Magnetic Resonance Imaging Findings Associated With Cardiac Arrest

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Background and Purpose: The frequency and prognostic significance of neuroradiological findings after cardiac arrest are unknown. Using healthy volunteers as control subjects, we studied the magnetic resonance imaging (MRI) findings associated with cardiac arrest, adjusted for confounding factors.

Methods: The presence of cerebral infarcts, leukoaraiosis, atrophy, and edema on ultra-low-field MRI was assessed in 58 community volunteers and 52 cardiac arrest survivors enrolled in a placebo-controlled, randomized, double-blind trial of nimodipine in out-of-hospital ventricular fibrillation.

Results: Cardiac arrest was an independent risk factor for the presence of infarcts in a logistic regression model adjusted for age, sex, and history of myocardial infarction, stroke, coronary heart disease, cardiac failure, and hypertension (odds ratio, 3.6; 95% confidence interval, 1.3 to 9.9; P=.01). Leukoaraiosis was associated with increasing age but not with cardiac arrest. Adjusted for age, the delay of advanced life support had an inverse correlation with the degree of atrophy in placebo-treated patients (r = -.62, P < .0001) but not in patients treated with nimodipine (r = -.10, P = .43). Lack of age-related atrophy, possibly implicating the presence of brain edema, predicted poor outcome after cardiac arrest (odds ratio, 4.6; 95% confidence interval, 1.4 to 15.8; P = .01).

Conclusions: Cardiac arrest was associated with deep cerebral infarcts but not with leukoaraiosis. MRI findings did not predict the functional outcome at 1 year. Nimodipine treatment had no significant effect on the MRI findings, but delayed resuscitation was associated with probable brain edema only in placebo-treated patients. (Stroke 1993;24:1005-1014)

Key Words: cerebral infarction • heart arrest • magnetic resonance imaging • nimodipine

Cardiac arrest (CA) followed by resuscitation is a combination of complete and incomplete global ischemia. As spontaneous circulation has been restored, multifocal hypoperfusion syndrome may result, depending on the severity and duration of ischemia as well as other hemodynamic factors.1-5 It is not known whether multifocal hypoperfusion can lead to completed infarction. Only a few neuroimaging studies have addressed either functional or structural aspects of human CA, and no controlled magnetic resonance imaging (MRI) studies have been published.3-8

Cerebral hypoperfusion of cardiac origin, especially in association with hypotension caused by cardiac failure or by arrhythmias, has been suggested as one of the underlying mechanisms of leukoaraiosis.9-11 Therefore, both watershed infarcts and leukoaraiosis might be expected to result from CA and resuscitation. To determine whether the victims of CA would have more cerebral infarcts, leukoaraiosis, or other pathological findings on MRI than would control subjects, we carried out a comparative study on survivors of out-of-hospital ventricular fibrillation and a group of healthy community volunteers matched by age and sex. Our second aim was to assess the prognostic significance of the MRI findings after CA and to assess the effects of nimodipine on MRI in a placebo-controlled clinical trial, the results of which have been previously published.12 Since the results of a subgroup analysis performed post hoc had suggested that the possible effect of nimodipine might be related to the delay of resuscitation, we also wanted to examine the relation between MRI findings, delay of advanced life support, and nimodipine treatment.

Subjects and Methods

Subjects

The present study included fifty-nine survivors out of 155 CA patients enrolled in a placebo-controlled, randomized clinical trial studying the effect of nimodipine on the outcome of patients resuscitated from out-of-hospital ventricular fibrillation by a physician-manned advanced life support unit. The complete study design has been reported earlier.12 Between January 1, 1986, and June 30, 1988, there were 677 out-of-hospital resuscitation attempts, and 210 patients had ventricular fibrillation as the presenting rhythm. Of these 210 patients, the spontaneous circulation could be restored and the entry criteria met for 155 (74%) of the patients, who were randomly assigned to receive either nimodipine or placebo in a randomized, double-blind fashion. The dosage was 10 μg/kg body weight as an intravenous
injection immediately after restoration of spontaneous circulation, followed by an infusion of 0.5 μg/kg per minute for 24 hours. The study treatment was always started at the site of the resuscitation outside the hospital. The delays of basic life support and advanced life support (defined as the time from the estimated CA time to the start of resuscitation by the ambulance personnel or by the physician-manned unit, respectively) and additional features of CA and resuscitation as well as medical history were obtained for all CA patients (Table 2). Blood pressure was carefully controlled during the treatment. Systolic blood pressure below 80 mm Hg any time during the first day after resuscitation was considered to indicate hypotension. The Mini-Mental State Examination (MMSE) was performed at 1 week and 1 year for all surviving patients. The results of the detailed neuropsychological examination and MMSE have been previously reported.

Of the 155 enrolled patients, MRI could be performed in 59 of 107 patients (55%) that survived for at least 2 weeks. Of the 59 scans, 52 could be completed and were legible for the analysis. Seven patients were too restless or their medical condition was too unstable to allow completed imaging. Of the 52 patients who underwent MRI, 28 were treated with nimodipine and 24 received placebo. The most common reasons for lack of MRI scan were unstable medical condition and difficulties in providing adequate intensive care during imaging; the presence of an implanted cardiac pacemaker, which is an absolute contraindication for MRI; and the refusal of the patient to enter the MRI scanner. The 1-year outcome of CA patients was assessed by careful neurological examination, MMSE score and detailed neuropsychological examination, and by questioning close relatives. The Glasgow Outcome Score of the patients was dichotomized into good (good recovery or moderate disability) or poor (severe disability, vegetative state, or death) outcome.

Eighty-eight control subjects were selected from a random cohort of normal aged community volunteers included in the Helsinki Aging Study to create a control group of equal age and sex. A detailed neurological examination, including MMSE, was performed in the control subjects before MRI. The histories of hypertension, coronary heart disease, previous myocardial infarction, cardiac failure, diabetes, and previous resuscitation were obtained for CA patients and control subjects using all available medical records. An oral informed consent was obtained from all control subjects, and a deferred oral consent was obtained from resuscitated patients or their relatives. The study was approved by the Ethical Committee of the University Central Hospital of Helsinki and the University of Helsinki.

Magnetic Resonance Imaging

The magnetic resonance imaging was performed with an ultra-low-field magnetic resonance imager (Acut-scan, Instrumentarium Corporation, Helsinki, Finland) operating at 0.02 T. Axial T2-weighted spin-echo images (repetition time/echo time, 2000/150 or 2300/120, with three averages) were obtained in each examination. Additional pulse sequences and sagittal or coronal slices were used in selected cases. The slice thickness was 10 mm, and there were no gaps between the slices. The field of view was 30 cm and the matrix size 128×256 pixels. Contrast enhancement was not used.

The MRI scans were performed an average of 12±8 (mean±SD; range, 1 to 47) days after CA. At the time of imaging, twelve patients were still comatose; all but eight patients ultimately regained consciousness. Comatose patients as well as those with respiratory problems were ventilated by hand during the imaging process.

The MRI scans were reviewed by a neuroradiologist (R.R.) blinded to the clinical data. Leukoaraiosis was defined as diffuse or patchy areas of increased signal intensity in T2-weighted images. Leukoaraiosis was separately evaluated in frontal, parietal, and occipital lobes, including both periventricular and deep white matter as well as subcortical areas. The changes were visually graded as mild (if less than one quarter of the white matter was affected), moderate (if one quarter to one half was affected), and severe (if more than one half of the white matter had increased signal intensity in T2-weighted images). Infarcts were recorded by number, size, and arterial territory and were classified as deep or cortical. Infarcts located in border zone areas of arterial territories, either in cortical or deep regions, were considered watershed infarcts. Wedge-shaped peripheral lesions and well-defined, small, round or oval hyperintensities in the basal ganglia, thalami, or deep white matter were considered infarcts. Because the differentiation of infarcts from other lesions was based mainly on the form of the lesions, the differentiation between infarcts and leukoaraiosis was arbitrary in some cases; therefore, the presence or absence of any white matter hyperintensities was also assessed.

Cortical, central, and posterior fossa atrophy were each rated as absent, mild, moderate, or severe, considering both sides of the brain simultaneously. Except for the most severe cases, generalized brain edema is difficult to diagnose by radiological means, but diminished size of subarachnoidal spaces and cerebral ventricles may signal its presence. Thus, cerebral atrophy on MRI indicates lack of concurrent edema, whereas the finding of missing cortical, central, and posterior fossa atrophy may represent generalized brain edema. Hereafter, the term “probable edema” is therefore used to describe the patients in whom generally reduced cerebrospinal fluid spaces are demonstrated by MRI.

The MRI scans of CA patients and control subjects were compared to clarify the frequency of pathological findings after CA and to identify the findings associated with CA. The impact of important prognostic factors of out-of-hospital cardiac arrest (namely, the delay of advanced life support and hypotension) was assessed in CA patients. The MRI findings were correlated with 1-year functional outcome of resuscitation to identify the findings with prognostic value. Finally, the results of MRI in CA patients treated with nimodipine or placebo were compared.

Statistical Methods

The homogeneity of CA and control patient groups regarding demographic data, and the homogeneity of nimodipine- or placebo-treated patient groups for the main characteristics of CA and resuscitation, outcome, and demographic data were tested using Fisher’s Exact Test.
Test or Student's t test. The frequencies of individual MRI findings in each group are given as percentages with probability values of Fisher's Exact Test. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for CA and other risk factors for the MRI findings, first in univariate models and subsequently in multivariate models. The effect of confounding factors unevenly distributed in CA and control groups was controlled by logistic regression analysis, which was used to identify parameters associated with the presence of different MRI findings, adjusted for all other risk factors in the model. Nonparametric correlations were calculated using Spearman's correlation coefficient, Kendall's rank correlation coefficient, or Kendall's partial rank correlation coefficient. The difference of two nonparametric correlation coefficients was tested using Fisher's z transformation. The two-sided α<.05 was considered statistically significant in all comparisons. The statistical analyses were performed using BMDP statistical software and a personal computer.

Results

The 52 CA patients did not differ from the 88 normal control subjects with respect to age and sex; however, a history of coronary heart disease, myocardial infarction, cardiac failure, or resuscitation was much more common than in the control group (Table 1).

Forty-four of 52 patients (85%) recovered consciousness (Table 2). Thirty-three patients (63%) survived for at least 1 year. Twenty-three patients (44%) reached the best Glasgow Outcome category, five (10%) had moderate disability, and five (10%) were severely disabled. Nineteen (37%) patients died during the 1-year follow-up, eleven (21%) due to anoxic encephalopathy. Thus, 24 patients (46%) had a poor outcome (defined as death by 1 year or severe disability) compared with 28 patients (54%) with good outcome (defined as good or moderate recovery). The outcome of the 52 studied patients was somewhat better than that of all the 155 enrolled patients, of whom 100 (65%) recovered consciousness (P=.008), 59 (38%) survived for at least 1 year (P=.003), and 50 (32%) had a good outcome (P=.01). Of the 96 patients who died during follow-up, death was related to anoxic encephalopathy in 50 cases (52%). The demographic data and the characteristics of cardiac arrest were similar in patients studied by MRI and in all 155 patients. The patients studied by MRI thus represented fairly well the victims of out-of-hospital ventricular fibrillation enrolled in the randomized trial.

The CA patient groups receiving either nimodipine or placebo did not differ in gender or history of main vascular disorders, but the patients treated with nimodipine were slightly younger (P=.06, Table 2). The delays of basic and advanced life support, the duration of coma, and the rate of recovery of consciousness were equal in both treatment groups.

Cerebral Infarcts

Cerebral infarcts demonstrated by MRI were more common after CA than in normal control subjects (Table 3 and Fig 1), but the difference was significant only for deep infarcts (P=.0007). The number of infarcts was increased as well (P=.0001), and 8 of 52 patients (15%) had multiple infarcts compared with 3 of 88 controls (3%) (P=.03).

CA was a univariate risk factor for the presence of cerebral infarcts (OR, 4.6; 95% CI, 2.0 to 10.3; P=.0003) and for the presence of any white matter hyperintensities (OR, 2.4; 95% CI, 1.2 to 4.8; P=.02) but not for leukoaraiosis (OR, 1.2; 95% CI, 0.5 to 2.5) or atrophy (OR, 1.2; 95% CI, 0.6 to 2.3).

In multivariate logistic regression analysis, CA was an independent risk factor (OR, 3.6; 95% CI, 1.3 to 9.9; P=.01) for the presence of infarcts, adjusted for the effects of age, sex, and previous myocardial infarction, stroke, coronary heart disease, cardiac failure, and hypertension. Age was another independent risk factor (OR, 1.08; 95% CI, 1.02 to 1.13; P=.006), whereas hypertension (OR, 1.0; 95% CI, 0.4 to 2.7; P=.95) and history of stroke (OR, 3.1; 95% CI, 0.5 to 17.2; P=.21) were not. CA was an especially important risk factor for deep infarcts (OR, 16.7; 95% CI, 2.6 to 108; P=.0001) when controlled for the factors above. CA was also an

| Table 1. Demographic Features of Cardiac Arrest Patients and Control Subjects |
|---------------------------------|------------------|------------------|
| Variable                        | Cardiac arrest (n=52) | Control subjects (n=88) | P     |
| Age (years; mean±SD)           | 65±11             | 65±7             | .92   |
| Range (36-85)                  | 28±2              | <.0001           |
| MMSE score (mean±SD)           | 0-30              | 21±12            |       |
| Males                          | 36 (69)           | 48 (55)          | .12   |
| Hypertension                   | 13 (25)           | 24 (27)          | .93   |
| Coronary disease               | 27 (52)           | 18 (21)          | .0003 |
| Myocardial infarction          | 18 (35)           | 5 (6)            | <.0001|
| Cardiac failure                | 25 (48)           | 4 (5)            | <.0001|
| Resuscitation                  | 5 (10)            | 0 (0)            | .013  |
| Diabetes                       | 3 (6)             | 5 (6)            | 1.00  |
| Stroke                         | 5 (10)            | 2 (3)            | .13   |

n, Number of patients or control subjects; MMSE, Mini-Mental State Examination (scale 0 to 30). Values in parentheses are percent. Probability values indicate the significance level of Student's t test for age and of Fisher's Exact Test for all other variables.
Table 2. Demographic Data and Main Characteristics of Cardiac Arrest Patients Treated With Nimodipine and Placebo

<table>
<thead>
<tr>
<th></th>
<th>Nimodipine (n=28)</th>
<th>Placebo (n=24)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years; mean±SD)</td>
<td>62±13</td>
<td>68±9</td>
<td>.06</td>
</tr>
<tr>
<td>Range</td>
<td>(36-85)</td>
<td>(49-80)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>21 (86)</td>
<td>15 (63)</td>
<td>.50</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (29)</td>
<td>5 (21)</td>
<td>.75</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>14 (50)</td>
<td>13 (54)</td>
<td>.98</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>14 (50)</td>
<td>11 (46)</td>
<td>.45</td>
</tr>
<tr>
<td>Previous resuscitation</td>
<td>4 (14)</td>
<td>1 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>1.00</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (18)</td>
<td>0 (0)</td>
<td>.08</td>
</tr>
</tbody>
</table>

Characteristics of resuscitation and outcome

- Basic life support delay (minutes; mean±SD)
  - Nimodipine: 6±3 (7-15)
  - Placebo: 6±3 (7-15)
  - P = .91

- Advanced life support delay (minutes; mean±SD)
  - Nimodipine: 19±7 (7-38)
  - Placebo: 19±6 (7-38)
  - P = .79

- Bystander-initiated resuscitation
  - Nimodipine: 7 (25)
  - Placebo: 10 (42)
  - P = .33

- Hypotension
  - Nimodipine: 13 (46)
  - Placebo: 12 (50)
  - P = 1.00

- Recovery of consciousness
  - Nimodipine: 25 (89)
  - Placebo: 19 (79)
  - P = .53

- Coma during MRI
  - Nimodipine: 6 (21)
  - Placebo: 6 (25)
  - P = 1.00

- 1-Year survival
  - Nimodipine: 19 (68)
  - Placebo: 14 (58)
  - P = .67

- Good 1-year outcome
  - Nimodipine: 16 (57)
  - Placebo: 12 (50)
  - P = .81

n, Number of patients; MRI, magnetic resonance imaging. Hypotension denotes systolic blood pressure <80 mm Hg during first 24 hours after cardiac arrest.

Numbers of patients, proportions as percentages in parentheses for binomial variables or mean±SD and range for continuous variables. Probability values indicate significance level of Mann-Whitney rank-sum test for number of infarcts and duration of coma, of Student's t test for age and basic and advanced life support delays, and of Fisher's Exact Test for all other variables.

Independent risk factor for the presence of any white matter hyperintensities (infarct or leukoaraiosis) when adjusted for the effect of age (OR, 2.7; 95% CI, 1.2 to 5.9; P = .02); however, when all the factors above were taken in the model, age was the only independent predictor of white matter hyperintensities (OR, 1.11; 95% CI, 1.06 to 1.17; P = .0001).

Leukoaraiosis

Leukoaraiosis was present in 14 of the 52 CA patients (27%) and in 24 of the 88 control subjects (27%). In addition to age (see below), the degree of leukoaraiosis correlated with the degree of atrophy in normal control subjects (r = .38, P = .0004) but not in patients with CA (r = .27, P = .05).

Factors predicting the presence of leukoaraiosis in all of the 140 subjects (patients and controls) were studied by logistic regression analysis with CA, age, sex, coronary disease or previous myocardial infarction, cardiac failure, history of stroke, and history of hypertension as factors in the model. In this model, leukoaraiosis was associated only with increasing age (OR, 1.14; 95% CI,

Table 3. MRI Findings in Cardiac Arrest Patients and Control Subjects

<table>
<thead>
<tr>
<th>Finding</th>
<th>Cardiac arrest patients (n=52)</th>
<th>Control subjects (n=88)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. %</td>
<td>No. %</td>
<td></td>
</tr>
<tr>
<td>Cortical infarct</td>
<td>13 25</td>
<td>12 14</td>
<td>.14</td>
</tr>
<tr>
<td>Cortical watershed infarct</td>
<td>7 14</td>
<td>6 7</td>
<td>.31</td>
</tr>
<tr>
<td>Deep infarct</td>
<td>11 21</td>
<td>2 2</td>
<td>.0007</td>
</tr>
<tr>
<td>Deep watershed infarct</td>
<td>2 4</td>
<td>1 1</td>
<td>.62</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>15 29</td>
<td>23 26</td>
<td>.87</td>
</tr>
<tr>
<td>White matter hyperintensities</td>
<td>30 58</td>
<td>30 34</td>
<td>.01</td>
</tr>
<tr>
<td>Atrophy</td>
<td>23 44</td>
<td>36 41</td>
<td>.83</td>
</tr>
<tr>
<td>Normal</td>
<td>11 21</td>
<td>40 46</td>
<td>.006</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; n, number of patients or controls; white matter hyperintensities denote leukoaraiosis or infarcts.

Numbers of patients, proportions as percentages, and probability values indicating the significance level of Fisher's Exact Test.
1.07 to 1.21; \( P = .0001 \)), whereas hypertension (OR, 1.4; 95% CI, 0.5 to 3.8; \( P = .51 \)) and history of stroke (OR, 2.1; 95% CI, 0.3 to 14.4; \( P = .48 \)) were not significant risk factors for leukoaraiosis.

White matter hyperintensities were more common in the CA group of patients than in healthy control subjects (\( P = .01 \), Table 3). The frequency of white matter hyperintensities increased in parallel with increasing age in both the CA patients (\( r = .96, P = .0005 \)) and control subjects (\( r = .94, P = .01 \)).

**Effects of Age**

Increasing age correlated with the frequency of infarcts in the CA group of patients (\( r = .86, P = .01 \); Fig 1). Infarcts were rare in the control group, and only the frequency of deep infarcts had a significant correlation with age (\( r = .89, P = .04 \)). A normal MRI was seen in 46% of control subjects but in only 21% of CA patients (\( P = .006 \)). In subjects younger than 65 years, MRI was normal in 48% compared with 23% in those 65 or older (\( P = .004 \)). The frequency of atrophy increased with advancing age in CA patients (\( r = .77, P = .04 \)) and normal control subjects (\( r = .75, P = .14 \)). In healthy control subjects, age correlated with the frequency (\( r = .96, P = .01 \)) and degree of central atrophy (\( r = .33, P = .0004 \)), but this was not the case in CA patients (\( r = .68, P = .09 \) and \( r = .22, P = .11 \), respectively). Nevertheless, the frequency of atrophy was the same in both groups (Table 3).

In CA patients, age correlated with the frequency (\( r = .91, P = .0004 \)) and degree of leukoaraiosis, especially in the frontal (\( r = .50, P = .0004 \)) and temporoparietal areas (\( r = .34, P = .01 \)). In control subjects, age had a similar correlation with the frequency (\( r = .89, P = .05 \)) and degree of leukoaraiosis, especially in the temporoparietal areas (\( r = .39, P = .0002 \)). The frequency of leukoaraiosis in different age groups in the control and CA patients is depicted in Fig 2. In CA patients, leukoaraiosis tended to occur earlier than in controls, although the difference was not significant.

**Delay of Advanced Life Support and Cerebral Edema**

The 19 patients with the longest (more than 10 minutes) delays of advanced life support did not have more infarcts, leukoaraiosis, or any other abnormalities on MRI than the 33 patients with shorter (10 minutes or less) delays of advanced life support (Table 4). The delay of advanced life support did not correlate with the degree of leukoaraiosis or the number of infarcts either, but it had an inverse correlation with the degree of cerebral atrophy (\( r = -.42, P = .003 \)).

Probable cerebral edema was observed in 13 of the 33 patients (39%) with short delays compared with 16 of the 19 patients (84%) with long delays of advanced life support (\( P = .0004 \)). Probable edema was somewhat more common in patients who underwent MRI during the first 3 days (5 of 6 patients [83%]), compared with patients imaged later (24 of 46 patients [52%], \( P = .32 \)), but it was even observed in 7 of 15 patients (47%) who underwent MRI later than 2 weeks after cardiac arrest. In two patients, a diffuse and generalized hyperintensity of the cerebral white matter was observed as a distinctive sign of severe edema and fatal hypoxic-ischemic encephalopathy after CA.

In a logistic regression model controlling for the effects of age, sex, delay of MRI scan in days, treatment by nimodipine or placebo, coronary disease or previous myocardial infarction, and history of stroke, cardiac failure, hypertension, and hypotension, the delay of advanced life support was the only independent risk factor of probable edema (OR, 1.28; 95% CI, 1.1 to 1.6; \( P = .01 \)). In other words, the risk of probable edema on MRI increased by 28 percentage units per each minute before the start of advanced life support.

**Hypotension**

Hypotension is commonly associated with cardiac arrest and resuscitation, and it has been proposed as one of the risk factors for both cerebral infarcts and leukoaraiosis. Therefore, we wanted to determine...
whether the presence of hypotension (defined as systolic blood pressure below 80 mm Hg any time during the first day) would be associated with any pathological findings on MRI. Hypotension was observed in 25 of 52 CA patients (48%). There was no difference in the frequency of hypotension in nimodipine- (13 of 28 [46%]) and placebo- (12 of 24 [50%]) treated patients. The frequencies of cortical (28% vs 22%) and deep (20% vs 22%) infarcts, also in watershed areas, leukoaraiosis (28% vs 30%), any white matter hyperintensities (52% vs 56%), atrophy (44% vs 44%), and the number of all infarcts (0.6 vs 0.6) were equal in hypotensive and normotensive patients. Hypotension was not associated with an increased risk of cerebral infarcts (OR, 1.02; 95% CI, 0.3 to 3.1; \( P = .97 \)) or LA (OR, 1.08; 95% CI, 0.3 to 3.7; \( P = .90 \)) in univariate models or in a logistic regression model controlling for the effects of age, sex, coronary disease or previous myocardial infarction, history of stroke, and history of hypertension (cerebral infarct: OR, 0.99; 95% CI, 0.3 to 3.8; \( P = .99 \); leukoaraiosis: OR, 1.04; 95% CI, 0.16 to 6.9; \( P = .97 \)). Hypotension following CA was not a risk factor for any of the abnormalities observed on MRI.

**Nimodipine**

Patients treated with nimodipine or placebo had similar demographic data, characteristics of CA and resuscitation, and similar 1-year outcome (Table 2). There was also no significant difference in any of the MRI findings between the treatment groups. The frequency of deep infarcts was 29% (7 of 24) in the placebo-treated group and 14% (4 of 28) in the nimodipine-treated group (\( P = .33 \), Table 5). The frequency of leukoaraiosis and atrophy were similar in each group. However, 8 of the 12 nimodipine-treated patients (67%) with atrophy had a good outcome compared with 8 of 16 patients (50%) without atrophy. In the placebo group, 9 of 11 patients (82%) with atrophy had a good outcome in contrast to the 3 of 13 (23%) without atrophy (\( P = .01 \)). The presence of atrophy was associated with reduced risk of poor outcome in placebo-treated patients (OR, 0.24; 95% CI, 0.07 to 0.86; \( P = .01 \)) but not in

### Table 4. MRI Findings in Cardiac Arrest Patients With Long (>10 minutes) and Short (≤10 minutes) Advanced Life Support Delays

<table>
<thead>
<tr>
<th></th>
<th>Long delay (n=19)</th>
<th>Short delay (n=33)</th>
<th>( P )</th>
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</thead>
<tbody>
<tr>
<td>Days since cardiac arrest (mean±SD)</td>
<td>12±9</td>
<td>11±6</td>
<td>.62</td>
</tr>
<tr>
<td>Cortical infarct</td>
<td>4 (21)</td>
<td>9 (27)</td>
<td>.88</td>
</tr>
<tr>
<td>Deep infarct</td>
<td>5 (26)</td>
<td>6 (18)</td>
<td>.72</td>
</tr>
<tr>
<td>Normal</td>
<td>6 (32)</td>
<td>5 (15)</td>
<td>.30</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; n, number of patients; white matter hyperintensities denote leukoaraiosis or infarcts.

Numbers of patients, proportions as percentages in parentheses for binomial variables. Probability values indicate significance level of Student’s \( t \) test for age and for delay of MRI scan and of Fisher’s Exact Test for all other variables.

### Table 5. MRI Findings in Cardiac Arrest Patients Treated With Nimodipine and Placebo

<table>
<thead>
<tr>
<th></th>
<th>Nimodipine (n=28)</th>
<th>Placebo (n=24)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days since cardiac arrest (mean±SD)</td>
<td>13±9</td>
<td>10±5</td>
<td>.29</td>
</tr>
<tr>
<td>Cortical infarct</td>
<td>7 (25)</td>
<td>6 (25)</td>
<td>1.00</td>
</tr>
<tr>
<td>Deep infarct</td>
<td>4 (14)</td>
<td>7 (29)</td>
<td>.33</td>
</tr>
<tr>
<td>Leukoaraiosis</td>
<td>9 (32)</td>
<td>6 (25)</td>
<td>.80</td>
</tr>
<tr>
<td>White matter hyperintensities</td>
<td>15 (54)</td>
<td>15 (63)</td>
<td>.71</td>
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<tr>
<td>Atrophy</td>
<td>12 (43)</td>
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<td>Normal</td>
<td>6 (21)</td>
<td>5 (21)</td>
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</tbody>
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MRI, magnetic resonance imaging; n, number of patients; white matter hyperintensities denote leukoaraiosis or infarcts.

Numbers of patients, proportions as percentages in parentheses for binomial variables. Probability values indicate significance level of Student’s \( t \) test for delay of MRI scan and of Fisher’s Exact Test for all other variables.
nifedipine-treated patients (OR, 0.67; 95% CI, 0.26 to 1.70; P = .62). Nimodipine-treated patients with probable edema also had good outcome (8 of 16 patients [50%]) more often than placebo-treated patients with this finding (3 of 13 patients [23%]), but the difference did not reach statistical significance (P = .27).

In the placebo group, increasing delays of advanced life support were associated with an increased risk of edema shown on MRI. The risk more than doubled each minute before the start of advanced life support (OR, 2.07; 95% CI, 1.1 to 3.8; P = .01). This was not observed in the nimodipine group (OR, 1.07; 95% CI, 0.9 to 1.3; P = .56).

Adjusted for age, the delay of advanced life support correlated inversely with the degree of atrophy in placebo-treated patients (r = -.62, P < .0001) but not in patients treated with nimodipine (r = -.10, P = .43; Fisher's z value for the difference, 2.06; P = .04). Thus, increasing delays of advanced life support were associated with increasing edema in placebo-treated but not in nimodipine-treated patients.

**Functional Outcome**

The 28 patients with good 1-year outcome (good recovery or moderate disability according to the Glasgow Outcome Scale) had fewer MRI-confirmed infarcts than those with poor outcome (severe disability or death by 1 year), but none of the differences reached significance (Table 6). Atrophy was much more common in patients with good outcome (17 of 28 [61%]) than in those with poor outcome (6 of 24 [25%], P = .02), most of whom had probable brain edema. The degree of atrophy also correlated with the Glasgow Outcome Score (r = .34, P = .01), whereas the degree of leukoaraiosis (r = -.09, P = .54) and the number of infarcts (r = -.17, P = .23) did not correlate with outcome. None of the MRI findings correlated with the MMSE score in any of the subgroups.

The results of the logistic regression analysis revealed that the presence of atrophy (or lack of edema) was the only significant factor predicting good outcome at 1 year (OR, 4.6; 95% CI, 1.4 to 15.8; P = .01) in a multivariate logistic regression model adjusting for the effects of age, sex, delay of MRI scan in days, treatment by nimodipine or placebo, coronary heart disease or previous myocardial infarction, previous stroke, cardiac failure, and hypertension. Probable edema shown on MRI had a sensitivity of 75% and a specificity of 61% in predicting poor outcome.

**Discussion**

In the present study, CA and age were independent risk factors for cerebral infarcts, especially deep ones, demonstrated by MRI. Cerebral infarcts were observed in 25% of the patients and deep infarcts in 21%. Cerebral infarcts, verified by autopsy, have previously been reported in only 5% of 135 CA survivors.20,21 If the association of CA and cerebral infarcts is explained by hemodynamic factors, an increased number of infarcts would be expected on watershed areas, which we did not observe. However, multiple infarcts were more common after CA.

The frequency and degree of leukoaraiosis were closely associated with increasing age, but not with CA or with any of the cardiovascular disorders in univariate or multivariate analysis. This is in contrast to some of the previous reports.22-25 However, Schmidt and coworkers26 recently analyzed the occurrence of white matter hyperintensities in stroke patients and normal volunteers. In multivariate analysis, white matter hyperintensities were independently associated with age and diabetes mellitus only. CA is a combination of complete and incomplete global ischemias often associated with hypertension during reperfusion. Unexpectedly, hypertension associated with CA was not a risk factor for any of the abnormalities observed on MRI, including leukoaraiosis, although global ischemia is believed to uncouple cerebral autoregulation, making the brain more vulnerable to fluctuations in blood pressure.7,21 Leukoaraiosis and watershed infarcts do not seem to be
associated with short-lived hemodynamic disturbances such as CA followed by hypotension.

Early computed tomographic (CT) findings (within 5 days of global cerebral ischemia) have previously been studied by Kjos and coworkers in 10 patients.4 The most common finding was diffuse cerebral edema, observed in all but 1 patient, accompanied by loss of normal gray-white matter differentiation in 6 patients. The diffuse mass effect with obliteration of the sulci with no areas of decreased density was hypothesized to reflect early cytotoxic edema.6 MRI and CT are known to have limited capacity to detect generalized brain edema except in the most severe cases, with markedly obliterated cerebrospinal fluid spaces and abnormal signal intensity in the brain parenchyma. We observed an increased signal intensity in the cerebral white matter in the T2-weighted images of 2 patients, both of whom died without recovery of consciousness. The generally diminished subarachnoid spaces and cerebral and cerebellar ventricles suggest the presence of brain edema. In CA patients, atrophy had no correlation with age as it did in control patients. Since the lack of atrophy was the only significant predictor of poor outcome in both univariate (Table 6) and multivariate analyses, the finding was most likely associated with cerebral edema. In addition, atrophy was usually absent in patients with delayed resuscitation but present in most patients with early resuscitation; again, this was the only difference between these two groups of patients demonstrated by MRI. Probable edema shown on MRI was associated with a fivefold risk of poor 1-year outcome. It had a high sensitivity (75%) in identifying the patients with poor 1-year outcome, but the specificity of the finding was insufficient for clinical purposes.

The risk of probable edema on MRI increased by approximately 30 percentage units per each day before the start of advanced life support. The delay of advanced life support, known to be an important predictor of survival in out-of-hospital CA,7 had an independent association with probable edema on MRI, which suggests that every minute of delay significantly increases the edema caused by global cerebral ischemia. However, increasing delays of resuscitation were not significantly associated with cerebral infarcts or leukoaraiosis.

Brain edema is related to increased intracranial pressure, which is believed to be rare after CA. Monitoring of intracranial pressure has not been routine in the postresuscitative intensive care of adult patients.27-29 However, the mean intracranial pressure measured by extradural electrodes was recently reported to exceed 25 mm Hg during the second postarrest day in 22 of 84 CA patients (26%) and to be associated with poor outcome.30 At present, there is no evidence that any treatment of increased intracranial pressure would alter the outcome of hypoxic-ischemic encephalopathy.

Nimodipine has not been proved to be beneficial after human CA, although it has reduced delayed ischemic deficits and the number of cerebral infarcts shown by CT after subarachnoid hemorrhage.12,31,32 In the present study, the frequency of abnormal MRI findings did not differ between the nimodipine- and placebo-treated patients. Nimodipine-treated patients tended to have fewer infarcts in deep and watershed areas, but the difference was not significant (Table 5).

Adjusted for age, the delay of advanced life support correlated with probable edema in placebo-treated but not in nimodipine-treated patients (P = .04). This finding may suggest that nimodipine limited brain edema and improved the tolerance for global ischemia associated with delayed resuscitation. It may also offer one explanation for the post hoc subgroup result obtained in the placebo-controlled, double-blind, randomized trial of 155 patients with out-of-hospital ventricular fibrillation, which suggested a beneficial effect of nimodipine for patients with delayed advanced life support.15 The present results agree with those of Gueugniaud et al,33 who reported that both the mean and maximum intracranial pressures after CA were significantly lower in 19 nimodipine-treated patients than in 20 control subjects. According to experimental evidence, nimodipine may prevent the development of cerebral edema and the increase of intracranial pressure associated with focal or global ischemia.34-38 Increased regional cerebral blood flow (CBF) in the ischemic core of hemispheric infarcts has been demonstrated by positron emission tomography in humans.39 According to Forsman and coworkers,40 nimodipine nearly doubled the postischemic CBF in humans, probably due to uncoupling of cerebral autoregulation. Nimodipine-treated patients, however, did not experience better recovery; but the patients with the highest CBF values had the worst outcome. Increased CBF is not a favorable prognostic sign; it may be associated with irreversible brain damage and death after human CA.7 Although nimodipine could make the brain more vulnerable to hypotension by its demonstrated ability to inhibit normal regulation of CBF, we found no evidence of such an effect.36,41,42

One of the limitations of the present study is the relatively low resolution of the 0.02-T ultra-low-field MRI scanner used. The smallest lesions (laminar necrosis in particular) are likely to remain unobserved. Low-field MRI is not the method of choice for detecting generalized edema, either. Using the same ultra-low-field MRI scanner, white matter hyperintensities have recently been shown to be associated with advanced age and increased blood pressure.43,44 Infarcts may not be successfully differentiated from leukoaraiosis using MRI; especially, the differentiation between recent and old lesions is impossible. However, CA and other cardiovascular disorders correlated well with the presence and number of cerebral infarcts, particularly deep infarcts; CA, however, did not correlate with the presence of leukoaraiosis, which suggests that the lesions were differentiated from each other. Furthermore, the correlation of leukoaraiosis and infarcts with age in CA patients and the correlation of atrophy with age and leukoaraiosis in control subjects are in accordance with results published earlier.45 In the present study, the MRI findings correlated with the MMSE score neither in CA patients nor in normal controls, which is in agreement with previous studies.46

Another limitation of the study was that in some patients MRI was performed too late for practical prognostic purposes and in others it could not be performed at all for reasons related to outcome, such as poor medical condition or early death. This biased the
population studied slightly toward better outcome and may have diminished the accuracy of MRI in outcome prediction.

Compared with other published methods predicting poor outcome after CA, MRI seemed to be comparable to single-photon emission computed tomography using Te-hexamethylpropyleneaminedioxide (HMPAO-SPECT) but less accurate than neuron-specific enolase measured from the cerebrospinal fluid.5,6 To avoid an overly pessimistic prognostication, tests used in critical care are generally required to have high specificity for poor outcome, which is more important than high sensitivity. The only distinctive MRI finding indicative of inevitable death may be the presence of severe edema, which we observed in two patients.

In conclusion, the present study demonstrated that CA was associated with deep cerebral infarcts on MRI but not with cortical watershed infarcts or leukoaraiosis, even in the presence of postarrest hypotension. Increasing delays of resuscitation were associated with probable brain edema, which seemed to be suppressed by nimodipine treatment. The use of nimodipine in resuscitation is not justified, however, since it has not altered the outcome of CA.12,14 MRI can reveal the presence of cerebral infarcts and probable brain edema associated with CA, but it seems to have only limited prognostic value and may not be the diagnostic method of choice in the management of patients with hypoxic-ischemic encephalopathy after CA.

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