Predictors of Early Neurocognitive Deficits in Low-Risk Patients Undergoing On-Pump Coronary Artery Bypass Surgery

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Background—Postoperative cognitive deficits (POCDs) are a source of morbidity and occur frequently even in low-risk patients undergoing cardiac surgery. Predictors of neurocognitive deficits can identify potentially modifiable risk factors as well as high-risk patients in whom alternate revascularization strategies may be considered.

Methods and Results—448 patients undergoing coronary surgery (coronary artery bypass graft [CABG]) underwent standardized preoperative and postoperative neurocognitive testing as part of 2 randomized trials evaluating the effects of mild hypothermia during coronary surgery. Prospectively collected data were used to identify univariate predictors of POCDs and multivariable logistic regression models were constructed. Models were bootstrapped 1000 times. POCDs occurred in 59% of patients. Significant univariate predictors included intraoperative normothermia, impaired left ventricular (LV) function, higher educational level, elevated serum creatinine and reduced creatinine clearance, prolonged intubation time, intensive care unit (ICU) stay, and hospital stay. Advanced age, presence of carotid disease, and cardiopulmonary bypass time were not associated with increased POCDs in this cohort. Multivariable modeling identified intraoperative normothermia (odds ratio [95% confidence interval] −1.15 [1.01, 1.31]), poor LV function (1.53 [1.02, 2.30]), and elevated preoperative creatinine (1.01 [1.00 to 1.03] for every 1 mmol/L increase), prolonged (>24 hours) ICU stay (1.88 [1.27 to 2.79]), and higher educational level (1.52 [1.01 to 2.28]) as independent predictors of POCD occurrence.

Conclusions—Mild hypothermia, in the intraoperative and perioperative period, may be a protective strategy for the prevention of POCDs. Patients with elevated pre-operative creatinine and poor LV function carry a higher risk of POCDs and may benefit from revascularization strategies other than conventional on-pump CABG. **(*Circulation*. 2006; 114[suppl I]:I-461–I-466.)**

Key Words: cardiopulmonary bypass ■ coronary artery bypass ■ neurocognitive deficits ■ risk factors

Neurocognitive decline in the early postoperative period after cardiac surgery is a commonly occurring phenomenon with an incidence varying from 30% to 60% in different studies.[1,2] Postoperative cognitive deficits (POCDs) can be alterations in memory, attention, or psychomotor function that can impair postoperative recovery, reduce quality of life, and delay return to work.[3] The majority of neurocognitive deficits identified early in the postoperative period improve in the weeks to months after surgery.[4,5] Although a number of surgical factors have been implicated, these deficits may be caused, in large part, by underlying cerebrovascular pathology in these patients rather than a consequence of the surgical procedure itself. Nevertheless, the occurrence of early deficits has been associated with long-term cognitive decline at 5 years in multiple studies.[2,6]

A number of observational and interventional studies have studied the natural history of neurocognitive deficits, identified predictors, and evaluated potential therapeutic interventions. Certain predictors of POCDs have been validated in multiple studies. These include advanced age, increased cardiopulmonary bypass time, and presence of cerebrovascular disease. Increased education has been identified as a protective characteristic.[2,7,8] Other predictors have been suggested by at least 1 group but have not been validated in multiple populations. Some of these include the presence of diabetes, peripheral vascular disease, postoperative atrial fibrillation, and other postoperative complications.[7,9] The validity and generalizability of the findings from these studies are limited often by the sample sizes of the cohorts, variable methods of neuropsychometric testing, and differing thresholds for identification of deficits.

The aim of this study was to characterize the incidence and predictors of neurocognitive decline in a cohort of low-risk patients undergoing on-pump coronary artery bypass surgery

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with the goal of identifying modifiable risk factors as well as patients who are at high-risk for POCDs.

Materials and Methods

Study Population

The study population consisted of patients undergoing nonemergent isolated coronary artery bypass surgery who were enrolled in 2 separate randomized controlled trials evaluating the effects of mild intraoperative and postoperative hypothermia on neurocognitive function. The study protocols were approved by the Institutional Review Board of the University of Ottawa Heart Institute and written informed consent was obtained from all participating subjects. The first study,[10] conducted between 1995 and 1998, randomized 223 patients to mild hypothermia (34°C) or normothermia (37°C) during the rewarming phase of cardiopulmonary bypass. The second study[11] was initiated to confirm the findings in a larger population and enrolled 263 patients from 2001 to 2004. In this study, patients were randomized to mild hypothermia (34°C) or normothermia (37°C) during the entire operative period. For the purpose of this analysis, both interventions of hypothermia were treated as being the same and interaction terms evaluating study-specific effects were evaluated in the final multivariate model.

Inclusion and exclusion criteria are presented in Table 1. Study subjects underwent preoperative neuropsychometric evaluation at 15±1 days preoperatively and postoperative evaluation before discharge home (mean 7.7±0.3 days postoperatively). To optimize the reliability of the neuropsychometric evaluation, the psychometrists were trained and periodically audited by the same neuropsychologist. All patients were ambulating and were fit for discharge at the time of postoperative assessment.

Intraoperative Protocol

The protocol for intraoperative temperature interventions has been previously described.[10,11] Nasopharyngeal temperatures were monitored and controlled throughout the intraoperative period. In the first study, patients were cooled to 32°C immediately on initiation of cardiopulmonary bypass. During rewarming, blood in the oxygenator was warmed so that nasopharyngeal temperature increased to either 34°C or 37°C. For the second study, high-efficiency thermal pads were applied to the patient's back and posterior aspect of the upper leg on arrival in the operating room. A water-circulating thermal control system (Arctic Sun; Medivance Corporation, Louisville, Colo) was used to cool the patients to 34°C or warm to 37°C throughout the entire operative period. The temperature of blood leaving the oxygenator was monitored and recorded and was not allowed to exceed 37.5°C or 34.5°C in the normothermic and hypothermic groups, respectively.

TABLE 1. Inclusion and Exclusion Criteria

Inclusion Criteria	Exclusion Criteria
Age ≥60	Neurologic deficit of any etiology
Agreement of attending surgeon	Parkinson's disease
Written informed consent	Physical disability preventing neuropsychometric tests
Nonemergent isolated CABG surgery	Abnormal NIH stroke scale results
Fluency in English or French	MMSE <24
	Patient on intravenous nitroglycerin
	Documented coagulopathy or INR >1.3
	Creatinine >2-times normal
	Preoperative atrial fibrillation

CABG indicates coronary artery bypass graft; MMSE, Mini-Mental Status Examination; NIH, National Institutes of Health; INR, International Normalized Ratio.

In both studies, cardiopulmonary bypass was performed via an ascending aortic cannula and a 2-stage right atrial cannula with membrane oxygenators and 43-μm arterial line filters (Cobe Cardiovascular, Arvada, Colo), with a nonpulsatile flow at 2.5 to 2.8 L/min per m^2, and without the use of left ventricular vents. Mean arterial pressure was maintained between 50 and 80 mm Hg using phenylephrine or isoflurane. After application of the aortic cross-clamp, cardiac arrest was induced and maintained with antegrade cold crystalloid cardioplegia. Proximal anastomoses were fashioned using a side-biting clamp on the aorta. Tranexamic acid was given to patients who had previous CABG in the first study and to all patients in the second study, to reduce blood loss.

Neuropsychometric Evaluation

Testing was conducted in accordance with the consensus statement on neurobehavioral evaluation after cardiac surgery.[12] Learning efficiency and memory consolidation were evaluated with a verbal list learning procedure (Buschke Selective Reminding administration and scoring). Alternate forms were used to reduce learning effects. Attention span was evaluated with the Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span. Psychomotor speed and dexterity were measured by Trails A and B, grooved pegboard, and the Symbol Digit Modalities Test (oral administration). From these tests, we calculated the following measures: (1) total learning free recall; (2) consistent long-term retrieval; (3) long-term retrieval; (4) long-term storage; (5) delayed recall; (6) digit span forward; (7) digit span backward; (8) Trails A; (9) Trails B; (10) grooved pegboard; and (11) Symbol Digit Modalities Test. In the second study, the Rey Auditory and Verbal Learning Test was used instead of the Buschke Selective Reminding and the Wechsler Memory Scale III/Mental

TABLE 2. Patient Characteristics (n=486)

Preoperative Characteristics	n=448
Age (years)	68.3±0.3
Male (%)	390 (87)
Diabetes (%)	137 (31)
CCS angina class	2.81±0.04
Lower extremity peripheral arterial disease (%)	59 (13)
Carotid artery disease (%)	20 (5)
Body mass index (kg/m^2)	28.7±0.2
Regular alcohol use (%)	190 (42)
Education (>grade 12) (%)	181 (40)
Preoperative serum creatinine	91.5±0.9
Estimated creatinine clearance	83.6±1.2
Abnormal left ventricular class (≥2) (%)	173 (39)
EuroSCORE	3.1±0.1
Intraoperative Data	
Redo (%)	24 (5)
Cardiopulmonary bypass time (minutes)	81.3±1.1
Cardiac anoxia time (minutes)	46.3±0.7
Intraoperative/perioperative hypothermia (%)	220 (49)
N of bypass grafts	3.05±0.03
Need for intra-aortic balloon pump (%)	6 (1)
Postoperative Data	
In-hospital mortality (%)	3 (0.7)
Time to extubation (hours)	12.6±0.5
Intensive care unit length of stay	1.01 (0.91, 1.74)
In-hospital length of stay	6 (5, 7)
Postoperative atrial fibrillation (%)	136 (31)

TABLE 3. Preoperative, Intraoperative, and Postoperative Characteristics in Patients With and Without POCDs

Variable	No POCD (n=183)	POCD (n=265)	*P*
Age	68.0±0.4	68.5±0.4	0.41
Sex (%)	157 (86)	233 (88)	0.51
Intraoperative/perioperative hypothermia (%)	100 (55)	120 (45)	0.05
Abnormal LV function (%)	61 (34)	112 (43)	0.06
Diabetes (%)	54 (30)	83 (31)	0.68
Cardiopulmonary bypass time (minutes)	81.4±1.9	81.3±1.4	0.77
Cardiac anoxia time (minutes)	46.2±1.2	46.2±0.9	0.61
Preoperative serum creatinine (mmol/L)	89±1.3	93±1.2	0.008
N of bypass grafts	3.1±0.05	3.1±0.04	0.76
Estimated creatinine clearance	86.1±1.9	81.0±1.5	0.04
Body mass index (kg/m^2)	28.8±0.3	28.6±0.3	0.95
Time to extubation (hours)	11.2±0.4	13.5±0.8	0.026
ICU length of stay (days)	1.23±0.05	1.52±0.10	0.002
In-hospitallLength of stay (days)	6.3±0.2	6.9±0.3	0.01
Postoperative atrial fibrillation (%)	48 (26.5)	88 (33.7)	0.11
Lower extremity arterial disease (%)	23 (13)	33 (14)	0.75
Carotid artery disease (%)	8 (4)	12 (5)	0.93
Regular alcohol use (%)	82 (45)	108 (41)	0.39
Redo (%)	12 (7)	12 (5)	0.35
Educational level (>grade 12) (%)	62 (34)	119 (45)	0.02

Univariate *P* derived using 2-sample *t* test or Wilcoxon rank-sum test for continuous variables and χ^2 or Fisher exact test for categorical variables.

Control was added. The psychometrist and the patient were unaware of the treatment assignment throughout the course of the study.

The 11 neuropsychometric tests were grouped into 3 cognitive domains: memory, speed, and attention. For each domain, a composite score was derived by the procedure of Townes et al;[13] that is, each component score of the domain was standardized by subtraction of the mean and division by the standard deviation of the preoperative scores for both groups combined. The mean of the standardized component scores was used as the score for the domain. On the basis of data from pilot series and the work of others,[13] it was decided a priori that patients would be classified as cognitively impaired if they demonstrated a decrease of ≥0.5 standard deviations compared with preoperative values in 1 or more of the 3 domains.

Statistical Analysis

The primary outcome for the clinical trials as well as for this analysis was the incidence of POCDs. No imputations were performed for missing covariate data and ordinal variables were dichotomized at a clinically meaningful threshold. Estimated creatinine clearance was calculated using the Cockcroft-Gault formula. The univariate relationship between predictors and POCDs was determined using Student *t* test or Wilcoxon rank-sum tests as appropriate for continuous variables and χ^2 or Fisher exact tests for categorical variables. A liberal threshold of $P \leq 0.20$ was used to select variables for the construction of the multivariable logistic regression model.

The multivariable model was constructed by first choosing the best single variable model as determined by the likelihood ratio test. The next covariate to be added was identified by considering all possible 2 variable models and selecting the one with the greatest likelihood. New variables were added to the model until the addition of covariates no longer significantly improved the model, as determined by the likelihood ratio test. Next, all significant univariate predictors that did not enter the final model were individually added to the final model to assess confounding. Interaction terms between the design variable (temperature) and the study number (1 or 2) were assessed.

The linearity assumption for continuous predictors was evaluated by dividing the variable into equal width bins and examining the adjusted odds ratio across the bins. Finally, the model was bootstrapped 1000 times to assess whether the model was overfit.

Continuous data are presented as mean±standard error of the mean or median (interquartile range) for highly skewed data and categorical data are presented as counts (%). Odds ratios are presented with their 95% confidence intervals. All analyses were conducted in SAS v9.1 (SAS Institute, Cary, NC).

Statement of Responsibility

The authors had full access to the data and take full responsibility for their integrity. All authors have read and agree to the manuscript as written.

Results

Descriptive data for the cohort is presented in Table 2. Postoperative cognitive deficits were observed in 59% (265 of 448) of the patients. 161 patients (61%) suffered a cognitive deficit in a single domain, whereas 81 (30%) had deficits in 2 domains and 23 (9%) had deficits in all 3 domains.

Univariate Predictors of POCDs

Table 3 depicts the preoperative, intraoperative, and postoperative characteristics of patients with and without POCDs. Preoperative variables associated with POCDs included abnormal left ventricular (LV) function, preoperative serum creatinine and estimated creatinine clearance, and educational level. Intraoperative and postoperative variables that reached significance in the univariate analysis included assignment to the mild hypothermia group, prolonged time to extubation,

TABLE 4. Final Multivariate Model*

Effect	Odds Ratio	95% Confidence Limits		P
Prolonged ICU stay (>24 hours)	1.88	1.27	2.79	0.002
Abnormal LV function	1.53	1.02	2.30	0.042
Preoperative serum creatinine	1.01	1.00	1.03	0.017
Intraoperative/perioperative normothermia	1.15	1.01	1.31	0.042
Level of education	1.52	1.01	2.28	0.042

*Hosmer-Lemeshow goodness of fit χ^2 test, $P=0.81$.

intensive care unit (ICU) stay and in-hospital stay. The occurrence of postoperative atrial fibrillation was weakly associated with POCDs ($P=0.11$). All of these covariates were included in the construction of the multivariate model. Age, presence of carotid disease, and cardiopulmonary bypass time were not significantly associated with POCDs in this cohort.

Multivariate Model

To construct the multivariate model, variables were entered into the model sequentially in order of their effect on the log likelihood score (−2 logL). Prolonged ICU stay was the first covariate to enter the model. Next, LV function, preoperative creatinine, hypothermia, and educational level were added to the model. None of the other variables was significant when added to this model. All univariate predictors, not included in the multivariate model, were sequentially added to the final model to check for confounding and no confounders were identified. Interaction terms between the design variable (intraoperative temperature) and study number (study 1 versus study 2) were also evaluated and found to be nonsignificant indicating that these effects were maintained across both studies. Thus, the final model identified increased educational level, elevated serum creatinine, abnormal LV function, intraoperative normothermia, and prolonged ICU stay as independent predictors of postoperative cognitive deficits.

Model Fit and Validation

To evaluate the stability of the effect estimates, the model was bootstrapped 1000 times. All variables initially included in the model remained significant after the bootstrap procedure. The final model with the bootstrapped probability values is shown in Table 4. The Hosmer Lemeshow goodness of fit test had $P=0.81$, suggesting a good model.

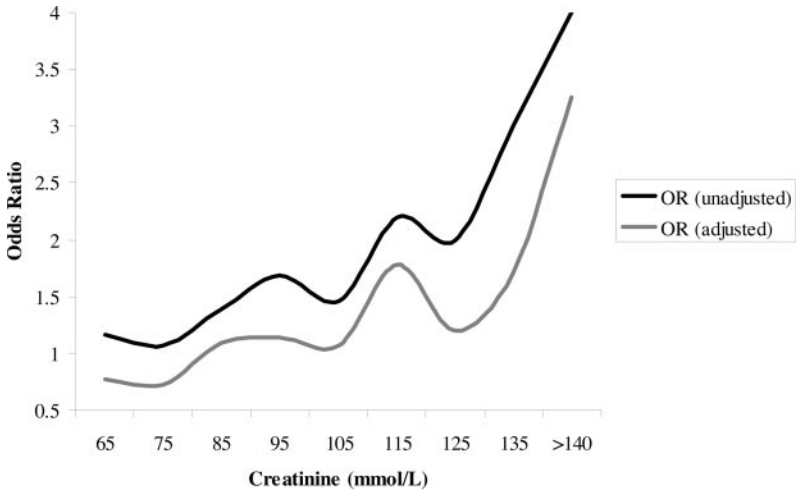
Preoperative Creatinine and POCDs

Linearity of the preoperative creatinine was evaluated by dividing it into uniform size bins, each with a width of 10 mmol/L, and examining the association with POCDs using the lowest bin as the reference value. The relationship appeared to be roughly linear with lower values for creatinine but the odds of POCDs appeared to increase sharply at higher values of serum creatinine suggesting a threshold effect at values ≈125 mmol/L (Figure 1). The relationship showed a similar pattern for both the unadjusted and the adjusted model with the odds ratios being slightly lower for the adjusted model.

Discussion

In this study, we describe the incidence and predictors of early postoperative neurocognitive deficits in a large cohort of low-risk patients undergoing coronary artery bypass surgery using cardiopulmonary bypass. We found that POCDs occurred in 59% of patients and we identified higher educational level, abnormal LV function, elevated preoperative serum creatinine, and prolonged ICU stay as independent predictors of POCDs. Mild intraoperative hypothermia was independently associated with reduced postoperative cognitive decline.

Neurocognitive decline after cardiac surgery has received significant attention in recent years, following the demonstra-



Effect of preoperative serum creatinine on the unadjusted and adjusted odds of postoperative cognitive deficits.

tion in multiple studies that cognitive deficits occurring early after cardiac surgery are predictive of late cognitive decline.[2,5,6] These findings have led to the hypothesis that a reduction in perioperative cognitive deficits may reduce late cognitive decline. However, the contribution of the surgical procedure and exposure to cardiopulmonary bypass to the occurrence of these deficits is not entirely clear. The stress of the cardiac surgical procedure may simply be unmasking underlying cerebrovascular pathology that puts patients at risk of late cognitive decline. However, specific maneuvers performed during the surgical procedure, eg, manipulation of an atherosclerotic ascending aorta, prolonged cardiopulmonary bypass time, and cerebral hyperthermia have been associated with poorer neurologic outcome.[7,14,15] Most studies examining predictors of POCDs have identified both patient-related and surgery-related factors, suggesting a multi-factorial etiology.

In our cohort, we identified a combination of preoperative, intraoperative, and postoperative variables that are independent predictors of early cognitive decline after surgical coronary revascularization. Preoperative factors included higher educational level, abnormal LV function, and elevated serum creatinine. Although some previous studies have demonstrated a protective effect of increased number of years of education on POCDs,[2,7] our study indicates that individuals with higher education level are at greater risk for POCDs. This may be because patients with higher education have higher baseline (preoperative) scores and, therefore, are more likely to demonstrate a reduction in scores after surgery compared with patients with lower baseline scores.

Abnormal LV function and elevated serum creatinine levels have been linked to poorer outcome after cardiac surgery.[16,17] They likely represent markers of underlying disease severity and the burden of atherosclerotic disease even in low-risk patients. Interestingly, another study, evaluating 282 patients, specifically examined the relationship between serum creatinine and postoperative cognitive decline and was unable to establish an association.[18] This discordance may be caused by a lack of power, misspecification of the covariates, or the different time frame of neurocognitive testing. In our cohort, preoperative serum creatinine was a strong predictor of cognitive decline and demonstrated a threshold relationship with the risk of POCDs with sharp increases in the odds of POCDs at creatinine levels >125 mmol/L. It is important to note that patients with severely abnormal serum creatinine levels (>2 times normal) were, by design, excluded from this study. Thus, these preoperative characteristics may be useful for the identification of patients who are at high risk for POCDs in whom strategies other than on-pump coronary artery bypass may be considered.

Although the primary aim of this analysis was not to evaluate the effect of temperature, intraoperative hypothermia was included because it was the design variable and was identified as the only intraoperative variable independently associated with reduced cognitive deficits. The effects of temperature on neurologic injury after cardiac surgery remains extensively debated. Some studies have demonstrated a protective effect of hypothermia,[10] whereas others have failed to do so.[19] Yet other studies have shown a detrimental effect of hyperthermia on cognitive outcomes.[15] The heterogeneity in the method, degree, and duration of hypothermia used are probably responsible, in large part, for the variability in the findings. A key feature of our study is the use of sustained hypothermia (without rewarming) compared with other trials, which may protect against the potentially harmful effects of cerebral hyperthermia. Whether these benefits of intraoperative hypothermia are sustained over the long-term remains to be determined.

Last, prolonged ICU stay was a strong independent predictor of POCDs. This variable likely captures the effect of various preoperative risk factors and postoperative complications that have previously been linked to poor neurocognitive outcome and may also be a marker of underlying disease severity. It is noteworthy that a number of predictors identified in other studies were not significant in this cohort. These include age, cardiopulmonary bypass time, diabetes, and carotid and peripheral arterial disease.

Strengths and Limitations

The strength of this study include its prospective design, well-defined patient population, high-quality data, and extensive neuropsychometric evaluation. Although this analysis was based on a large and relatively homogenous cohort, it is limited to the evaluation of early POCDs. Furthermore, the homogeneity and low-risk nature of the study population did not permit a sufficiently powered analysis to assess certain characteristics and their association with POCDs. Ascending aortic disease, which is linked to neurologic injury, was not systematically evaluated using methods, like epi-aortic scanning, that have recently become available.

Conclusions

Postoperative cognitive deficits occur frequently even in low-risk patients undergoing on-pump coronary artery bypass surgery. In this large prospective cohort, higher education level, elevated serum creatinine, abnormal LV function, and prolonged ICU stay were independently associated with increased risk of postoperative neurocognitive decline. Mild intraoperative hypothermia was independently associated with reduced cognitive deficits and represents a potential neuroprotective strategy in these patients.

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Disclosures

None.

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