American Journal of Alzheimer's Disease & Other Dementias®
Volume 22 Number 3
June/July 2007 223-228

10.1177/1533317507299415
http://ajadd.sagepub.com
hosted at
http://online.sagepub.com

The Role of Apolipoprotein E in Cognitive Decline and Delirium after Bypass Heart Operations

Georgios I. Tagarakis, MD, Fani Tsolaki-Tagaraki, MD, Magdalini Tsolaki, MD, PhD, Anno Diegeler, MD, PhD, Nikolaos B. Tsilimingas, MD, PhD, Andreas Papassotiropoulos, MD, PhD

Cognitive decline and delirium are common complications after heart bypass surgery. Based on the reported role of the APOE-ε4 allele in neurodegenerative diseases, we studied its association with these complications. A neuropsychological test battery consisting of the Mini Mental State Examination, the Wechsler's Memory Scale Revised, the Brief Psychiatric Rating Scale, and the Delirium Rating Scale was applied to 137 APOE-genotyped patients on admission and 1 month after bypass surgery. We correlated the APOE (apolipoprotein E) polymorphism with the postoperative test outcome by taking into account all factors known to influence cognitive capacity after heart surgery. There was a significant decline in all test results 1 month after surgery and a high frequency of postoperative delirium. Neither this decline nor the frequency of delirium was associated with the APOE-ε4 allele. This study confirms the high incidence of cognitive decline and delirium after coronary surgery, but it does not support the role of the APOE-ε4 allele in the occurrence of these complications.

Keywords: CABG; neurocognitive deficits; dementia; genetics

Cognitive decline (CD) and postoperative delirium (PD) are commonly observed complications after coronary artery bypass surgery. Known risk or precipitating factors include age, previous stroke, internal carotid artery stenosis, peripheral arterial occlusive disease, diabetes mellitus, atrial fibrillation, left heart failure (ejection fraction < 30%), renal insufficiency, and urgent operation.[1,2] The above mentioned complications cause a significant increase in postoperative morbidity, average length of hospital stay, and treatment costs. Depending on the postoperative follow-up period, the incidence of CD lies between 33% and 83%[1] and that of PD between 8.4% and 32%.[2,3]

The ε4 allele of the APOE (apolipoprotein E) genotype is a well-established genetic risk factor for Alzheimer's disease and for related neurodegenerative disorders[4] and has been implicated in delayed and/or impaired recovery after intracerebral hemorrhage and close head trauma,[5-7] as well as in late posttraumatic seizures after the latter, with a relative risk up to 2.41.[8] The reported role of the APOE-ε4 allele in neuronal vulnerability has led to studies examining its putative association with cognitive deterioration after heart surgery. The results of these studies are contradictory and thus inconclusive.[9-13] The aim of the present study was to examine with a broader sample of patients the role of the APOE-ε4 in the occurrence of cognitive decline and, for the first time, of delirium after bypass heart surgery.

Herz- und Gefaess-Klinik, Rhoen Klinikum, Bad Neustadt a.d. Saale, Germany, Herz- und Gefaess- Klinik, Rhoen Klinikum, Bad Neustadt a.d. Saale, Germany, 3rd Department of Neurology, Aristotle University of Thessaloniki, Greece, Herz- und Gefaess-Klinik, Rhoen Klinikum, Bad Neustadt a.d. Saale, Germany, Cardiothoracic Department, University of Thessaly, Greece. Department for Psychiatric Research, University of Zurich, Switzerland.

Authors' Note: Expenses for the study were covered by the Swiss National Science Foundation (PPOOB-68859) and the Olga Mayenfisch Stiftung A.P. (not-for-profit organization). The authors have reported no conflicts of interest.

Please address correspondence to Georgios I. Tagarakis, Anaximandrou 24, 54250, Thessaloniki, Greece, Phone: 00302310326472; Fax: 00302310912645; E-mail: gtagarakis@hotmail.com.

Material and Methods

Patients

After obtaining ethics committee approval and written informed consent, we recruited 154 patients due to have planned coronary artery bypass surgery in the 6-month period between January and June 2004. Patients with severe hepatic disease, acute neuropsychiatric disorders, and/or serious problems of vision were excluded. The research was based on a consecutive series of study-eligible patients. From the potential recruitable number of patients (174) in the scheduled time period, 10 refused participation in the study, 7 had serious neuropsychiatric problems, 2 had liver insufficiency, and 1 had blindness. Genotypic and complete neuropsychological information (pre- and postoperative) was obtained from 137 patients (from the total number of 154 patients, 6 patients refused to be subjected to the follow-up tests, 6 could not be included in the genetic analysis owing to destruction of blood samples, and 5 patients died during or right after surgery).

Neuropsychological Battery

We applied a neuropsychological battery consisting of the Mini Mental State Examination (MMSE),[14,15] Wechsler Memory Scale Revised (WMS-R)[16,17] (in the standardized German form), Brief Psychiatric Rating Scale (BPRS),[18] and Delirium Rating Scale (DRS).[19] With these tests we aimed to control a wide range of neuropsychological characteristics, including recent and delayed verbal and visual memory, orientation in time and space, executional ability, stress, and depression. All tests were performed by the same examiner on admission and 1 month after surgery (patients suspected to develop delirium were examined with the DRS on any postoperative day). For better interpretation, following is some information about the test scoring scales: (1) the MMSE has a maximum score of 30 points; (2) the WMS-R has a total maximum score for all subtests of 318 points; (3) the BPRS has a total maximum pathological score of 168 points, with a minimum (normal) score of 24 points; (4) the DRS scoring scale ranges between 0 (normal) and 33 points (for a totally disorientated, hostile patient).

DNA Analysis

Standard DNA extraction was done from 9-mL EDTA tubes (Sarstedt, Germany), which were stored at -20°C. APOE genotyping was performed on the LightCycler (Roche Diagnostics, Basel, Switzerland), as described by Nauck et al.[20]

Surgery and Perioperative Management

The patients were premedicated the night prior to surgery with 10 mg to 20 mg of Tranxilium (dikalium clorazepate). On surgery day they were premedicated with 1 mg to 2 mg of Fluminoc. Main anesthesia was induced with 6 mg of Pancuronium, 2 mg to 3 mg of Midazolam, 0.2 mg to 0.3 mg of Fentanyl, and 15 mg to 20 mg of Etomidate. If necessary, narcosis was enhanced with sevoflurane (0.8% vol).

During surgery, the monitoring included measurement of the central venous pressure, 5-lead ECG, oxygen saturation, arterial blood gas analysis, arterial blood pressure measurement (both invasive and noninvasive), and controlling of the rectal temperature. To induce cardiac arrest, we used normothermic blood cardioplegia. The heart–lung machine was a type HL-20 Dideco machine with a membrane oxygenator.

Statistical Methods

In the statistical analysis, we checked for statistically significant differences between APOE-ε4 positive and negative groups concerning factors known to influence cognitive capacity after bypass heart operations. These factors are age, gender, years of education, preoperative test performance, duration of surgery, bypass time, aortic cross clamp time, diabetes,[21] atrial fibrillation, renal failure, heart insufficiency, and neurologic disease (Table 1). We used the x2 criterion for categorical parameters (gender) and the Student *t* test (unpaired) for continuous parameters. APOE-ε4 was the independent variable. The *t* test of paired samples was used to compare the neuropsychological test results pre- and postoperatively (within-patient difference). The analysis of variance (ANOVA) continuous measurements were used to control for statistically significant differences in postoperative test results between the 2 groups. As for the APOE-ε4 genotype, we defined as APOE-ε4 positive both homozygotic and heterozygotic ε4 patients (ε2ε4, ε3ε4, ε4ε4) and the rest as APOE-ε4 negative. In contrast to other studies which used arbitrary limits for cognitive decline,[22-24] we used within-subject cognitive decline as the dependent variable in the repeated measurements model.

Table 1. Patient Demographics and Risk Factors

	APOE-ε4 Noncarriers (n = 104)		APOE-ε4 Carriers (n = 33)		
	No.	%	No.	%	Statistics
Age (y)	70.1 ± 7.7		67.8 ± 7.4		NS
Female	29	27.9	9	27.3	NS
Education (y)	9.2 ± 1.1		9.2 ± 1.1		NS
No risk factors	31	41.9	10	47.6	NS
Diabetes mellitus	11	14.9	5	23.8	NS
Atrial fibrillation	9	12.2	2	9.5	n.s
Previous stroke, internal carotid artery stenosis	12	16.2	2	9.5	NS
Peripheral arterial occlusive disease	3	4.1	1	4.8	NS
Renal failure	3	4.1	-		NS
Multiple risk factors	5	6.8	1	4.8	NS
Operation time (min)	157 ± 38		163 ± 40		NS
By-pass time (min)	81 ± 24		81 ± 23		NS
Aortic cross-clamp time (min)	39 ± 15		42 ± 16		NS
Nadir temperature	31 ± 2		31 ± 2		NS
Ejection fraction (%)	57 ± 13		55 ± 12		NS
MMSE[a] (30)	27 ± 1		27 ± 2		NS
WMS-R[a] (318)	150 ± 12		142 ± 11		NS
Orientation[a] (14)	13.4 ± 1.3		13.2 ± 1.4		NS
Mental control[a] (6)	4.7 ± 0.8		4.4 ± 0.8		NS
Figural memory[a] (10)	5.7 ± 1.2		5.2 ± 1.1		NS
Logical memory[b] (50)	31.3 ± 2.9		30.4 ± 2.8		NS
Visual paired associates[b] (18)	7.1 ± 1.4		6.4 ± 1.4		NS
Verbal paired associates[b] (24)	9.5 ± 1.7		8.7 ± 1.7		NS
Visual reproduction[b] (41)	27 ± 5		24 ± 4		NS
Digit span[a] (24)	10.5 ± 1.5		10.1 ± 1.5		NS
Visual span[a] (26)	10.5 ± 1.6		10.1 ± 1.6		NS
Logical memory[c] (50)	30.9 ± 2.4		29.6 ± 2.2		NS
Visual paired associates[c] (6)	3.2 ± 0.5		3.1 ± 0.4		NS
Verbal paired associates[c] (8)	3.8 ± 0.7		3.4 ± 0.5		NS
Visual reproduction[c] (41)	26 ± 4		22 ± 4		NS

Note: The table shows patient demographics, preoperative neuropsychological test scores, and the incidence of risk factors known to influence cognitive function after heart surgery in both APOE-ε4 positive and negative patient groups. The x2 criterion was used for categorical parameters, the Student *t* test (unpaired) for continuous. Continuous variables are presented with means and standard deviations. The numbers in parentheses stand for the maximum possible test scores in the relating tests.

a. preoperative test

b. the first testing on several WMS-R subtests that need to be performed twice in the same session

c. the second testing on the above mentioned subtests

NS indicates not significant; MMSE, Mini Mental State Examination; WMS-R, Wechsler's Memory Scale Revised.

Results

There was no difference between the 2 groups with regard to demographic data and brain damage precipitating factors (Table 1). We noted a significant decline in all test results and a high frequency of postoperative delirium (41 patients, 29.92%) (Table 2), both with a female predominance. The statistically significant difference between male and female was $p < .05$ for CD and $p < .33$ for PD (female delirium frequency 31.57% vs. 29.29% male delirium frequency).

However, none of these complications could be statistically correlated with the APOE-ε4 genotype (Table 3).

Discussion

Neither the postoperative delirium nor the cognitive decline could be connected to the presence of the APOE-ε4 genotype, a result coinciding with the findings by Steed et al., Robson et al., and Askar et al. A

Table 2. Postoperative Cognitive Decline and Delirium Frequency

Test	Preoperatively	Postoperatively	*p* Value
MMSE	27.34 ± 1.65	26.50 ± 1.6	< .001
WMS-R	148.66 ± 11.9	141.23 ± 11.2	< .001
Orientation	13.38 ± 1.32	12.78 ± 1.23	< .001
Mental control	4.69 ± 0.83	4.07 ± 0.8	< .001
Figural memory	5.62 ± 1.2	4.95 ± 1.0	< .001
Logical memory 1	31.22 ± 2.88	30.80 ± 2.8	< .05
Logical memory 2	30.06 ± 2.35	30.02 ± 2.35	< .05
Visual paired associates 1	6.90 ± 1.37	3.18 ± 0.85	< .001
Visual paired associates 2	6.38 ± 0.65	2.86 ± 0.4	< .001
Verbal paired associates 1	9.35 ± 1.65	3.75 ± 0.45	< .001
Verbal paired associates 2	8.68 ± 0.65	3.48 ± 0.4	< .001
Visual reproduction 1	26.08 ± 4.48	24.81 ± 4.4	< .05
Visual reproduction 2	25.06 ± 4.26	24.32 ± 4.2	< .05
Digit span	10.43 ± 1.49	9.69 ± 1.44	< .05
Visual span	10.42 ± 1.63	9.71 ± 1.45	< .05
BPRS	26.92 ± 0.9	28.13 ± 1.3	< .05
DRS	–	41 delirious patients (29 male)	

Note: The table shows the findings of the statistical analysis with the *t* test of paired samples concerning the neuropsychological test results pre- and postoperatively. The increased mean score in the BPRS postoperatively shows a decline from the psychiatric-psychological aspect. MMSE indicates Mini Mental State Examination; WMS-R, Wechsler's Memory Scale Revised; BPRS, Brief Psychiatric Rating Scale; DRS, Delirium Rating Scale.

Table 3. Relation of APOE-ε4 Genotype to Postoperative Cognitive Decline and Delirium

Test	APOE-ε4 Noncarriers	APOE-ε4 Carriers	Statistical Significance
MMSE	3.055 ± 0.6	3.125 ± 0.6	NS
WMS-R	5.05 ± 0.75	4.80 ± 0.65	NS
Orientation	4.30 ± 0.35	5.04 ± 0.5	NS
Mental control	13.15 ± 1.2	13.39 ± 1.4	NS
Figural memory	11.80 ± 1.25	12.32 ± 1.25	NS
Logical memory1	1.34 ± 0.12	1.34 ± 0.14	NS
Logical memory 2	0.13 ± 0.005	0.14 ± 0.005	NS
Visual paired associates 1	53.94 ± 5.6	53.81 ± 5.6	NS
Visual paired associates 2	55.17 ± 7.1	55.15 ± 6.95	NS
Verbal paired associates 1	59.89 ± 8.2	59.87 ± 8.2	NS
Verbal paired associates 2	59.90 ± 8.2	59.91 ± 8.3	NS
Visual reproduction 1	4.75 ± 0.55	5.23 ± 0.64	NS
Visual reproduction 2	2.95 ± 0.2	2.97 ± 0.2	NS
Digit span	7.09 ± 0.9	7.12 ± 0.9	NS
Visual span	6.76 ± 0.9	6.96 ± 0.95	NS
BPRS	4.49 ± 0.6	4.49 ± 0.6	NS
DRS	31 delirious patients	10 delirious patients	NS

Note: The table shows the decline (in percentages) in postoperative test results and the frequency of the postoperative delirium in correlation with the absence or presence of the APOE-ε4 allele. NS indicates not significant; MMSE, Mini Mental State Examination; WMS-R, Wechsler's Memory Scale Revised; BPRS, Brief Psychiatric Rating Scale; DRS, Delirium Rating Scale.

different conclusion was drawn in the studies by Tardiff et al. and Lelis et al. In agreement with frequencies observed in previous studies,[9,10] 33 (24.1%) patients were identified as APOE-ε4 carriers. This frequency also matches the known APOE-ε4 genotype frequency in the German population.[25]

We were motivated to search for the role of the APOE-ε4 genotype in neurological injury after coronary artery surgery, also based on its known role in patients with Alzheimer's disease. We have to note that the age and gender characteristics of our sample were quite different than that of the Alzheimer's patients, whose mean age is much older (highest distribution over the 80s), and where the female to male distribution is 2:1.[26]

The aetiology of PD and CD seems to be multifactorial, including micro- and macroembolism and reduction of cerebral perfusion during surgery.[27-30] The role of other genetic factors possibly influencing postoperative neurologic outcome has yet to be researched. In this direction, the study of lipid-related polymorphisms other than APOE-ε4, which are also involved in the pathology of the central nervous system, can be proven useful.

Comparison with Similar Studies

In this study we included a larger sample of patients than were included in the previous similar studies.[9-13] The patients in this studies were examined with a comparable or broader neuropsychological battery (Table 4). To the best of our knowledge, the present study is

Table 4. Basic Characteristics of Studies Dealing with APOE-ε4 Genotype and Cognitive Decline after Bypass Heart Surgery

Study	Association of Cognitive Decline to APOE-ε4	Follow-up Exams Postoperatively	No. of Patients	Tests of Neuropsychiatric Battery
Tagarakis et al.	Negative	1 month	137	MMSE, BPRS, DRS, WMS-R
Tardiff et al.	Positive	6 wk	65	Trail Making Test B (Wechsler Advanced Intelligence Scale Revised, or WAIS-R), Digits Forward, Digits Backward, Digit Symbols, Delayed Components of the Randt Short Story Memory Test, Benton Visual Retention
Steed et al.	Negative	4-7 wk	111	Trail Making Test A and B (WAIS-R), Grooved Pegboard, Symbol Digit, Nonverbal Memory, Letter Cancellation, Rey and Choice Reaction Time
Robson et al.	negative	3 mo	86	Trail Making Test A and B (WAIS-R), Paced Auditory Serial Addition Task, Auditory Verbal Learning Test
Lelis et al.	positive	24 h, sixth day	87	MMSE, Glascow Coma Scale
Askar et al.	negative	discharge, 3 mo	78	Cognistat

Note: The table shows the basic characteristics of studies (including the present one) dealing with cognitive decline after bypass heart surgery. MMSE indicates Mini Mental State Examination; WMS-R, Wechsler's Memory Scale Revised; BPRS, Brief Psychiatric Rating Scale; DRS, Delirium Rating Scale.

also the only study dealing with delirium after bypass heart operations and APOE polymorphisms. As far as the postoperative decline is concerned, we think that with a high level of statistical security, the results are conclusive. Based on the fact that the decline was present in all subtests with p values much smaller than .05 and that the examinees had the advantage of acquaintance with the tests in the repeated examination postoperatively, we believe that this decline, although it may not be permanent, is clinically significant.

Regarding the length of follow-up, we can state that this particular time setting (1 month postoperatively) was chosen because it coincides with, or is very close to, the time of discharge from rehabilitation centers, which are visited by the vast majority of surgery patients in Germany, where the study was performed. This practically means that we aimed to control the mental status of cardiac surgery patients just before they return without direct medical supervision to "society" and their usual activities. At this point we must emphasize the fact that our patients received no standard analgesic or sedative treatment after the day of discharge (from the tenth to the fourteenth day); thus, a pharmacologic influence to the postoperative test results can be excluded.

References

1. Newman MF, Croughwell ND, Blumenthal JA, et al. Predictors of Cognitive Decline After Cardiac Operation. *Ann Thorac Surg*. 1995;59:1326-1330.
2. Bucerius J, Gummert JF, Borger MA, et al. Predictors of delirium after cardiac surgery: effect of beating-heart (off-pump) surgery. *J Thorac Cardiovasc Surg*. 2004;127: 57-64.
3. Rolfson DB, Mac Elhaney JE, Rockwood H, et al. Incidence and risk factors for delirium and other adverse outcomes in older adults after coronary artery bypass graft surgery. *Can Jour Cardiol*. 1999;15:771-776.
4. Huang W, Qiu C, von Straus E, Winblad B, Fratiglioni L. APOE genotype, family history of dementia, and Alzheimer's disease risk: a 6-year follow-up study. *Arch Neurol*. 2004;61:1930-1934.
5. Nicoll J, Roberts G. Graham D. Apolipoprotein E epsilon 4 allele is associated with deposition of amyloid beta- protein following head injury. *Nat Med*. 1995; 1:135-137.
6. Sorbi S, Nacmias B, Piacentini S. Apolipoprotein E genotypes and outcome after posttraumatic coma. *Neurology*. 1996;46:A307.
7. Alberts MJ, Graffagnino C, McClenny C, et al. APOE genotype and survival from intracerebral hemorrhage. *Lancet*. 1995;346:575.

8. Diaz-Arrastia R, Gong Y, Fair, S, et al. Increased risk of late posttraumatic seizures associated with the inheritance of APOE ε4 allele. *Arch Neurol*. 2003;60:818-822.
9. Tardiff BE, Newman MF, Saunders AM, et al. Preliminary report of a genetic basis for cognitive decline after cardiac operations. *Ann Thorac Surg*. 1997;64:715-720.
10. Steed L, Kong R, Stygall J, et al. The role of Apolipoprotein E in Cognitive Decline after Cardiac Operation. *Ann Thorac Surg*. 2001;71:823-826.
11. 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.
12. Lelis RG, Krieger JE, Pereira AC, et al. Apolipoprotein E4 genotype increases the risk of postoperative cognitive dysfunction in patients undergoing coronary artery bypass graft surgery. *J Cardiovasc Surg (Torino)*. 2006;47:451-456.
13. Askar FZ, Cetin HY, Kumral E, et al. Apolipoprotein E epsilon 4 allele and neurobehavioral status after on-pump coronary artery bypass grafting. *J Card Surg*. 2005; 20:501-505.
14. Folstein MF, Folstein SE, MacHugh RR. Mini Mental State: a practical method for grading the state of patients for the clinician. *J Psychiatr Res*. 12:189-198.
15. Kessler J, Markowitsch HJ, Denzler P. *Der Mini Mental Status Test*. Weinheim, Germany: Beltz Verlag; 1990.
16. Wechsler D. *Wechsler Memory Scale Revised*. San Antonio, Tx: The Psychological Corporation 1987- Harcourt Brace Jovanovich; 1987.
17. Haerting C, Markowitsch HJ, Neufeld H, Calabrese P, Deisinger K, Kessler J. *Wechsler Gedaechtnis Test- Revidierte Fassung (WMS-R)*. Bern: Huber; 2000.
18. Ventura MA, Green MF, Shaner A, Liberman RP. Training and quality assurance with the brief psychiatric rating scale: "The drift buster." *Int J Methods Psychiatr Res*. 1993;3:221-244.
19. Trzepacz PT, Baker RW, Greenhouse J. A symptom rating scale for delirium. *Psychiatry Res*. 1988;23:89-97.
20. Nauck M, Hoffmann MM, Wieland H, Marz W. Evaluation of the APOE genotyping kit on the Light Cycler. *Clin Chem*. 2000;46:722-724.
21. Bucerius J, Gummert JF, Walther T, et al. Impact of Diabetes Mellitus on Cardiac Surgery Outcome. *Thorac Cardiovasc Surg*. 2003;51:11-16.
22. Mahanna EP, Blumenthal JA, White WD, et al. Cognitive Decline and Cardiac Operation. *Ann Thorac Surg*. 1996; 61:1342-1347.
23. Savagneau JA, Stanton BA, Jenkins CD, Frater RW. Neuropsychological dysfunction following elective cardiac operation. II: A six- month reassessment. *J Thorac Cardiovasc Surg*. 1982;84:595-600.
24. Stump DA. The effect of age on neurologic outcome after cardiac surgery. *Anesth Analg*. 1992;74:S310.
25. Schiefermeier M, Kollegger H, Niadl C, et al. The impact of apolipoprotein E genotypes in age and onset of symptoms and phenotypic expression in Wilson's Disease. *Brain*. 2000;123:585-590.
26. Hendrie HH. The epidemiology of Alzheimer's disease. *Am J Geriatr Psychiatry*. 1998;65:3-18.
27. Sellman M, Holm L, Ivert T, Semb BKH. A randomized study of neuropsychological function in patients undergoing coronary bypass surgery. *Thorac Cardiovasc Surg*. 1993;41:349-354.
28. Taggart DP, Westaby S. Neurological and cognitive disorders after coronary artery bypass grafting. *Curr Opin Cardiol*. 2001;16:271-276.
29. Harrison MJ. Neurological complications after bypass grafting: diffuse or focal ischemia? *Ann Thorac Surg*. 1995;59:1356-1358.
30. Clark RE, Brillman J, Davis DA, Lorell MR, Price TR, Magovern GJ. Microemboli during coronary artery bypass grafting. Genesis and effect on outcome. *J Thorac Cardiovasc Surg*. 1995;109:249-257; discussion 257-258.