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Abstract – We examined the relationship between short- and medium-term POCD and anesthetic depth using bispectral index (BIS) values in patients undergoing coronary artery bypass graft (CABG) surgery using cardiopulmonary bypass (CPB). We identified 89 patients in whom BIS monitoring was used. Memory and executive functions were assessed before, one week, and three months after surgery. Two cognitive tests showed at least two standard deviation (SD) decrease from baseline in patients one week after surgery. After three months, six tests showed at least one SD decrease from baseline. BIS scores were significantly higher after CPB in patients with versus without POCD one week after surgery. The BIS scores during and after CPB and throughout the surgery were also higher in patients with versus without POCD three months after surgery. The results suggest that there may be a relationship between POCD and anesthetic depth in patients undergoing CABG.

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Abstract - We examined the relationship between short- and medium-term **POCD** and anesthetic depth using bispectral index **(BIS)** values in patients undergoing coronary artery bypass graft **(CABG)** surgery using cardiopulmonary bypass **(CPB)**. We identified 89 patients in whom **BIS** monitoring was used. Memory and executive functions were assessed before, one week, and three months after surgery. Two cognitive tests showed at least two standard deviation **(SD)** decrease from baseline in patients one week after surgery. After three months, six tests showed at least one SD decrease from baseline. BIS scores were significantly higher after **CPB** in patients with versus without **POCD** one week after surgery. The BIS scores during and after CPB and throughout the surgery were also higher in patients with versus without **POCD** three months after surgery. The results suggest that there may be a relationship between **POCD** and anesthetic depth in patients undergoing **CABG**.

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I. Introduction

Postoperative cognitive dysfunction (POCD) is an important cause of morbidity in patients undergoing cardiac surgery.(Newman et al., 2001) POCD is characterized by a reduced ability to concentrate, impaired understanding of language, memory deficits, and diminished social reintegration.(Moller et al., 1998; Rasmussen, Christiansen, Hansen, & Moller, 1999) Patients with POCD frequently have prolonged intensive care unit and hospital stays, may be less able to care for themselves, may not participate fully in rehabilitation efforts, and often require readmission to the hospital.(Marshall & Chung, 1999; Roach et al., 1996; Wilmore & Kehlet, 2001) Major risk factors for POCD include preexisting cognitive dysfunction, co-existing diseases, and age.(Ancelin et al., 2001; Moller, et al., 1998) Whether the type of anesthesia plays a role in the development of POCD remains somewhat controversial, although recent data suggest that incidence and severity of POCD are not likely influenced by anesthetic technique. (Rasmussen, 2006; Wu, Hsu, Richman, & Raja, 2004) However, Farag et al reported that cognitive processing speed was greater in patients who received deeper levels of general anesthesia, as measured using bispectral index (BIS) values, after noncardiac surgery.(Farag, Chelune, Schubert, & Mascha, 2006) These intriguing findings suggested the hypothesis that POCD and the depth of anesthesia may be related. However, the only study conducted to date that tested this hypothesis failed to demonstrate such relationship between anesthetic depth and short-term POCD in patients undergoing orthopedic, gynecologic, or plastic surgery.(Steinmetz, Funder, Dahl, & Rasmussen, 2010)

The relationship between anesthetic depth and POCD has not been examined in patients undergoing cardiac surgery. This patient population is particularly vulnerable to developing POCD because of exposure to potentially adverse consequences of cardiopulmonary bypass (CPB) and intraoperative manipulation of the heart and proximal great vessels.(Butler, Rocker, & Westaby, 1993; Slogoff, Girgis, & Keats, 1982) Our group has studied POCD in cardiac surgical patients for several years.(Hudetz, Gandhi, Iqbal, Patterson, & Pagel, 2011; Hudetz et al., 2009; Hudetz, Patterson, Byrne, Pagel, & Warltier, 2009; Hudetz, Patterson, Iqbal, Gandhi, & Pagel, 2010) As a result, our group has an established database of cardiac surgical patients in whom short- and medium-term POCD has been examined. We used this database to retrospectively examine the hypothesis that a relationship between intraoperative BIS values and POCD exists in patients undergoing coronary artery bypass graft (CABG) surgery using CPB.

II. Subjects 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.

Eighty nine patients undergoing CABG were identified in our database in whom intraoperative BIS

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monitoring was used. Inclusion criteria included ≥55 years of age, providing written informed consent, and scheduled for elective coronary artery surgery with CPB. We used historical nonsurgical patients from our database to establish the diagnosis of POCD in CABG patients.(Hudetz, et al., 2011) These nonsurgical patients also had coronary artery disease; inclusion of this group was important to account for practice effects of repeated cognitive testing. Exclusion criteria included a history of a cerebrovascular accident in the last three years, permanent ventricular pacing, previously documented cognitive deficits, or vascular dementia (Hachinski score(Hachinski & Munoz, 2000) greater than four). 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.

a) Cognitive testing

Baseline cognitive functions were assessed with a standard neuropsychometric battery, including recent verbal and nonverbal memory and executive functions, within one week before surgery as previously described.(Hudetz, et al., 2011) Briefly, cognitive functions were reassessed one week or at hospital discharge (whichever occurred first) and three months after surgery. Three parallel forms of the tests were used except for Stroop and Digit Span; the latter tests are not vulnerable to practice effects. Story Memory(Wilson, Cockburn, Baddeley, & Hiorns, 1989) and Word List Memory(H. B. Benedict, Schretlen, Groninger, & Brandt, 1998) were used to test recent verbal memory. Recent nonverbal memory(R. H. Benedict, Schretlen, Groninger, Dobraski, & Shpritz, 1996) and executive functions (Backward Digit Span,(Wechsler, 1997) Semantic Fluency,(Randolph, 1998) Phonemic Fluency(Benton & Hamsher, 1989), and the Color-Word Stroop Test, third part(Bohnen, Twijnstra, & Jolles, 1992)) were also tested. Depression was assessed with the Geriatric Depression Scale 15-item version.(Yesavage et al., 1982)

b) BIS monitoring

BIS electrodes were applied according to the manufacturer's instructions (Aspect Medical Systems, Inc, Newton, MA). BIS monitoring started immediately after anesthesia induction and continued until the end of surgery. BIS values were recorded at five minute intervals throughout surgery.

c) Anesthetic technique and conduct of cardio-pulmonary bypass

Midazolam, fentanyl, and etomidate were used for anesthetic induction and isoflurane and fentanyl were used for maintenance. This is our standard anesthetic protocol for all of our patients undergoing cardiac surgery assigned for POCD testing.(Hudetz, et al., 2011) All CABG patients underwent a standard median sternotomy. Myocardial protection during CPB consisted of antegrade and retrograde cold blood cardioplegia administered at regular intervals, topical hypothermia, and systemic hypothermia. A dose of continuous warm blood cardioplegia was administered during rewarming before removal of the aortic cross clamp. CPB flows and mean arterial pressure were maintained between 2.4 and 2.5 L/min/m^2 and between 55 and 70 mmHg, respectively, during CPB.

d) 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 one week or discharge and to three months after surgery.(Moller, et al., 1998) The z-score for the change in performance on each neuropsychological test was calculated by using the following formula: z-score = [(Change Score) - (Mean Change Score$_{control}$)] / (SD Change Score$_{control}$). An average z-score for each test was calculated. Cognitive dysfunction for each patient was defined as a deterioration of at least two standard deviations from baseline on at least two measures of the ten-test cognitive battery.(Moller, et al., 1998) Cognitive dysfunction was assessed for each patient at both one week and three month time-points. Patients were divided into groups with versus without POCD at both time points. BIS values between these patient groups were compared using the Wilcoxon rank-sum test. 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.

III. Results

Baseline medical and demographic data including age and education were similar between patients with or without POCD (Table 1). Baseline cognitive scores were also similar between groups (Table 2). Performance on two cognitive tests showed at least a two SD decrease from baseline (immediate word list recall and delayed word list recall) and performance on five additional tests demonstrated at least a one SD decrease (figure reconstruction, immediate story recall, delayed story recall, digit span, and Stroop) at one week after surgery in patients undergoing coronary artery surgery (Table 3). After three 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 one SD decrease from baseline (Table 3). Thus, cognitive function appeared to be somewhat improved three months compared with one week after surgery. Except for a significantly prolonged ICU stay in patients with POCD one week after CABG, surgical parameters were similar between groups (Table 4). The average values were significantly higher after in patients with versus without one week after surgery (Table 5). Average BIS values were also significantly ($p<0.01$) higher during and after in patients with versus without three months after surgery (Table 5). Notably, average BIS scores were also significantly ($p<0.0001$) higher during the entire surgical procedure in patients with three months after surgery (Table 5).

IV. Discussion

The results of this retrospective analysis suggest that there may be a relationship between the depth of anesthesia as evaluated using BIS and POCD in patients undergoing CABG using CPB. Patients who did not meet the diagnostic criteria for POCD one week and three months after surgery had modestly lower BIS values compared with those with POCD. Although the differences between groups were statistically significant (table 5), their clinical relevance remains unclear because BIS values are normally quite variable. Additionally, BIS monitoring does not necessarily provide a linear indicator of “anesthetic depth.” Nevertheless, the current findings suggest the intriguing hypothesis that deeper planes of anesthesia may exert relatively greater degrees of neuroprotection in patients during cardiac surgery. The precise mechanisms responsible for these findings are unclear and were not examined here. However, the total amounts of isoflurane, fentanyl and midazolam used during surgery were similar between groups and most likely do not account for the observed results. Similarly, no differences in patient demographics or the duration of surgery, CPB, or aortic cross clamp time were observed between groups.

The current findings in patients undergoing CABG are supported by the results of two earlier studies. Farag et al(Farag, et al., 2006) randomized 74 patients to a lower (median 38.9) or higher (median 50.7) BIS regimen during spinal, abdominal, or pelvic surgery. Cognitive testing was performed before and 4-6 weeks after surgery. The processing speed index was significantly higher in patients in the low compared with the high BIS group. These results suggested that deeper levels of anesthesia may be associated with improved cognitive function after surgery. Our results also suggest that a lower BIS value (38 ± 3) was associated with preservation of cognitive performance compared with a modestly higher (but statistically different) BIS value (42 ± 3) in which POCD was more frequently observed. More recently, Steinmetz et al(Steinmetz, et al., 2010) examined the effects of anesthetic depth on short-term cognitive function in 70 patients undergoing orthopedic, gynecologic, or plastic surgery. Cognitive functions were assessed before and within one week after surgery. The authors reported that there did not appear to be an association between depth of anesthesia quantified using BIS and the presence of POCD one week after surgery. Our findings with CABG patients are also in general agreement with those Steinmetz et al,(Steinmetz, et al., 2010) as lower average BIS values throughout the entire procedure were not associated with improved cognitive functions one week after CABG surgery. Our findings further suggest, in agreement with the data of Farag et al,(Farag, et al., 2006) that lower BIS values during the entire surgery are associated with improved medium-term cognitive functions three months after surgery. It is highly likely that patients are less affected by immediate postoperative factors and pain medications when cognitive testing is performed at least one month after surgery, in contrast to the median of three to four days after surgery reported in the Steinmetz et al(Steinmetz, et al., 2010) study. The ability to examine BIS values before, during, and after CPB provided a framework by which we may subsequently examine specific periods of cardiac surgery with their potential relationship to subsequent cognitive function. Indeed, the data suggested that lower BIS values after bypass alone were associated with improved short-term cognitive performance, whereas lower BIS values both during and after CPB were predictive of less POCD three months after surgery. However, the current retrospective observational study was not designed to prospectively address this issue.

The current results should be interpreted within the constraints of several other potential limitations. Our study is small, as only 89 patients undergoing CABG were retrospectively examined. Whether the current results may be extrapolated to patients undergoing other types of cardiac surgery is unknown. BIS and other processed EEG monitors have well-known limitations because these devices analyze EEG signals from the frontal lobe alone(Azim & Wang, 2004; Dahaba, 2005; Merat et al., 2001) and the current results should be considered with these technical limitations in mind. Cognitive performance was reassessed three 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 CABG surgery is unknown. The current findings that lower BIS values may exert more profound neuroprotective effects against POCD are very preliminary, and will have to be confirmed by a larger randomized trial that includes both sexes before any change in anesthetic practice could be suggested.

In summary, the current results suggest that there may be a relationship between the incidence of short- and medium-term POCD and anesthetic depth assessed using BIS in patients undergoing coronary artery surgery using CPB. Further studies are warranted to examine this hypothesis.

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Table 1 : Demographics and medical data

	(+)POCD *N=48*	(-)POCD *N=41*	*p*(s)
Age, yr	68±9	68±7	0.82
Education, yr	12±2	12±2	0.5
Caucasian (%)	41(85)	40(98)	0.06
Married (%)	27(56)	28(68)	0.24
Current smoker (%)	9(19)	11(27)	0.36
Hypertension (%)	44(92)	37(90)	0.82
Hypercholesterolemia (%)	43(90)	37(90)	0.92
Angina (%)	18(38)	18(44)	0.54
Arrhythmia (%)	7(15)	8(20)	0.54
Myocardial infarction (%)	8(17)	7(17)	0.96
Peripheral vascular disease (%)	7(15)	3(7)	0.33
Diabetes (%)	25(52)	24(59)	0.54
Congestive heart failure (%)	8(17)	4(10)	0.38
Stroke (%)	4(8)	1(2)	0.37
Sleep disorder (%)	16(33)	18(44)	0.31
Depression (%)	9(19)	8(20)	0.93
GDS-15	3±3	3±3	0.25
Antihypertensive drug (%)	39(81)	30(73)	0.36
Diuretic drug (%)	18(38)	16(39)	0.88
Lipid lowering drug (%)	43(90)	32(78)	0.13
Hachinski score >=4, baseline (%)	0(0)	0(0)	

Data are mean±SD or number (%), POCD: groups are separated to (+) and (-) POCD based on cognitive performance 1 week after surgery, GDS-15: geriatric depression score (fifteen items), the *p* values are from *t*-test for continuous variables and Chi-square or Fisher's exact test for dichotomous variables; p(s): p values between the two surgical groups

Table 2 : Cognitive scores under baseline conditions

	(+) POCD *N=48*	(-) POCD *N=41*	*p*(s)
Figure Reconstruction	20±8	20±7	0.91
Delayed Figure Reproduction	8±3	7±3	0.79
Immediate Story Recall	18±5	18±5	0.60
Delayed Story Recall	10±3	9±3	0.20
Immediate Word List Recall	27±8	24±6	0.05
Delayed Word List Recall	6±3	5±3	0.10
Digit Span	9±2	8±2	0.10
Semantic Fluency	15±4	16±3	0.09
Phonemic Fluency	11±4	12±5	0.44
Stroop	39±13	38±12	0.90

Data are mean±SD, POCD: groups are separated to (+) and (-) POCD based on cognitive performance 1 week after surgery, *p*(s): p values between the two surgical groups

Table 3 : Z-scores at 1 week and 3 months after surgery in patients with or without POCD

	1 week		3 months	
	(+) POCD	(-) POCD	(+) POCD	(-) POCD
Figure Reconstruction	-2.7	-0.9	-2.9	0.0
Delayed Figure Reproduction	-1.1	0.1	-1.2	0.5
Immediate Story Recall	-2.0	-0.3	-3.6	0.0
Delayed Story Recall	-2.5	-0.4	-3.7	0.1
Immediate Word List Recall	-3.0	-1.1	-2.5	-0.9
Delayed Word List Recall	-3.4	-1.4	-2.8	-0.8
Digit Span	-1.8	-0.6	-2.3	-0.9
Semantic Fluency	-0.6	-0.3	-0.4	-0.1
Phonemic Fluency	-0.9	-0.3	-0.3	-0.2
Stroop	-1.6	-1.0	-1.3	-0.4

Data are mean±SD

Table 4 : Surgical and postoperative parameters in patients with or without POCD

	1 week			3 months		
	p_{all}	(+) POCD 1w	(-) POCD 1w	p_{all}	(+) POCD 3m	(-) POCD 3m
Anesthesia, min	0.62	458±78	450±62	0.46	421±55	437±65
Surgery, min	0.94	355±79	356±65	0.14	309±51	338±54
ACC time, min	0.26	115±43	125±41	0.31	102±39	120±50
Before CPB, min	0.77	194±45	192±41	0.74	187±48	181±2
During CPB, min	0.62	147±53	152±47	0.24	127±45	148±54
After CPB, min	0.39	120±32	114±30	0.44	110±16	119±38
Isoflurane, %	0.21	0.81±0.23	0.75±0.19	0.23	0.74±0.18	0.82±0.17
Fentanyl, mcg	0.46	1131±349	1193±433	0.45	1227±644	1083±322
Midazolam, mg	0.31	6±3	5±3	0.03	7±3	5±2
ICU stay, day	0.008	4±2	3±1	0.45	3±2	3±1
Hospital stay, day	0.09	7±3	6±3	0.44	6±1	6±2

Data are mean±SD, ACC: aortic cross clamp, CPB: cardiopulmonary bypass, p_{all}: p values at 1 week and 3 months after surgery

Table 5 : Average BIS values in patients with and without POCD

	BIS value			
	Entire Surgery	Before CPB	During CPB	After CPB
POCD 1 week				
(+)	40±3	40±1	39±3	41±2
(-)	39±3	41±3	38±3	39±1
p value	0.08	0.69	0.55	<0.05
POCD 3 months				
(+)	42±3	41±2	41±3	43±1
(-)	38±3	40±2	36±3	38±1
p value	<0.0001	0.34	<0.01	<0.01

Data are mean±SD, *p* values are from *t*-tests

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