic tests in cardiac surgery. Ann Thorac Surg 59: 1351-1355.
30. Dijkstra JB, Houx PJ, Jolles J (1999) Cognition after major surgery in the elderly: test performance and complaints. Br J Anaesth 82: 867-874.
31. Johnson T, Monk T, Rasmussen LS, Abildstrom H, Houx P, et al. (2002) Postoperative cognitive dysfunction in middle-aged patients. Anesthesiology 96: 1351-1357.
32. Monk TG, Weldon BC, Garvan CW, Dede DE, van der Aa MT, et al. (2008) Predictors of cognitive dysfunction after major noncardiac surgery. Anesthesiology 108: 18-30.
33. Gunning-Dixon FM, Raz N (2003) Neuroanatomical correlates of selected executive functions in middle-aged and older adults: a prospective MRI study. Neuropsychologia 41:1929-1941.
34. Ihara H, Berrios GE, London M (2000) Group and case study of the dysexecutive syndrome in alcoholism without amnesia. J Neurol Neurosurg Psychiatry 68: 731-737.