Chronic Exposure to Nicotine Does Not Prevent Neurocognitive Decline After Cardiac Surgery

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Objective: **To establish the association between smoking and cognitive decline in patients undergoing coronary artery bypass graft (CABG) surgery.**

Design: **Retrospective review.**

Setting: **Referral center for cardiothoracic surgery at a university hospital.**

Participants: **Four hundred seventeen patients undergoing CABG surgery.**

Interventions: **Based on preoperative data, patients were divided into 2 groups: smokers (n = 185) and nonsmokers (n = 232). Patients who smoked half a pack of cigarettes per day within the last 2 years were identified as smokers, and patients who did not smoke were included in the nonsmoker group. Patients with less than a seventh grade education; an inability to read; or a history of one of the following medical conditions: prior stroke with residual deficit, psychiatric illness, renal disease (creatinine > 2.0 mg/dL), or active liver disease; or patients who quit smoking prior to surgery were excluded from the study. Both groups received similar anesthetic and surgical management. All patients received a battery of neurocognitive tests both preoperatively and 6 weeks after CABG surgery. Neurocognitive test scores were separated into 4 cognitive domains, with a composite cognitive index (the mean of the four domain scores) determined for each patient at every testing period.**

Measurements and Main Results: **The overall rate of cognitive decline at 6 weeks after surgery in smokers was 36.2%, whereas nonsmokers showed a deficit rate of 36.6%. Nonsmokers were significantly older and presented for surgery on average 6 years later than the smokers. Female sex represented a considerably larger proportion of patients in the nonsmoker group. Smokers had a higher prevalence of myocardial infarction. The univariate analysis of cognitive change at 6 weeks adjusted for age, baseline cognitive index, and education years showed no difference between the 2 groups. Sex, history of myocardial infarction, hypertension, stroke, transient ischemic attack, and duration of cardiopulmonary bypass did not contribute to the multivariate logistic regression model and were dropped from the final analysis. Significant multivariate predictors of neurocognitive dysfunction included age, left ventricular ejection fraction, baseline education level, and baseline cognitive index.**

Conclusions: **This study confirmed previous findings that age, baseline cognitive function, years of education, and impaired left ventricular function are independent predictors of neurocognitive decline at 6 weeks after CABG surgery. Smoking is neither preventive nor causative of cognitive decline after CABG surgery.**

KEY WORDS: coronary artery bypass graft surgery, cognitive dysfunction, smoking

COGNITIVE DYSFUNCTION AFTER cardiac surgery is a significant problem. The incidence of neurocognitive decline after coronary artery bypass graft (CABG) surgery is 50% to 80% at discharge, 20% to 50% at 6 weeks, and 10% to 30% at 6 months.[1,2] In addition, a considerable neurocognitive dysfunction is still present at both 3-[3] and 5-year[4] follow-up periods. Its long-term persistence is predicted by neurocognitive testing at 6 weeks after surgery.[3,4]

The causes of neurocognitive dysfunction are not clearly defined. Identification of mechanisms of cognitive decline and development of strategies for brain protection during cardiac surgery are critical to the further improvement of perioperative care in cardiac surgical patients.

There is an increasing body of evidence suggesting that cholinotherapy may be of symptomatic benefit in degenerative disorders and that cholinergic agents have additional neuroprotective effects.[5] Furthermore, chronic nicotine administration has been associated directly and indirectly with neuronal protection.[6-8] The purpose of this study was to establish the association between smoking and cognitive decline in patients undergoing CABG surgery.

METHODS

After institutional review board approval, this study examined data collected prospectively on 417 patients undergoing first-time elective CABG surgery as part of the Duke Neurocognitive Outcomes Database and the Duke Cardiovascular Outcomes Database. Data were collected between February 1999 and March 2000. Patients with less than a seventh grade education; an inability to read; or a history of one of the following medical conditions: prior stroke with residual deficit, psychiatric illness, renal disease (creatinine $>$ 2.0 mg/dL), or active liver disease; or patients who quit smoking before surgery were excluded from the study. Similarly, patients who were either tobacco chewers or cigar smokers were not included in the analysis. Patients who smoked half a pack of cigarettes per day within the last 2 years were identified as smokers, and patients who did not smoke were included in the nonsmoker group.

All patients were operated on by the same team of surgeons at the Duke Heart Center. Previously described surgical and anesthetic management was used in both groups.[9] Routine monitoring included continuous direct arterial blood pressure, central venous and pulmonary artery pressures, transesophageal echocardiography, 5-lead electrocardiographic monitoring with continuous ST-segment analysis, pulse oximetry, capnography, and temperature measurements. Management of cardiopulmonary bypass (CPB) included cooling patients to 32°C, alpha-stat pH management, mean perfusion pressure between 50 and 90 mmHg, pump flow rates of 2.0 to 2.4 L/min/m^2, and hematocrit $>$18%. Before separation from CPB, a previously described rewarming strategy was used.[10]

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Table 1. Demographic Data and Patient Characteristics

	Smokers (n = 185)	Nonsmokers (n = 232)	*p* Value
Age (yr)	57 ± 10	63 ± 10	0.001
Females (%)	23	35	0.007
Education (yr)	12.2 ± 2.9	12.8 ± 3.2	0.08
Baseline CI	0.38 ± 1.9	0.17 ± 2.0	0.27
LVEF (%)	54 ± 12	57.0 ± 11	0.005
Duration CPB (min)	102 ± 27	107 ± 73	0.27
History of MI (%)	33	21	0.004
History of HTN (%)	58	64	0.18
History of stroke or TIA (%)	1.5	1.2	0.8

Abbreviations: CI, cognitive index; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; MI, myocardial infarction; HTN, hypertension; TIA, transient ischemic attack.

All patients were examined by experienced psychometricians with a battery of well-validated and established cognitive tests in accordance with the statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery.[11] The battery of 6 tests resulted in 18 raw scores for each testing period and included the short story module of the Randt MemoryTest,[12] the Digit Span subtest of the Wechsler Adult Intelligence Scale,[13] the Wechsler Memory Scale Figural Memory test,[14] the Digit Symbol subtest of the Wechsler Adult Intelligence Scale,[13] the Trail-Making Test (Part B),[15] and the Rey Auditory-Verbal Learning Test.[16]

Testing took place the day before CABG surgery (baseline) and 6 weeks postoperatively. To assess neurocognitive function over time, a factor analysis was used to correlate the raw scores of each test to construct a smaller set of 4 independent factor scores, each representing a separate domain of cognitive function. The 4 factors represented the cognitive domains of (1) verbal learning, short-term and delayed; (2) discourse memory and oral language comprehension, short-term and delayed; (3) visuospatial orientation, psychomotor processing speed, and figural memory, short-term and delayed; and (4) attention and concentration.[4] An overall dichotomous cognitive deficit outcome was defined as a decline in performance of 1 standard deviation or more in any of the 4 independent domains.

The factor analysis yields 4 separate standardized factor scores, each with a mean of 0.0 and a standard deviation of 1.0. The cognitive index (CI) was defined as the sum of these 4 factor scores, which results in a mean of 0 and a standard deviation of 2.0. The mean of each subject's 4 factor scores formed their composite CI. The composite cognitive change score was then calculated by subtracting the baseline index from the 6-week follow-up index in each patient. Delta CI was compared in smokers and nonsmokers with univariate and multivariate models using analysis of variance. Covariates tested included age, sex, education, left ventricular ejection fraction, duration of cardiopulmonary bypass, history of hypertension, myocardial infarction, stroke and transient ischemic attack, and baseline CI. Significant covariates were included in the model. Interactions were investigated for significance. Categoric and numerical data were analyzed with chi-square test, *t* test, and analysis of variance as appropriate. A *p* value of less than 0.05 was considered statistically significant. Data are expressed as mean ± standard deviation.

RESULTS

There was no difference between smokers and nonsmokers on the cognitive deficit variable, which was defined as a standard deviation decline of any of the 4 factors. Smokers showed a deficit rate of 36.2%, whereas nonsmokers showed a deficit rate of 36.6%.

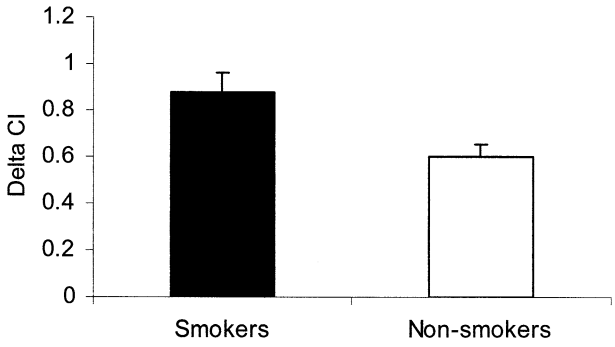

Fig 1. Univariate analysis of cognitive change at 6 weeks after coronary artery bypass graft surgery. A trend towards higher cognitive index in smokers ($p = 0.18$). Data expressed as mean (SEM).

Nonsmokers were significantly older and presented for surgery on average 6 years later than the smokers. Female sex represented a considerably larger proportion of patients in the nonsmoker group. Although the difference in baseline left ventricular ejection fraction was statistically significant between the 2 groups, clinically this difference was insignificant. All patients had left ventricular ejection fraction >40%. Smokers had a higher prevalence of myocardial infarction (Table 1).

The univariate analysis of cognitive change at 6 weeks showed a trend toward higher CI in smokers; however, when adjusted for age, baseline CI, and education years, there was no significant difference between the 2 groups (Fig 1 and 2).

Sex, history of myocardial infarction, hypertension, stroke and transient ischemic attack, and duration of CPB did not contribute to the multivariate logistic regression model and were dropped out from the final analysis. Significant multivariate predictors of neurocognitive dysfunction included age, left ventricular ejection fraction, baseline education level, and baseline cognitive index (Table 2).

The sample size of 417 patients (232 nonsmokers and 185 smokers) had 80% power to detect a difference in means of 0.36 or larger, assuming a common standard deviation of 1.3 and a 0.05 2-sided significance level.

DISCUSSION

This study of 417 patients undergoing primary elective CABG surgery has shown that smoking is not preventive of

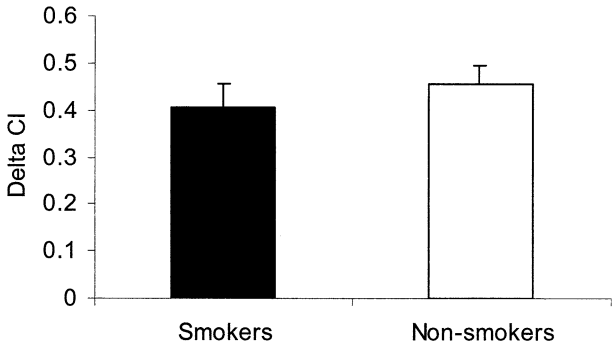

Fig 2. Means are adjusted for age, baseline CI, and education years. Data expressed as mean (standard error of the mean).

Table 2. Multivariate Predictors of Neurocognitive Dysfunction at 6 Weeks After CABG Surgery

Predictors	Parameter Estimate (F Value)	*p* Value
Smoking	0.03	0.86
Age	11.15	0.0009
LVEF	4.68	0.03
Years of education	3.85	0.05
Baseline CI	20.36	<0.0001

Abbreviations: LVEF, left ventricular ejection fraction; CI, cognitive index.

cognitive decline 6 weeks postoperatively. Although unadjusted means show that smokers tend to score higher than nonsmokers on the CI score, this trend is reversed after adjusting for age. The explanation for this trend is that smokers are presenting an average of 6 years younger for CABG surgery than nonsmokers, and age is an important factor in assessment of cognitive function.

The authors have shown that age, baseline cognitive index, left ventricular ejection fraction, and years of education are the most powerful predictors of neurocognitive decline at 6 weeks after CABG surgery. Advanced age has been previously recognized as an independent predictor of neurocognitive decline after cardiac surgery.[17,18] In contrast, Smith et al[19] followed a cohort of 381 patients who were stratified into 3 age groups: (1) less than 55, (2) 55 to 65, and (3) over 65 years old. Neurocognitive function was assessed with a standard battery of neuropsychologic testing at baseline and 1 month after cardiac surgery. The authors reported no significant difference in neurocognitive function with increasing age; however, a trend was observed with highest cognitive deficit rate in the over-65-year olds.[19] This study confirmed previous reports that age represents a considerable risk of perioperative neurocognitive dysfunction during both the short- and long-term follow-up periods.[1,4] In addition, it showed that patients with impaired cardiac function may be at increased risk for overall neurocognitive dysfunction after CABG surgery. These findings agree with the authors' previous reports[1,4,9] as well as studies by other investigators identifying predictors of neurocognitive decline after cardiac surgery.[18,19]

To compare cognitive function between smokers and nonsmokers, the authors assessed cognitive function by using a previously validated method of cognitive change.[4] A patient who scores 0 on factor 1 at baseline and a −1 on factor 1 at 6 weeks would be classified as having a cognitive deficit, independent of the patient's scores on factors 2, 3, or 4. This method allows a comparison of cognitive improvement and decline. The use of factor analysis decreases the chance of type I errors resulting from multiple testing. The use of a factor-loading system separates components of each individual test into the previously described domains, with all domains remaining consistent from baseline to 6-week follow-up testing, allowing for a direct comparison among each subject's baseline and follow-up domain scores using CI change.

Smoking has been implicated as an independent risk factor for the development of coronary artery disease and indirectly associated with increased risk of cerebral complications after cardiac surgery.[20-23] However, current evidence demonstrates that nicotine administration may be associated with neuronal protection.[6-8] The loss of cholinergic function in Alzheimer's disease is known to occur at an early stage in the disease. Furthermore, reduced cholinergic function has been found in both normal and Alzheimer's disease brain tissue in subjects with apolipoprotein E4 (APOE4) genotype, emphasizing the involvement of APOE4 in cholinergic decline.[24] Genetic basis of neurocognitive decline is currently an area of intense research. Patients with the APOE4 allele are more likely to be cognitively impaired after a stroke.[25] Previously, the authors reported that APOE4 was associated with cognitive decline at 6 weeks after CABG surgery.[26] However, the mechanism by which this occurs is unknown. Currently, the leading hypothesis is that APOE4 fails to protect and repair neurons of the central nervous system during cardiac surgery. It may be of further interest to investigate if APOE4 polymorphism influences neurocognitive outcome in smokers and nonsmokers after cardiac surgery.

The main limitation of this study relates to the retrospective design to evaluate the association between smoking and cognitive decline. However, Duke Neurocognitive and Cardiovascular Outcomes Databases contain a prospectively collected complete data set that provides an appropriate tool to analyze the association between smoking and cognitive decline. In addition, this study has adequate power to support the results. Although power and sample size considerations are always important issues when reporting a nonsignificant finding, the authors would like to emphasize that the means actually show a trend in the opposite direction that would be expected if cigarette smoking were neuroprotective.

A further limitation of this study is that cigarette smoking is a surrogate for cholinotherapy. The plethora of additives present in cigarettes may have negated the potential benefits of pure nicotine. In addition, patients were not exposed to nicotine during surgery or in the early postoperative period, which may have limited potential benefits of cholinotherapy perioperatively.

Quitting cigarette smoking produces minimal loss of chronic tolerance to nicotine. Furthermore, chronic tolerance is fully maintained for at least weeks after quitting smoking, and the sensitivity to nicotine's effects is not different as a function of years after quitting smoking.[27] These observations indicate that chronic tolerance to nicotine is not lost within several weeks of quitting smoking and may not change even after years of abstinence from tobacco use. Recent evidence suggests novel mechanisms through which preconditioning by nicotine and the desensitization of the major subtypes of acetylcholine receptors can modify neurotransmission and neuronal function by inhibiting apoptosis.[28] Furthermore, it is possible that chronic stimulation of nicotinic receptors exerts its effects beyond the cessation of smoking. It is interesting to note that nicotine mood-enhancing effects occur only after tolerance has been acquired to its primary adverse effects (ie, in chronic smokers).[29]

Several reports have addressed the issue of cognitive performance and nicotine administration in nonsmokers. Perkins et al[30] reported dose-dependent improvements in cognitive task

performance on a recognition memory task (and a finger-tapping task), and Foulds et al[31] reported improvement in performance on a task of sustained attention. Furthermore, it is known that nicotine antagonists such as mecamylamine can produce significant cognitive impairment in nonsmokers.[32,33] Further research is required to elicit if perioperative cholinotherapy has beneficial effects on neurocognitive function in nonsmokers undergoing cardiac surgery.

In conclusion, this study confirms the authors' previous findings that age, baseline cognitive function, years of education, and impaired left ventricular function are independent predictors of neurocognitive decline at 6 weeks after CABG surgery. Smoking is neither preventive nor causative of cognitive decline after CABG surgery.

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