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APOE-ε4 predisposes to cognitive dysfunction following uncomplicated carotid endarterectomy

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Abstract

Background: Between 9% and 23% of patients undergoing otherwise uncomplicated carotid endarterectomy (CEA) develop subtle cognitive decline 1 month postoperatively. The APOE-ε4 allele has been associated with worse outcome following stroke. *Objective:* To investigate the ability

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of *APOE*- ϵ 4 to predict post-CEA neurocognitive dysfunction. **Methods:** Seventy-five patients with CEA undergoing elective CEA were prospectively recruited in this nested cohort study and demographic variables were recorded. Patients were evaluated before and 1 month after surgery with a standard battery of five neuropsychological tests. *APOE* genotyping was performed by restriction fragment length polymorphism analysis in all patients. Neuropsychological deficits were identified by comparing changes (before to 1 month post-operation) in individual performance on the test battery. Logistic regression was performed for *APOE*- ϵ 4 and previously identified risk factors. **Results:** Twelve of 75 (16%) CEA patients possessed the *APOE*- ϵ 4 allele. Eight of 75 (11%) patients experienced neurocognitive dysfunction on postoperative day 30. One month post-CEA, *APOE*- ϵ 4 –positive patients were more likely to be cognitively injured (42%) than *APOE*- ϵ 4 –negative patients (5%) ($p = 0.002$). In multivariate analysis, the presence of the *APOE*- ϵ 4 allele increased the risk of neurocognitive dysfunction at 1 month 62-fold (62.28, 3.15 to 1229, $p = 0.007$). Diabetes (51.42, 1.94 to 1363, $p = 0.02$), and obesity (24.43, 1.41 to 422.9, $p = 0.03$) also predisposed to injury. **Conclusion:** The *APOE*- ϵ 4 allele is a robust independent predictor of neurocognitive decline 1 month following CEA.

Despite the fact that carotid endarterectomy (CEA) reduces the incidence of stroke in patients with high-grade carotid artery stenosis,¹⁻³ increasing evidence suggests that up to 28% of operated patients show significant neuropsychological dysfunction 1 day following CEA, with between 9% and 23% exhibiting continued cognitive decline 1 month postoperatively.⁴⁻⁶ Although the etiology of this cognitive injury is as yet poorly understood, controlled studies have excluded anesthesia as a culprit and have suggested that the injury is in part due to either cerebral hypoperfusion or microembolization of atheroma, thrombus, or gaseous bubbles as a result of carotid cross-clamping.^{5,7}

The apolipoprotein E (*APOE*)- ϵ 4 allele is a known risk factor for Alzheimer disease (AD) and is associated with worse outcome in traumatic brain injury in humans.⁸ In addition, the *APOE*- ϵ 4 allele has variably been associated with worse outcome following ischemic and hemorrhagic stroke in both rodents and humans.^{9,10} Although whether the *APOE*- ϵ 4 allele increases the risk of stroke is unclear, it has been associated with delayed cognitive impairment following cerebral ischemia.¹¹ Although early reports indicated that the *APOE*- ϵ 4 allele predisposes to worsened cognitive outcomes following cardiopulmonary bypass, recent studies have been unable to confirm this association.¹²

Given the large number of patients undergoing CEA in whom the benefit of the operation is statistically small due to extreme old age, borderline stenosis, or lack of cerebrovascular autoregulatory dysfunction,^{1,13-15} we sought to evaluate whether patients harboring the *APOE*- ϵ 4 allele were more likely to develop delayed neuropsychological dysfunction 1 month following CEA than patients lacking the *APOE*- ϵ 4 allele, thereby further defining the appropriate selection of surgical candidates while simultaneously shedding light on the potentially modifiable biologic mechanisms underlying this phenomenon.

Methods

Subjects

We performed a nested cohort study of 75 patients, all of whom gave informed consent for this institutional review board–approved study. These patients represent a subgroup of our previous larger study investigating the relationship between traditional stroke risk factors and post-CEA neurocognitive dysfunction who consented to genetic testing.⁶ Eligible patients were native English speakers with no history of drug abuse, axis I psychiatric disorders, or previous ipsilateral CEA. Patient demographic and intraoperative variables are presented in table 1. In

addition, 46 similarly educated and aged patients undergoing lumbar laminectomy with a comparable anesthetic regimen were contemporaneously recruited to serve as controls.

Treatment of patients during CEA and laminectomy

All patients received general anesthesia with routine monitoring as previously described.⁵ An intraoperative EEG was used for determining significant hemispheric ischemia during endarterectomy. Significant ischemia was defined as a decrease in spectral edge power $\geq 50\%$. Two patients were shunted based on this criterion.

Genotyping of APOE- $\epsilon 4$ allele

APOE genotyping was performed by restriction fragment length polymorphism analysis using DNA extracted from buffy coats of whole blood samples. DNA samples were amplified with PCR and digested with the appropriate restriction enzymes.¹⁶

Neuropsychometric evaluation

All patients were administered five standard neuropsychological (NPM) tests, (Boston Naming Test [BNT], Halstead-Reitan Trails parts A [Trails A] and B [Trails B], Controlled Oral Word Association Test [COWA], and the copy portion of the Rey Complex Figure test [Rey]) preoperatively and 1 month postoperatively, as previously described.^{4,5} This battery of neuropsychological tests offers a detailed assessment of higher cortical functioning.

Statistical analysis

Each preoperative and postoperative test was scored individually for both the enrolled CEA patients and the control group of 46 contemporaneous lumbar laminectomy (LL) patients. For each patient, a change score was calculated by determining the differences in preoperative and postoperative raw scores for each test. As previously described,⁵ each change score (one for each test) was converted to a Z score as follows: $Z \text{ score} = (\text{change score} - \text{mean change score}_{LL}) / \text{SD of change score}_{LL}$.

Z scores for each test per patient were then transformed into point scores according to the following method, as previously described:⁵ Z score greater than $-0.50 = 0$; Z score between -1.00 and $-0.50 = 1$; Z score between -1.50 and $-1.00 = 2$; Z score between -2.00 and $-1.50 = 3$; Z score between -2.50 and $-2.00 = 4$; Z score between -3.00 and $-2.50 = 5$; Z score less than $-3.00 = 6$.

For each patient, point scores were summed across all five tests to generate a total deficit score (TDS) that quantifies a patient's global level of cognitive decline. A higher TDS indicates a worse performance. CEA patients were considered injured if their TDS was greater than 2 SD above the mean performance of the control laminectomy patients ($\text{TDS} \geq 7$).

Univariate logistic regression was performed for *APOE- $\epsilon 4$* and the following previously validated risk factors for post-CEA neurocognitive dysfunction: obesity, age, diabetes mellitus, and weight-adjusted dose of midazolam.⁶ Hypertension, hypercholesterolemia, smoking, gender, symptomatic stenosis, previous myocardial infarction, operative side, duration of surgery, duration of carotid cross-clamping, use of statin medication, and weight-adjusted doses of fentanyl were not included as variables because no relationship was established between these risk factors and post-CEA neurocognitive dysfunction in our larger previously studied cohort.⁶ Those variables achieving univariate $p < 0.10$ were included in an age-adjusted multivariate analysis.

Results

Demographic and intraoperative variables of the 75 CEA patients are presented in table 1. No significant differences in mean age and years of education existed between the CEA and control groups (mean age of CEA cohort = 69.1 ± 8.5 years, mean age of control group = 70.9 ± 7.6 years; mean CEA cohort years of education = 14.5 ± 3.1 year, mean control group years of education = 14.7 ± 3.3 years). No significant differences between the *APOE*- $\epsilon 4$ –positive and *APOE*- $\epsilon 4$ –negative populations existed in any of the demographic and intraoperative variables recorded, including years of education. No statistical differences in baseline test scores existed except in the case of COWA, in which *APOE*- $\epsilon 4$ –positive patients had higher preoperative scores than $\epsilon 4$ –negative patients (table 1). Among those patients undergoing CEA, allele frequencies were as follows: $\epsilon 2$ (2.7%), $\epsilon 3$ (81.3%), and $\epsilon 4$ (16.0%). The frequency of the $\epsilon 4$ allele in our study was comparable to that observed in several healthy control populations and other large-scale population studies.^{17,18} Twelve CEA patients were carriers of the *APOE*- $\epsilon 4$ allele, and no patients were homozygous ($\epsilon 4/\epsilon 4$).

Eight (10.7%) CEA patients experienced neurocognitive dysfunction on postoperative day 30. *APOE*- $\epsilon 4$ –positive patients showed a higher percentage of neuropsychological injury compared to those who were not $\epsilon 4$ positive (5/12 [41.7%] *APOE*- $\epsilon 4$ positive vs 3/63 [4.8%] *APOE*- $\epsilon 4$ negative, $p = 0.002$, figure 1, A). *APOE*- $\epsilon 4$ carriers also had higher TDS when compared to *APOE*- $\epsilon 4$ noncarriers (4.75 ± 1.02 vs 2.33 ± 0.39 , $p = 0.02$). All *APOE*- $\epsilon 4$ carriers showed some decline in test scores in at least one cognitive domain (TDS >0), although 23.8% (15/63) of *APOE*- $\epsilon 4$ noncarriers experienced no decline in any test score (TDS = 0). The greatest differences in 30-day change scores between *APOE*- $\epsilon 4$ carriers and noncarriers were observed on the COWA test and Trails A. On average, the COWA change score of *APOE*- $\epsilon 4$ carriers was 8.0 points lower than that of *APOE*- $\epsilon 4$ noncarriers, corresponding to a difference in identification of eight words. The mean Trails A change score of *APOE*- $\epsilon 4$ carriers was 7.3 points greater than that of noncarriers, meaning that, relative to preoperative scores, *APOE*- $\epsilon 4$ carriers required 7.3 seconds longer to complete the test than noncarriers. In addition to the association with *APOE*- $\epsilon 4$, there was also greater frequency of postoperative neuropsychological dysfunction in patients with diabetes mellitus (26.3% vs 5.4%, $p = 0.02$ [figure 1B] and in obese [body mass index >30] patients (33.3% vs 6.3%, $p = 0.02$ [figure 1C]). In an age-adjusted multivariate analysis, *APOE*- $\epsilon 4$, diabetes, and obesity independently predicted neurocognitive dysfunction (table 2). *APOE*- $\epsilon 4$ –positive patients experienced a 62-fold increase in the risk of post-CEA cognitive injury (odds ratio [OR] 62.28, 95% CI: 3.16 to 1229, $p = 0.007$). Diabetes increased the risk of neurocognitive dysfunction more than 50 times (OR 51.42, 95% CI: 1.94 to 1363, $p = 0.02$), whereas obesity increased the risk nearly 25 times (OR 24.43, 95% CI: 1.41 to 422.9, $p = 0.03$). Age trended toward significance in multivariate analysis (OR 6.19 per decade, 95% CI: 0.82 to 47.12, $p = 0.08$).

Discussion

Although the incidence of major stroke following CEA is low (1 to 2%), the prevalence of more subtle post-CEA neurocognitive dysfunction is being increasingly recognized. Recent studies suggest that approximately 25% of CEA patients demonstrate declines in cognitive performance within 24 hours.^{4,5} Prior studies indicate that between 9% and 23% of these patients continue to demonstrate impaired cognition 30 days following surgery.^{5,6} Elevations of protein S100b, a marker of glial cell death, are associated with post-CEA cognitive decline, implicating subtle cerebral injury in the pathogenesis of this phenomenon.¹⁹ Postoperative neurocognitive dysfunction is also a well-established phenomenon following cardiac bypass (CABG), occurring in up to 79% of CABG patients.²⁰

We demonstrate that the presence of the *APOE*- ϵ 4 allele is an independent risk factor for neuropsychological dysfunction following CEA, increasing the risk 62 times in our cohort. The predictive ability of *APOE*- ϵ 4 was assessed in conjunction with four risk factors for post-CEA neurocognitive dysfunction that were identified by our previous larger scale study: obesity, diabetes, age, and weight-adjusted dose of midazolam.⁶ Aside from *APOE*- ϵ 4, diabetes mellitus (OR = 51.4) and obesity (OR = 24.4) remained independently predictive of neurocognitive decline. In multivariate analysis, neither variable negated the effect of the *APOE*- ϵ 4 allele on neuropsychological dysfunction.

This is the first study to show an association between a common apolipoprotein polymorphism and cognitive outcome following CEA. No significant educational differences existed between the *APOE*- ϵ 4 carriers and noncarriers in our cohort, excluding the possibility that differences in level of education between these two groups confound our results. In addition, baseline test scores between the ϵ 4-positive and ϵ 4-negative groups were similar, except in the case of COWA, in which *APOE*- ϵ 4 carriers displayed higher baseline scores. This demonstrates that those patients harboring the *APOE*- ϵ 4 allele performed, on average, as well as or better on our neuropsychometric battery than the ϵ 4-negative patients before CEA, but experienced increased rates of cognitive dysfunction post-CEA. There are nonsignificant trends for *APOE*- ϵ 4 carriers to be older and symptomatic. However, symptomatology did not predispose to cognitive dysfunction in our larger study,⁶ and because age is included in our multivariate model, the association of *APOE*- ϵ 4 and cognitive decline stands independent of age.

Our study is limited by small cohort sizes and a relatively narrow neuropsychometric battery that excludes memory testing. Despite these limitations, however, the association that we present between *APOE*- ϵ 4 and post-CEA neurocognitive decline is robust. Although the clinical significance of the subtle changes in cerebral function detected by our neuropsychometric battery has yet to be established, we are initiating a quality-of-life study to determine how these changes personally affect patients.

Although our previous work has examined the ability of traditional stroke risk factors to predict post-CEA neurocognitive dysfunction,⁶ no previous study has investigated whether genetic polymorphisms predispose CEA patients to cognitive insults. This finding suggests a genetic basis for subtle changes in cerebral function following CEA, implying that some patients may be predisposed to develop neuropsychological dysfunction after CEA. The preoperative identification of important risk factors may prove important in determining the real risk of operative intervention. We believe that future investigations are indicated to determine whether a subgroup of patients can be reliably identified for whom the benefits of CEA are small and the risk of post-CEA neurocognitive dysfunction is high. The additional cognitive risk conferred by the *APOE*- ϵ 4 allele may play a role in deciding whether to intervene in the 15% of CEA patients (25,000/year) operated for “borderline indications” and may aid in decisions regarding carotid stenting vs CEA.¹⁵

Although the *APOE*- ϵ 4 allele is a known genetic risk factor for AD²¹ and is associated with cognitive decline in large population studies,²²⁻²⁴ previous investigations have variably implicated that *APOE*- ϵ 4 allele in the pathogenesis of stroke. One such study demonstrated that stroke patients harboring the ϵ 4 allele had a 3-year stroke recurrence rate of 53%, compared to 16% of patients without the ϵ 4 allele (relative risk = 4.11).²⁵ Other groups, however, have been unable to demonstrate increased ischemic risk in ϵ 4-positive patients.²⁶ Investigations of the association between *APOE*- ϵ 4 and cognitive dysfunction following CABG have also yielded conflicting results.^{20,27}

Although it remains unclear whether the ϵ 4 allele elevates stroke risk, among patients experiencing a stroke, those with the ϵ 4 allele are more likely to suffer poststroke cognitive

decline and demonstrate a greater progression of cognitive dysfunction at follow-up.¹¹ Thus, in addition to playing a role in the development of neuropsychological dysfunction, the $\epsilon 4$ allele may play a biologic role in the ability to recover from neuropsychological injury suffered perioperatively. An isoform-dependent role of ApoE in neuronal regeneration has been widely suggested, with the $\epsilon 4$ protein believed to demonstrate a diminished capacity for regeneration.²⁸⁻³¹

Although data from these animal studies suggests that the effect ApoE may be mediated through alterations in amyloid precursor protein (APP) metabolism, lipid transport in regenerating neurons, proinflammatory cytokine release from activated microglia, increased blood-brain barrier permeability, and alterations in platelet function, the data presented here call for additional studies aimed at elucidating the mechanism by which ApoE $\epsilon 4$ contributes to cerebral dysfunction in this particular context. Given the reproducibility of the insult and resulting injury seen with CEA, mechanistic studies in this patient population are likely to have considerable implications for ApoE's role in other settings such as stroke, vascular dementia, and normal aging.

References

1. Ferguson GG, Eliasziw M, Barr HW, et al. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. *Stroke* 1999;30:1751–1758. [PubMed: 10471419]
2. Study ACA. Endarterectomy for asymptomatic carotid artery stenosis. *JAMA* 1995;273:1421–1428. [PubMed: 7723155]
3. Study ECftACA. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. *JAMA* 1995;273:1421–1428. [PubMed: 7723155]
4. Heyer E, Adams D, Todd G, et al. Neuropsychometric changes in patients after carotid endarterectomy. *Stroke* 1998;29:1110–1115. [PubMed: 9626280]
5. Heyer EJ, Sharma R, Rampersad A, et al. A controlled prospective study of neuropsychological dysfunction following carotid endarterectomy. *Arch Neurol* 2002;59:217–222. [PubMed: 11843692]
6. Mocco J, Wilson D, Komotar R, et al. Predictors of neurocognitive dysfunction following carotid endarterectomy. *Neurosurgery*. under review
7. Crawley F, Stygall J, Lunn S, Harrison M, Brown MM, Newman S. Comparison of microembolism detected by transcranial Doppler and neuropsychological sequelae of carotid surgery and percutaneous transluminal angioplasty. *Stroke* 2000;31:1329–1334. [PubMed: 10835452]
8. Horsburgh K, McCarron MO, White F, Nicoll JA. The role of apolipoprotein E in Alzheimer's disease, acute brain injury and cerebrovascular disease: evidence of common mechanisms and utility of animal models. *Neurobiol Aging* 2000;21:245–255. [PubMed: 10867209]
9. Woo D, Sauerbeck LR, Kissela BM, et al. Genetic and environmental risk factors for intracerebral hemorrhage: preliminary results of a population-based study. *Stroke* 2002;33:1190–1195. [PubMed: 11988589]
10. Mori T, Town T, Kobayashi M, Tan J, Fujita SC, Asano T. Augmented delayed infarct expansion and reactive astrogliosis after permanent focal ischemia in apolipoprotein E4 knock-in mice. *J Cereb Blood Flow Metab* 2004;24:646–656. [PubMed: 15181372]
11. Ballard CG, Morris CM, Rao H, O'Brien JT, Barber R, Stephens S, et al. APOE epsilon4 and cognitive decline in older stroke patients with early cognitive impairment. *Neurology* 2004;63:1399–1402. [PubMed: 15505155]
12. Robson MJ, Alston RP, Andrews PJ, Wenham PR, Souter MJ, Deary IJ. Apolipoprotein E and neurocognitive outcome from coronary artery surgery. *J Neurol Neurosurg Psychiatry* 2002;72:675–676. [PubMed: 11971065]
13. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. *Brain* 2001;124:457–467. [PubMed: 11222446]
14. Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the Medicare population: trial hospitals, volume, and patient characteristics. *JAMA* 1998;279:1278–1281. [PubMed: 9565008]

15. Halm EA, Chassin MR, Tuhim S, et al. Revisiting the appropriateness of carotid endarterectomy. *Stroke* 2003;34:1464–1471. [PubMed: 12738896]
16. Hixson JE, Vernier DT. Restriction isotyping of human apolipoprotein E by gene amplification and cleavage with HhaI. *J Lipid Res* 1990;31:545–548. [PubMed: 2341813]
17. Saunders AM, Strittmatter WJ, Schmechel D, et al. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. *Neurology* 1993;43:1467–1472. [PubMed: 8350998]
18. Kaprio J, Ferrell RE, Kottke BA, Kamboh MI, Sing CF. Effects of polymorphisms in apolipoproteins E, A-IV, and H on quantitative traits related to risk for cardiovascular disease. *Arterioscler Thromb* 1991;11:1330–1348. [PubMed: 1911720]
19. Connolly ES Jr, Winfree CJ, Rampersad A, et al. Serum S100B protein levels are correlated with subclinical neurocognitive declines after carotid endarterectomy. *Neurosurgery* 2001;49:1076–1083. [PubMed: 11846900]
20. Steed L, Kong R, Stygal J, Acharya J, et al. The role of apolipoprotein E in cognitive decline after cardiac operation. *Ann Thorac Surg* 2001;71:823–826. [PubMed: 11269459]
21. Saunders AM, Trowers MK, Shinkets RA, et al. The role of apolipoprotein E in Alzheimer's disease: pharmacogenomic target selection. *Biochim Biophys Acta* 2000;1502:85–94. [PubMed: 10899434]
22. Kuller LH, Shemanski L, Manolio T, et al. Relationship between ApoE, MRI findings, and cognitive function in the Cardiovascular Health Study. *Stroke* 1998;29:388–398. [PubMed: 9472879]
23. Bretsky P, Guralnik JM, Launer L, Albert M, Seeman TE. The role of APOE-epsilon4 in longitudinal cognitive decline: MacArthur Studies of Successful Aging. *Neurology* 2003;60:1077–1081. [PubMed: 12682309]
24. Dik MG, Jonker C, Comijs HC, et al. Memory complaints and APOE-epsilon4 accelerate cognitive decline in cognitively normal elderly. *Neurology* 2001;57:2217–2222. [PubMed: 11756600]
25. Kim JS, Han SR, Chung SW, et al. The apolipoprotein E epsilon4 haplotype is an important predictor for recurrence in ischemic cerebrovascular disease. *J Neurol Sci* 2003;206:31–37. [PubMed: 12480082]
26. Slooter AJ, Cruts M, Hofman A, et al. The impact of APOE on myocardial infarction, stroke, and dementia: the Rotterdam Study. *Neurology* 2004;62:1196–1198. [PubMed: 15079025]
27. Tardiff BE, Newman MF, Saunders AM, et al. Preliminary report of a genetic basis for cognitive decline after cardiac operations. The Neurologic Outcome Research Group of the Duke Heart Center. *Ann Thorac Surg* 1997;64:715–720. [PubMed: 9307463]
28. Ignatius MJ, Gebicke-Harter PJ, Skene JH, et al. Expression of apolipoprotein E during nerve degeneration and regeneration. *Proc Natl Acad Sci USA* 1986;83:1125–1129. [PubMed: 2419900]
29. Bellosta S, Nathan BP, Orth M, Dong LM, Mahley RW, Pitas RE. Stable expression and secretion of apolipoproteins E3 and E4 in mouse neuroblastoma cells produces differential effects on neurite outgrowth. *J Biol Chem* 1995;270:27063–27071. [PubMed: 7592957]
30. Nathan BP, Bellosta S, Sanan DA, Weisgraber KH, Mahley RW, Pitas RE. Differential effects of apolipoproteins E3 and E4 on neuronal growth in vitro. *Science* 1994;264:850–852. [PubMed: 8171342]
31. Nathan BP, Jiang Y, Wong GK, Shen F, Brewer GJ, Struble RG. Apolipoprotein E4 inhibits, and apolipoprotein E3 promotes neurite outgrowth in cultured adult mouse cortical neurons through the low-density lipoprotein receptor-related protein. *Brain Res* 2002;928:96–105. [PubMed: 11844476]

Figure.

Association of APOE-ε4, diabetes mellitus, and obesity with post-endarterectomy neurocognitive injury. (A) APOE-ε4 –positive patients experienced a 41.7% incidence of neurocognitive dysfunction compared to 4.8% among APOE-ε4 –negative patients ($p = 0.002$). (B) The rate of dysfunction was 26.3% among those with diabetes and 5.4% among those without diabetes ($p = 0.02$). (C) 33.3% of obese and 6.3% of nonobese patients experienced neurocognitive decline ($p = 0.02$).

Table 1
Demographic and intraoperative parameters of carotid endarterectomy patients

	All patients	<i>APOE</i> -ε4+	<i>APOE</i> -ε4-
No. of patients	75	12	63
Age, y	69.1 ± 8.5	71.1 ± 6.5	68.7 ± 8.8
Male	46 (61%)	9 (75%)	37 (59%)
Education, y	14.5 ± 3.1	15.0 ± 2.9	14.4 ± 3.1
Right side	42 (56%)	7 (58%)	35 (56%)
Diabetes mellitus	19 (25%)	3 (25%)	16 (25%)
Hypertension	46 (61%)	6 (50%)	40 (63%)
Symptomatic	35 (47%)	8 (67%)	28 (44%)
Prior MI	20 (27%)	4 (33%)	16 (25%)
Obesity	12 (16%)	3 (25%)	9 (14%)
Smoker	41 (55%)	8 (67%)	33 (52%)
Hypercholesterolemia	42 (56%)	8 (67%)	34 (54%)
Statin	43 (57%)	7 (58%)	36 (57%)
Duration of surgery	158.7 ± 42.6	143.3 ± 34.0	161.8 ± 43.7
Duration of cross-clamping	43.3 ± 16.1	40.2 ± 13.0	43.9 ± 16.6
Fentanyl	2.25 ± 1.04	1.81 ± 0.63	2.34 ± 1.09
Midazolam	0.035 ± 0.015	0.035 ± 0.011	0.035 ± 0.015
Shunt placement	2 (3%)	0 (0%)	2 (3%)
Baseline neuropsychometric test scores			
BNT	54.1 ± 4.1	54.7 ± 4.1	54.0 ± 4.1
COWA	44.6 ± 12.2	54.0 ± 10.7	42.9 ± 11.6
Rey	29.2 ± 4.7	28.2 ± 3.7	29.4 ± 4.8
Trails A	48.1 ± 17.9	50.2 ± 18.3	47.8 ± 17.9
Trails B	107.6 ± 46.3	121.2 ± 60.0	105.0 ± 43.4

Hypertension is defined as systolic blood pressure >140 or use of antihypertensive medication. Hypercholesterolemia is defined as blood cholesterol >200 or use of anticholesterol medication. *APOE*-ε4-positive patients had significantly higher baseline scores on the Controlled Oral Word Association test ($p = 0.003$). No other variables differed significantly between *APOE*-ε4-positive and -negative patients. Obesity is defined as body mass index >30. Continuous data are presented as mean ± SD.

MI = myocardial infarction; BNT = Boston Naming Test; COWA = Controlled Oral Word Association test; Rey = Rey Complex Figure copy portion; Trails A/B = Halstead-Reitan Trails parts A/B, respectively.

Table 2
Risk factors for post-CEA neurocognitive decline multivariate analysis

	OR	95% CI	p
Age	6.19	0.82–47.12	0.08
Diabetes mellitus	51.42	1.94–1363	0.02*
Obesity	24.43	1.41–422.9	0.03*
<i>APOE</i> -ε4+	62.28	3.16–1229	0.007*

OR is expressed in units of decades for age. No other variables met univariate $p < 0.10$ for inclusion in multivariate analysis. Obesity is defined as body mass index >30 .

CEA = carotid endarterectomy; OR = odds ratio.

*
 $p < 0.05$.