Effect of Apolipoprotein E Genotype on Cerebral Autoregulation During Cardiopulmonary Bypass

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Background and Purpose—The presence of the apolipoprotein E ε4 (apoE4) allele has been associated with cognitive decline after cardiac surgery. We compared autoregulation of cerebral blood flow (CBF), cerebral metabolic rate for oxygen (CMRO$_2$), and arterial–venous oxygen content difference [C(A-V)O$_2$], during cardiopulmonary bypass (CPB) in patients with and without the apoE4 allele to help define the mechanism of association with cognitive decline.

Methods—One hundred fifty-four patients underwent coronary artery bypass grafting with CPB, nonpulsatile flow, and α-stat management. CBF was measured by using $^{133}$Xe washout methods. C(A-V)O$_2$, CMRO$_2$, and oxygen delivery were calculated. Pressure-flow autoregulation was tested by using 2 CBF measurements at stable hypothermia: the first at stable mean arterial pressure (MAP) and the second 15 minutes later, when MAP had increased or decreased $\pm 20\%$.

Results—In patients with (n=41) or without (n=113) the apoE4 allele, there were no differences in CBF, CMRO$_2$, C(A-V)O$_2$, pressure-flow and metabolism-flow autoregulation corrected for age, gender, non–insulin-dependent diabetes, hemoglobin, CPB time, and temperature.

Conclusions—We conclude that apoE genotype does not affect global CBF and oxygen delivery/extraction during CPB, which suggests that other mechanisms are responsible for the apoE isoform–related neurocognitive dysfunction seen in patients undergoing CPB. (Stroke. 2001;32:1514-1519.)

Key Words: apolipoproteins ■ autoregulation ■ cerebral blood flow

Apolipoprotein E (apoE) alters outcome after cerebral injury in an isoform-specific manner. Specifically, the apoE ε4 (apoE4) allele appears to be independently associated with greater neurological dysfunction following central nervous system injuries, such as closed head injury, nonaneurysmal intracerebral hemorrhage, and thromboembolic stroke. In a preliminary report from our research group (Neurological Outcomes Research Group of the Duke Heart Center), it was suggested that apoE genotype may also play a role in the cognitive dysfunction commonly seen after cardiopulmonary bypass (CPB). However, the mechanism by which this occurs is not clear. Potential etiologies include apoE-specific effects on cerebral blood flow (CBF), altered responses to neuronal injury, modulation of the inflammatory response, cerebral metabolic decline, and increased cerebral microemboli secondary to increased atheroma burden.

The pathogenesis of Alzheimer’s disease, which has been the subject of intense research in the last decade, has provided some clues. While more than 40 putative risk factors for the development of Alzheimer’s disease have been reported, a majority of these risk factors have been shown to hold an association with a reduction in CBF. It has even been hypothesized that CBF reduction is a necessary cofactor for the development of Alzheimer’s disease. Late-onset and sporadic Alzheimer’s disease has also been closely related to the apoE4 allele, and that, in turn, has been associated with hypoperfusion of the temporal, parietal, and occipital cortices of Alzheimer’s patients. Preservation of CBF and oxygen delivery is critically important during CPB, a period associated with low systemic flows, lack of pulsatility, and hemodilution. Although the subject of considerable debate, intraoperative hypotension may be associated with as much as a 30% incidence of postoperative neurological deficits.

The purpose of this study was to determine whether patients with the apoE4 allele experience a greater decrease in CBF during CPB. In addition, we assessed autoregulation of CBF in response to changes in mean arterial pressure (MAP) and metabolism, in the presence of the apoE4 allele. Finally, we compared the effect of the apoE4 allele on cerebral arterial-venous oxygen content difference during rewarming from hypothermic CPB, the period during which patients are most vulnerable to inadequate cerebral oxygen delivery.

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Subjects and Methods

After obtaining Institutional Review Board approval and written informed consent, 154 patients undergoing elective coronary artery bypass grafting (CABG) surgery were studied. Patients with a history of cerebrovascular disease, insulin-dependent diabetes, psychiatric illness, renal disease, active liver disease, and those with less than a seventh-grade education were excluded. Before induction of anesthesia, catheters were placed in a radial artery and the right jugular bulb, retrograde through the right jugular vein, for simultaneous sampling of systemic arterial and jugular venous bulb blood, respectively. Continuous arterial blood pressure, central pressure (central venous or pulmonary artery) and temperature (nasopharyngeal, bladder) monitoring was used in all patients. All hemodynamic data were stored for subsequent retrieval using Arkive (DiaTek Inc), an automated anesthesia information system.

Patient Management

Anesthetic induction and maintenance with midazolam, fentanyl, and vecuronium was standardized with a computer assisted continuous infusion (CACI) technique as previously described.13 The perfusion apparatus consisted of a Cobe CML oxygenator (Cobe Laboratories), a Sarns 7000 max pump (Sarns Inc), and a Pall SP 3840 arterial line filter (Pall Biomedical Products Co). Nonpulsatile perfusion of 2 L·min⁻¹·m⁻² was maintained throughout the study periods. The pump was primed with crystalloid solution designed to achieve a hematocrit of 0.18 during CPB, with packed red blood cells added when necessary to reach the desired hematocrit. Arterial inflow was administered through an ascending aortic cannula, with venous drainage via a dual-stage cannula in the right atrium. Arterial CO₂ tension was maintained throughout CPB at 35 to 40 mm Hg in all patients. The perfusate circuit of the pump oxygenator, as previously validated and described,16 was consistent with the expected frequency of the apoE4 allele were compared by using the Wilcoxon rank sum test for continuous measures and Fisher exact test for categorical attributes. CBF and C(A\textsubscript{V})\textsubscript{O\textsubscript{2}} were compared and used to determine apoE allele frequencies, as previously described.10 For the current analysis, homozygote and heterozygote carriers of the apoE4 allele were grouped together and compared with patients without any apoE4 allele.

Physiological Measurements

CBF was measured using \(^{133}\text{Xe}\) (3 mCi dissolved in 3 mL sterile saline solution) administered into an injection port of the arterial perfusate circuit of the pump oxygenator, as previously validated and described.14 Two extracranial, cardiac tefludium detectors with wide-angle collimators were placed over the right and left temporal lobes, and the average of the 2 values was used to determine CBF. CBF was calculated by a modification of the initial slope index methods described by Olesen et al15:

\[
\text{CBF (mL·100 g}^{-1}\text{·min}^{-1}) = (-\text{slope}) \times \lambda \times 100,\]

where slope is the slope of the natural logarithm of the count rate during the first minute of the \(^{133}\text{Xe}\) washout curve obtained by linear regression and \(\lambda\) is the temperature- and hematocrit-corrected blood-brain partition coefficient.

Blood was drawn from the radial artery and jugular bulb catheters for determination of hemoglobin, pH, oxygen tension, and oxygen saturation 1 minute after \(^{133}\text{Xe}\) injection. Arterial-venous oxygen content difference [C(A−V)\textsubscript{O\textsubscript{2}}], cerebral metabolic rate for oxygen (CMRO\textsubscript{2}), and oxygen delivery were calculated as described previously.15 Four sets of measurements were performed (all during CPB): the first on inception of CPB at normothermia (36°C), twice at stable hypothermia (28°C to 32°C), and after rewarming to 36°C. The last normothermic value was compared with the previous hypothermic value (at a similar perfusion pressure) to describe the metabolism-flow autoregulation.

Only those patients in whom PaCO\textsubscript{2}, PaO\textsubscript{2}, and pump flow were within the defined ranges were entered into the evaluation of autoregulation. Patients with a change in nasopharyngeal temperature >1°C between the 2 hypothermic determinations of CBF were excluded from analysis owing to the major confounding effect of temperature and temperature-related changes in metabolism on CBF.16 ApoE genotyping, from peripheral blood samples collected preoperatively and stored at 4°C before processing, was performed by a technician blinded to group assignment. Genomic DNA was prepared and used to determine apoE allele frequencies, as previously described.10 For the current analysis, homozygote and heterozygote carriers of the apoE4 allele were grouped together and compared with patients without any apoE4 allele.

Assessment of CBF Autoregulation

Pressure-flow autoregulation was evaluated by measuring the relationship of MAP to CBF at 2 different pressures. Arterial blood pressure was controlled with phenylephrine and nitroprusside infusions. Once stable hypothermia was achieved, the first set of measurements was made and repeated 15 minutes later after either increasing or decreasing the MAP by at least 20% from the initial measurement. Metabolism-flow autoregulation was determined by describing the relationship of CBF to CMRO\textsubscript{2} at 2 different temperatures at least 4°C apart. CBF and CMRO\textsubscript{2} were calculated at baseline (36°C), at hypothermia (28°C to 32°C), and again after rewarming to 36°C. The new normothermic value was compared with the previous hypothermic value (at a similar perfusion pressure) to describe the metabolism-flow autoregulation.

Statistical Methods

Differences between the groups of patients with or without the apoE4 allele were compared by using the Wilcoxon rank sum test for continuous measures and Fisher exact test for categorical attributes. CBF and C(A−V)\textsubscript{O\textsubscript{2}} were compared between groups at each measurement time with the Wilcoxon rank sum test. Association of apoE4 with pressure-flow autoregulation was evaluated with multiple linear regression, using change in CBF between the 2 hypothermic measurement times as the dependent variable and testing change in MAP as the independent variable. The interaction between change in MAP and apoE4 status was also included in the model, testing whether apoE4 presence affected the pressure-flow relationship. A backward stepwise variable selection method was used to account for possible covariable effects of age, gender, hemoglobin, non–insulin-dependent diabetes, time on CPB, and temperature, potentially influential factors identified in a previous study.17 Metabolism-flow autoregulation was studied in a similar manner, utilizing the change in CBF from hypothermia to rewarmed normothermia and substituting change in CMRO\textsubscript{2} for change in MAP as the independent variable. \(P < 0.05\) was considered significant.

Results

One hundred and fifty-four patients undergoing CABG surgery with CPB were enrolled in this study. Forty-one of these patients (27%) carried at least 1 apoE4 allele. This percentage was consistent with the expected frequency of the apoE4 allele in large population studies.18 Two of the 41 patients were homozygote for the apoE4 allele. Patient demographics including age, sex, prevalence of non–insulin-dependent diabetes, CPB time, cross-clamp time, and years of education, were similar between groups (Table 1, \(P = \text{NS}\)).
Ninety-one patients met the criteria for evaluation of pressure-flow and metabolism-flow autoregulation. There was no difference in the relationship of change in CBF to change in MAP between the group of patients with or without the apoE4 allele, after accounting for possible covariable effects of age, gender, hemoglobin, non–insulin-dependent diabetes, time on CPB, and temperature (Figure 1). Overall, CBF did not change in response to changes in MAP, signifying preserved autoregulation, but CBF expectedly increased in response to an increase in CMRO2. After correcting for age, gender, hemoglobin, non–insulin-dependent diabetes, and time on CPB, the slope of change in CBF to change in CMRO2 was, however, not influenced by the presence of the apoE4 allele (Figure 2). At rewarming, there was no difference in CMRO2 between patients with or without the apoE4 allele.

The changes in C(A−V)O2 difference and CBF from normothermia to hypothermia and rewarming for patients with and without the apoE4 allele are represented graphically in Figure 3. With the induction of hypothermia, both C(A−V)O2 difference and CBF declined significantly in both groups. The apoE4 allele had no affect on CBF and C(A−V)O2 difference at any measurement point after correction for the covariables defined above. Of particular significance is the similarity in the C(A−V)O2 curves during rewarming.

In a finding of no difference between groups, it is important to determine the smallest difference that would have been considered statistically significant. A post hoc sensitivity (power) analysis based on the results of this study and the unequal e4 group sizes showed that our analysis had 80% power to detect a difference between groups in the change in CBF of 2.47 mL·100 g−1·min−1 after adjustment for effects of change in MAP and other significant covariates. Furthermore, to determine that the difference of 0.63 mL·100 g−1·min−1 observed in our study between e4 groups is statistically significant, a total sample size of 1367 would have been required. With respect to e4 group differences in CMRO2 and C(A−V)O2 at rewarming, we had 80% power to detect a difference of 0.183 mL/min in CMRO2 and 0.80 mL/dL in C(A−V)O2 adjusted for significant covariables, whereas we observed a difference of 0.085 mL/min in CMRO2 and 0.02 mL/dL in C(A−V)O2.
Discussion

In this study with sufficient power to detect a clinically significant effect, we found no evidence that the presence of the apoE4 allele altered CBF during CPB. Autoregulation of CBF in response to changes in both MAP and metabolism was preserved. In particular, during rewarming, differences in cerebral arterial-venous oxygenation were not altered by the presence of the apoE4 allele. Therefore, it appears unlikely that the apoE4 allele exerts any detrimental effect on CBF and oxygen delivery during CPB. In addition, the worsened cognitive outcome demonstrated in apoE4 patients compared with non-apoE4 patients cannot be explained by apoE4-mediated changes in CBF or autoregulation.

The role of cerebral hypoperfusion in neurological injury during CPB is uncertain. While there are some data showing that prolonged hypotension may lead to cerebral injury,12 it is generally accepted that there is a tremendous amount of “luxury perfusion” during CPB.11 Several studies investigating the effects of perfusion pressure, principally determined by MAP, on CBF during CPB found that autoregulation was preserved and CBF remained relatively stable within a wide range of MAP (20 to 100 mm Hg), so long as pH and arterial carbon dioxide were kept constant.19–21 Furthermore, hypothermia confers additional protection by lowering the metabolic and flow requirements of the central nervous system.16 Studies for the most part have failed to correlate systemic flows, which presumably have a direct impact on CBF, to postoperative stroke and other adverse neurological outcomes.22 A recent, large retrospective study failed to demonstrate any advantage of maintaining a higher MAP during CPB in reducing the incidence of perioperative strokes, even in high-risk patients.23

Cerebral hypoperfusion, a prominent feature of Alzheimer’s disease, has been hypothesized to be a primary pathophysiological mechanism behind this disease.8 It has also become clear that the presence of the apoE4 allele in patients with Alzheimer’s disease, at least in the homozygous form, significantly affects the degree of cerebral hypoperfusion demonstrated directly by radiological means and indirectly by studying glucose uptake.3,24,25 However, in a recent study of apoE-deficient mice, Sheng et al26 demonstrated that while apoE deficiency worsens ischemic outcome, it has no effect on CBF at baseline and at 5 minutes after the onset of and 30 minutes after reperfusion from 10 minutes of forebrain ischemia. Thus apoE, by itself, may have minimal, if any, effects on CBF. This is in agreement with our study of patients undergoing CABG surgery with CPB, where we have demonstrated that the presence of the apoE4 allele has no effect on CBF during CPB.

Autoregulation is generally well preserved during CPB and is not affected by advancing age.11,17 It is, however, adversely affected in insulin-dependent diabetic patients undergoing CPB, and its failure has been touted as the reason for the higher incidence of neurocognitive deficits seen in diabetic patients.27 In patients without insulin-dependent diabetes undergoing CPB, it appears that both pressure-flow and metabolism-flow autoregulation are unaffected by the presence of the apoE4 allele.

If cerebral hypoperfusion is involved in the genesis of neurological injury during CPB, it may have its most profound effect during the rewarming phase. Rewarming has been shown to be associated with decreased jugular bulb saturations, a predictor of adverse neurological outcome.28,29 Any hypoperfusion or loss of autoregulation during this period would lead to a mismatch between oxygen delivery and the heightened cerebral metabolic demands brought about by the rise in temperature. The central nervous system compensates for any shortfall of oxygen supply by increasing the amount of oxygen extraction, which appears as a widened cerebral arterial-venous oxygen content difference. A widened C(A–V)O2 is prominent in diabetic patients, and to a lesser extent the aging patient, undergoing CPB.17,27 The current study, however, suggests that the presence of the apoE4 allele does not change cerebral oxygen delivery and/or extraction during CPB.

Limitations to our study include the fact that we only demonstrated preservation of global cerebral flow and autoregulation in patients with the apoE4 allele. The methods used in our study are not sensitive enough to detect regional flow abnormalities. However, because CBF and CMRO2 remained well coupled and the C(A–V)O2 difference during rewarming was not affected by the presence of the apoE4
allele, a clinically significant regional defect likely did not occur. Second, the apoE4 gene dose may play a significant role in modifying our results. It is possible that effects visible only in the homozygous carriers were masked by our combination of heterozygous and homozygous carriers into one group and by the small number of homozygous carriers present in the study. Third, because cerebral flow is intimately related to cerebral metabolism, disturbances of cerebral metabolism similar to that seen in patients with Alzheimer’s disease may have influenced cerebral flow. However, the apoE4 allele does not appear to be an independent determinant of cerebral metabolism and does not affect the activity of cytochrome oxidase (complex IV). The enzyme of the oxidative phosphorylation pathway affected in Alzheimer’s disease.

In conclusion, the mechanism by which the apoE4 allele contributes to the neurocognitive dysfunction commonly seen after CPB still remains uncertain. It may well be that the apoE4 allele magnifies the detrimental effects of CPB, perhaps by altering neuronal repair, affecting neuronal susceptibility to injury, increasing atherosclerotic embolic load, or failing to modulate or perhaps even potentiating the inflammatory response to CPB. Although it is attractive to subscribe to a common mechanism for apoE4-associated Alzheimer’s disease and post-CPB neurocognitive dysfunction, our study demonstrates that global cerebral perfusion and autoregulation are generally intact in patients with the apoE4 allele.

Appendix

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for the C.A.R.E. Investigators

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