Apolipoprotein E Polymorphism
Survival and Neurological Outcome After Cardiopulmonary Resuscitation

M. Schiefermeier, PhD; H. Kollegger, MD; C. Madl, MD; C. Schwarz, MSc; M. Holzer, MD; J. Kofler, MD; F. Sterz, MD

Background and Purpose—The apolipoprotein E 3/3 (apoE 3/3) genotype is associated with a reduced risk of developing Alzheimer’s disease and with a favorable neurological outcome after traumatic head injury. In vitro studies suggest that the most common genotype, apoE 3/3, may be involved in neuroprotective and neuroregenerative mechanisms. The aim of this study was to determine whether the apoE 3/3 genotype has an impact on survival and neurological outcome after cardiopulmonary resuscitation.

Methods—Eighty patients with cardiac arrest were investigated prospectively for their apoE genotype. Epidemiological data were assessed according to recommended guidelines. Patients were divided into 2 groups, ie, with the apoE 3/3 genotype present or absent, and tested for differences in survival and neurological outcome. Further statistical analysis with respect to survival and neurological outcome was performed by using a stepwise logistic regression analysis.

Results—Patients with the apoE 3/3 genotype had a significantly higher survival rate (64% versus 33%, \( P = 0.007 \)) and more often a favorable neurological outcome (55% versus 27%, \( P = 0.013 \)) compared with patients with other apoE genotypes. The apoE 3/3 genotype was shown to be a substantial predictive factor for a favorable neurological outcome (odds ratio 3.2) and was, apart from other essential factors, predictive for survival (odds ratio 4.4) after cardiopulmonary resuscitation.

Conclusions—These data give evidence that patients with the apoE 3/3 genotype have a better chance of recovery after cardiopulmonary resuscitation than do patients with apoE genotypes other than 3/3. (Stroke. 2000;31:2068-2073.)

Key Words: apolipoproteins E ■ heart arrest ■ polymorphism ■ resuscitation ■ stroke outcome

The prognosis of patients after cardiopulmonary resuscitation (CPR) due to cardiac arrest essentially depends on the length of time until circulation is restored. Additional factors such as epidemiological, etiological, and metabolic parameters as well as the characteristics of medical treatment of CPR have been investigated with the intention to predict the outcome after CPR.1–7 Moreover, various imaging and electrophysiological techniques, such as computed tomography, magnetic resonance imaging, single-photon emission computed tomography, and sensory evoked potentials, are applied for an early evaluation of brain damage after ischemia.8 In contrast, our knowledge of the influence of genetic factors on neurological recovery is sparse.

The cessation of blood flow induces ischemic cell damage and a complex cascade of postischemic injury. Several organs can withstand complete ischemia for a prolonged time because initial cell damage is low and the ability to repair and regenerate tissue is relatively pronounced, whereas the brain is most susceptible to ischemic damage and has a very limited potential to regenerate. An essential component of nerve regeneration is apolipoprotein E (apoE), which serves as the major carrier of cholesterol, cholesterol esters, and lipids in the nervous system. It has been proposed that apoE production is stimulated by nerve injury to preserve the integrity of cell membranes.9,10 Moreover, it has been shown that apoE-deficient knockout mice have a worse neurological outcome after cerebral ischemia than do wild-type mice.11 The polymorphic structure of the human apoE gene in particular gave rise to intensive investigation of apoE. Two point mutations of the human apoE gene cause 3 apoE isoforms (apoE 2, apoE 3, and apoE 4) and consequently, 6 apoE genotypes. Initially, the apoE e4 allele was identified as a risk factor for the development of Alzheimer’s disease.12 Recently, it has been shown that patients with the predominant, homozygous apoE 3/3 genotype have a better neurological outcome after traumatic head injury13–16 as well as a later onset of neurological symptoms in Wilson disease than do patients with other apoE genotypes.17 The molecular basis of these observations is unclear, but the hypothesis that apoE 3 contributes to regenerative mechanisms more efficiently than do other apoE proteins appears likely.
ApoE polymorphism may have a decisive influence on the outcome after CPR. Therefore, we attempted to clarify whether patients with the apoE 3/3 genotype have (1) a better neurological outcome and (2) a higher survival rate after CPR compared with patients with other apoE genotypes (apoE non-3/3).

Subjects and Methods

Patients and Design

Eighty patients (15 women, 65 men) admitted to the Department of Emergency Medicine, University of Vienna, Austria, were investigated prospectively from July 1998 to June 1999. All patient data, including neurological outcome as the primary outcome measure, were assessed without knowledge of the patients’ apoE genotypes. The procedures followed were in accordance with the ethical standards of the responsible institutional committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 1983. Patient selection criteria were set to avoid the investigation of patients with neurological symptoms from causes other than cessation of circulation or of patients with an interruption of blood flow to an extent that did not allow them to survive.

Included were adults of all ethnic origins with a witnessed, nontraumatic, normothermic cardiac arrest of presumed cardiac or pulmonary origin. Patients were excluded from the study when the duration of cardiac arrest was >20 minutes and when primary CPR failed to achieve any return of spontaneous circulation within 60 minutes. Furthermore, we excluded patients with known malignancy, pregnancy, and unfavorable overall and/or cerebral performance before cardiac arrest.

Epidemiology and Laboratory Measurements

Epidemiological data were assessed according to the recommended guidelines (Utstein style) for uniform documentation of cardiac arrest.14 Data were obtained through interviews with the ambulance physicians, paramedics, bystanders, and family. The recording of periods of time during cardiac arrest is an estimate and cannot be determined accurately. Owing to the fact that only 1 person was responsible for collecting the patients’ charts according to the Utstein style, highly comparable data were available for every patient. Personal interviews of the witnesses served to reduce inaccuracy concerning the time of recognition of collapse and the period of emergency medical activation.

Patient protocols included location (within the hospital or out of hospital); presumed etiology (cardiac or pulmonary causes) of collapse of the circulation; the initial rhythm, referring to the first recorded electrocardiographic activity (ventricular fibrillation or asystole and pulseless electrical activity); a detailed time protocol of collapse of the circulation (time to return of spontaneous circulation, no-flow time, and low-flow time); the number of defibrillations; and the cumulative amount of epinephrine administered during resuscitation. No-flow time was defined as the period from collapse of the circulation until the beginning of basic and/or advanced life support. Low-flow time was defined as the interval from the beginning of basic and/or advanced life support until the return of spontaneous circulation or termination of resuscitative efforts. Finally, the duration until the first meaningful reactivity to phonics, visual, or tactile stimulation, and in the case of death within 6 months, the interval until death, were determined. Age, sex, and typical laboratory parameters such as blood pH, plasma lactate, and plasma glucose were determined in each patient after admission to the Emergency Clinic. The apoE genotype was determined by a common polymerase chain reaction technique previously described.19 In brief, DNA was isolated from peripheral blood samples with a commercially available DNA isolation kit (Purgene, Gentra Systems). Thereafter, a 228-bp fragment of the apoE gene was amplified by polymerase chain reaction with the use of specific primers. The amplified product was cleaved with CfoI. Mutation-specific fragments were then visualized with ethidium bromide after separation by vertical polyacrylamide gel electrophoresis. ApoE genotype was determined by the genotype-specific fragment pattern.

Neurological Outcome and Survival

Neurological outcome was assessed on the basis of the cerebral performance categories (CPCs) after 6 and 12 hours; on days 1, 2, and 7; and at months 1 and 6. CPC is based on the Glasgow overall performance categories20 and is defined as follows: CPC 1, conscious and alert, with normal function or only slight disability; CPC 2, conscious and alert with moderate disability; CPC 3, conscious with severe disability; CPC 4, comatose or in a persistent vegetative state; and CPC 5, brain death. The main primary outcome measure was the best-ever-achieved CPC within 6 months. A CPC of 1 or 2 was assigned a “good neurological outcome”; a best-ever-achieved CPC >2 within 6 months was assigned a “bad neurological outcome.” Patients who died within 6 months were classified as nonsurvivors.

Statistical Analysis

Patients were divided into 2 groups: apoE 3/3, patients homozygous for the apoE ε3 allele, and apoE non-3/3, patients with the genotypes apoE 4/3, apoE 2/3, apoE 4/4, apoE 4/2, and apoE 2/2. The software package SPSS for Windows, version 8.0, was used for statistical analysis. After confirmation of a normal distribution, we tested for differences in mean values of normal data between the 2 groups with Student’s t test and in differences of nonnormal, continuous data with the Mann-Whitney rank-sum test. Continuous data are summarized by mean±SD. Nominal data are given as frequencies and were compared with continuity-corrected χ² tests or Fisher’s exact tests when expected cell frequencies were <5. Generally, P values <0.05 were considered statistically significant. For multivariate stepwise regression analysis, patients were divided according to outcome variables into those with good or bad neurological outcomes and those who survived or died. We tested for differences between these groups with univariate methods (t test, Mann-Whitney rank-sum test, and χ² analysis of contingency tables). Variables causing a difference in the outcome variable at P<0.1 according to the univariate analysis were included for a stepwise backward logistic regression. Variables with a log-likelihood ratio of P>0.05 were excluded stepwise until each remaining variable was statistically significant. The effect of every significant model parameter is given by its odds ratio.

Results

Eighty of 208 patients who were admitted to the Department of Emergency Medicine, University of Vienna, from July 1998 to June 1999 were included in this investigation. Inclusion was prevented mainly by the following facts: unwitnessed cardiac arrest, time to return of spontaneous circulation >60 minutes or no-flow time >20 minutes, and cerebral or other unknown cause of cardiac arrest. Forty-four percent of our patients were assigned a good neurological outcome, and 51% survived.

The apoE genotype frequency of our 80 patients did not deviate from known apoE genotype frequencies of healthy Europeans.21–23 Fifty-nine percent had the apoE 3/3 genotype; 30%, apoE 3/4; 6%, apoE 2/3; 3%, apoE 4/2; 1%, apoE 4/4; and 1%, apoE 2/2 genotype. Consequently, 47 patients were assigned to the group of the predominant apoE 3/3 genotype and the other 33 patients were assigned to the group non-apoE 3/3 genotype.

Patients of both groups were afflicted by a collapse of the circulation to a comparable extent, were in similar physiological condition, and underwent the same emergency support procedures. Neither age nor sex nor any of the laboratory parameters such as blood pH, plasma lactate, and plasma
TABLE 1. Epidemiological and Laboratory Data, Initial Rhythm, Treatment, and Time Protocol During CPR in Patients With Different ApoE Genotypes

<table>
<thead>
<tr>
<th>Variable</th>
<th>ApoE 3/3</th>
<th>ApoE Non-3/3</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>54±12</td>
<td>58±16</td>
<td>t=1.32 P=0.19</td>
</tr>
<tr>
<td>No. of men</td>
<td>40</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>No. of women</td>
<td>7</td>
<td>8</td>
<td>P=0.29</td>
</tr>
<tr>
<td>Blood pH</td>
<td>7.19±0.18</td>
<td>7.25±0.16</td>
<td>U=688 P=0.39</td>
</tr>
<tr>
<td>Plasma lactate, mmol/L</td>
<td>9.6±4.0</td>
<td>8.7±3.7</td>
<td>t=1.05 P=0.30</td>
</tr>
<tr>
<td>Plasma glucose, mmol/L</td>
<td>14.5±5.2</td>
<td>14.7±5.8</td>
<td>t=0.11 P=0.92</td>
</tr>
<tr>
<td>Cardiac arrest within the hospital, n</td>
<td>6</td>
<td>3</td>
<td>x²=0.23</td>
</tr>
<tr>
<td>Cardiac arrest out of hospital, n</td>
<td>41</td>
<td>30</td>
<td>P=0.88</td>
</tr>
<tr>
<td>Cardiac arrest with basic life support, n</td>
<td>17</td>
<td>9</td>
<td>x²=0.70</td>
</tr>
<tr>
<td>Cardiac arrest without basic life support, n</td>
<td>30</td>
<td>24</td>
<td>P=0.40</td>
</tr>
<tr>
<td>Cardiac arrest due to cardiac causes, n</td>
<td>40</td>
<td>29</td>
<td>x²=0.00</td>
</tr>
<tr>
<td>Cardiac arrest due to pulmonary causes, n</td>
<td>7</td>
<td>4</td>
<td>P=0.98</td>
</tr>
<tr>
<td>Initial rhythm: ventricular fibrillation, n</td>
<td>36</td>
<td>21</td>
<td>x²=1.59</td>
</tr>
<tr>
<td>Initial rhythm: asystole or pulseless electrical activity, n</td>
<td>11</td>
<td>12</td>
<td>P=0.21</td>
</tr>
<tr>
<td>No. of defibrillations</td>
<td>3±3</td>
<td>4±4</td>
<td>t=0.84 P=0.40</td>
</tr>
<tr>
<td>Epinephrine administered, mg</td>
<td>3±4</td>
<td>3±3</td>
<td>t=0.17 P=0.87</td>
</tr>
<tr>
<td>Time to return of spontaneous circulation, min</td>
<td>21±16</td>
<td>20±12</td>
<td>t=0.36 P=0.72</td>
</tr>
<tr>
<td>Low-flow time, min</td>
<td>17±15</td>
<td>14±10</td>
<td>t=0.83 P=0.41</td>
</tr>
<tr>
<td>No-flow time, min</td>
<td>5±5</td>
<td>6±6</td>
<td>t=1.16 P=0.25</td>
</tr>
<tr>
<td>First meaningful reactivity, d</td>
<td>5±6</td>
<td>10±10</td>
<td>t=1.97 P=0.06*</td>
</tr>
</tbody>
</table>

Data are given as number of patients in each category or as mean±SD of 47 patients with the apoE 3/3 genotype (*n=29) and 33 patients with the apoE non-3/3 genotype (*n=13).

Glucose concentrations were different in patients with the apoE 3/3 genotype in comparison with those with other apoE genotypes (Table 1). Similarly, no differences were found in the frequencies of collapses of the circulation within the hospital or out of hospital, the frequency of resuscitation initiated with basic life support, the frequency of ventricular fibrillation as the initial rhythm, and cardiac or pulmonary etiology. In addition, no-flow time, low-flow time, and time to return of spontaneous circulation as well as the emergency procedures applied were similar in both groups (Table 1).

The distributions of good versus bad neurological outcome and of survivors versus nonsurvivors in patients with the apoE 3/3 genotype and in those with a different apoE genotype are given in Table 2. Patients with the apoE 3/3 genotype more often achieved a good neurological outcome than did patients with other apoE genotypes (P=0.013). The duration until the first period of permanent consciousness was shorter in patients with the apoE 3/3 genotype than in patients with other genotypes (Table 1), although statistical significance was not reached (P=0.06). In addition, the rate of survival was greater in patients with the apoE 3/3 genotype than in patients with other genotypes (P=0.007).

Because apoE 4 has been implicated in neurodegenerative diseases, the proportion of patients with a poor neurological outcome and with an apoE ε4 but without an apoE ε2 allele (and vice versa) was of interest. Therefore, we analyzed the data in more detail by disregarding those patients with the apoE 4/2 genotype and dividing the rest of the group of apoE non-3/3 patients into those with the apoE 3/4 or the apoE 4/4 genotype and those with the apoE 2/3 or the apoE 2/2 genotype. In brief, 28% of the patients with the apoE 3/4 or the apoE 4/4 genotype (P=0.027) and 17% of the patients with the apoE 2/3 or the apoE 2/2 genotype (P=0.100) achieved a good neurological outcome compared with 55% of the patients with the apoE 3/3 genotype. Similarly, 36% of the patients with the apoE 3/4 and apoE 4/4 genotypes (P=0.024) and 17% of the patients with the apoE 2/3 and apoE 2/2 genotypes (P=0.071) survived compared with 64% of the patients with the apoE 3/3 genotype. Although the number of patients with apoE ε2 and no apoE ε4 allele was too small to reach statistical significance in this separate analysis, these data strongly suggest that the presence of both alleles is unfavorable for patients outcome.

Logistic regression analysis for neurological outcome (good, CPC 1 to 2; unfavorable, CPC 3 to 5) initially included the following parameters: a constant, cardiac arrest within or out of the hospital; initial rhythm; the cumulative amount of...
epinephrine administered; time to return of spontaneous circulation; no-flow time; blood pH and lactate concentration on admission; and presence or absence of the apoE 3/3 genotype. The final model parameters are given in Table 3. The parameter "cardiac arrest within or out of the hospital" was the last parameter removed from the model (P of log-likelihood ratio=0.066). Independent, significant, predictive parameters were the cumulative amount of epinephrine administered, the initial rhythm, and the apoE 3/3 genotype. The relative chance (odds ratio) of having a good neurological outcome increased 3.5-fold when the patient had the apoE 3/3 genotype and decreased by 0.74-fold per milligram of epinephrine administered. Patients with an initial ventricular fibrillation had a 5.3-fold relative chance for a good neurological outcome compared with patients with asystole or pulseless electrical activity. Therefore, the type of initial rhythm, the apoE genotype, and the cumulative amount of epinephrine administered were essential, independent determinants of neurological recovery.

Logistic regression analysis for general outcome (survival or death) initially included the following parameters: a constant, cardiac arrest within or out of the hospital; initial rhythm; the cumulative amount of epinephrine administered; time to return of spontaneous circulation; no-flow time; cardiac or pulmonary etiology of cardiac arrest; age; and the presence or absence of the apoE 3/3 genotype. The final model parameters are given in Table 3. Independent, significant, predictive parameters for survival were cardiac arrest within or out of the hospital, the cumulative amount of epinephrine administered, cardiac or pulmonary causes of cardiac arrest, age, and the apoE 3/3 genotype. The chance of survival increased 12.9-fold when a patient was afflicted with cardiac arrest within the hospital, 8.3-fold when the cause of cardiac arrest was cardiac rather than pulmonary, and 4.4-fold when the patient had the apoE 3/3 genotype and decreased by 0.81-fold per milligram of epinephrine administered and by 0.96-fold per year of age.

Discussion
This investigation provides strong evidence that the apoE polymorphism is correlated with the outcome of patients after CPR. Among the parameters that we evaluated, the predominant apoE 3/3 genotype was identified as an important predictive factor for favorable neurological recovery after cardiac arrest. Moreover, approximately two thirds of the patients with the apoE 3/3 genotype survived, whereas two thirds of the patients with other apoE genotypes died within 6 months, which clearly demonstrates that patients with the apoE 3/3 genotype have a better chance to survive.

Despite considerable improvement in the treatment of cardiac arrest, many resuscitated patients suffer from the consequences of irreversible damage to the nervous system. Although reinstallation of the circulation with the least possible delay is most important in preventing persistent neurological damage, many other factors may influence the patients’ neurological outcomes. We were interested in whether a genetic factor in patients with early and adequate treatment of cardiac arrest had an impact on their neurological outcome and survival rate. Therefore, this study was designed to investigate the influence of the apoE genotype in well-characterized patients without a considerably prolonged cerebral impairment before cardiac arrest. These selection criteria may also explain the relatively good outcome of our patients and may limit the observations of this study to patients who meet these selection criteria.

The outcome of patients with cardiac arrest can be predicted by various parameters. The identification of essential, singular observations is hampered by the fact that 1 parameter may be reflected in part by another. For example, in witnessed cases of cardiac arrest, most probably basic or advanced life support takes place early, resulting in a short no-flow time. A short no-flow time is regarded as highly predictive of survival. We attempted to identify the most reliable predictive parameters that described the outcome of our patients best through a transparent procedure for both models. Therefore, we included factors in the multivariate analysis in the order of their univariate test significance and excluded them from the model when they did not strictly contribute to the prediction of outcome in the multivariate analysis.
model. In this study, the time to return of spontaneous circulation was correlated with the amount of epinephrine administered, which can be explained by the fact that prolonged CPR usually requires application of higher doses of epinephrine. However, the amount of epinephrine administered appeared to be a better predictor of neurological outcome, as well as survival, than did the time to return of spontaneous circulation. Apart from the presence of the apoE 3/3 genotype, ventricular fibrillation was highly predictive of a good neurological outcome. It has been argued that in patients with ventricular fibrillation, a small amount of perfusion is present. In contrast to the model for neurological outcome, the absence of ventricular fibrillation as the initial rhythm was not as crucial for survival. Young patients with the apoE 3/3 genotype, a low cumulative amount of administered epinephrine, and a cardiac etiology of cardiac arrest appear to have had an increased chance for survival. Eight of 41 survivors had a poor neurological outcome, whereas only 2 of 35 patients with a good neurological outcome died within 6 months. Obviously, progress in medical treatment enables survival after CPR in some cases but unfortunately, not neurological recovery when the central nervous system is injured beyond a certain extent.

ApoE, the major apolipoprotein of the nervous system, plays a central role in the mobilization and distribution of cholesterol, cholesterol esters, and other lipid structures. ApoE expression increases substantially after injury of nervous tissue, and apoE concentration is elevated in the cerebrospinal fluid of patients with neurological diseases. It has been proposed that apoE is secreted locally by macrophages, astrocytes, and oligodendrocytes in response to nerve degeneration to initiate cholesterol-phospholipid recycling. ApoE synthesis is stimulated by oxidized LDLs in macrophages. In the absence of apoE, as in the case of apoE-knockout mice, survival rate and neurological recovery are markedly reduced after cerebral ischemia. In addition, these mice are more susceptible to oxidative stress, as shown by increased plasma and lipoprotein lipid peroxidation. In vitro studies have shown that apoE itself protects against peroxidative stress by mechanisms that may involve the binding of certain metals, thus blocking the generation of cytotoxic radicals.

The intention of this study was to investigate the influence of apoE polymorphism on neurological outcome after CPR, because several lines of evidence had indicated that the extent of neurorepair, neuroregeneration, and neuroprotection depended on the apoE isotypes present. ApoE 3 is the most common apoE isoform. Homozygosity for apoE 3 in humans reduces the risk for the development of late-onset dementia of the Alzheimer type, which may protect against early vascular morbidity, is associated with a better neurological outcome after head trauma and intracerebral hemorrhage, and delays the onset of neurological symptoms in Wilson disease. Human apoE 3–transgenic mice recover better from focal ischemia than do human apoE 4–transgenic mice. Moreover, in vitro investigations have revealed that apoE 3 promotes axonal sprouting. Humans with an apoE ε4 allele show mild hypercholesterolemia and have lower apoE plasma concentrations. In contrast to apoE 3, the presence of the apoE ε4 allele favors the development of Alzheimer’s disease and has a negative impact on the effects of the in vivo and in vitro parameters in the investigations mentioned above. The role of apoE 2 has not yet been clarified. Most studies have not investigated or focused on the apoE ε2 allele because of its rare occurrence, and other studies have produced conflicting results. ApoE 2 is associated with a reduced risk for the development of Alzheimer’s disease. Although the presence of an apoE ε2 allele has favorable effects on the lipid profile and cardiac disease, it may also be a risk factor for promoting microangiopathy-related cerebral damage. ApoE 2 acts as an antioxidant in vitro. Nevertheless, heterozygous apoE 2 patients with Wilson disease develop neurological signs of early copper toxicity. In the present study, patients with at least 1 apoE ε2 as well as patients with at least 1 apoE ε4 allele had a poor neurological outcome and a lower survival rate after CPR compared with patients homozygous for the apoE ε3 allele. Therefore, it can be suggested that our results are in part a reflection of the reduction or absence of the apoE 3 isoform and are not exclusively caused by the presence of the potentially neurodegenerative apoE 4 isoform. Nonetheless, for a better understanding of apoE genotype–specific effects, further studies based on a larger number of subjects as well as further investigations with molecular biological techniques are required. Among other parameters, the singular effects of each isoform should be investigated by focusing on apoE 3 homozygous patients and the extremely rare homozygous genotypes apoE 4/4 and apoE 2/2.

The results of this study identify apoE as a genetic factor modulating outcome after CPR. Although independent studies have elucidated some biochemical allele-specific effects of the apoE gene, the molecular basis of our results is still unclear. Further investigations are required to answer the question of whether the neuroprotective and neuroregenerative properties of apoE can be exploited for therapeutic purposes. We conclude that patients with the apoE 3/3 genotype may benefit from their genetic background during their recovery after cardiac arrest.

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References


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