Coenzyme Q10 Combined With Mild Hypothermia After Cardiac Arrest

A Preliminary Study

Maxwell Simon Damian, MD, PhD; Diana Ellenberg, MD; Ramona Gildemeister, MD; Jörg Lauermann, MD; Gregor Simonis, MD; Wolfgang Sauter, MD; Christian Georgi, MD

Background—Therapeutic hypothermia can improve survival after cardiopulmonary resuscitation (CPR). Coenzyme Q10 (CoQ10) has shown a protective effect in neurodegenerative disorders. We investigated whether combining mild hypothermia with CoQ10 after out-of-hospital cardiac arrest provides additional benefit.

Methods and Results—Forty-nine patients were randomly assigned to either hypothermia plus CoQ10 or hypothermia plus placebo after CPR. Hypothermia with a core temperature of 35°C was instituted for 24 hours. Liquid CoQ10 250 mg followed by 150 mg TID for 5 days or placebo was administered through nasogastric tube. Age, sex, premorbidity, cause of arrest, conditions of CPR, and degree of hypoxia were similar in both groups; no side effects of CoQ10 were identified. Three-month survival in the CoQ10 group was 68% (17 of 25) and 29% (7 of 24) in the placebo group (P=0.0413). Nine CoQ10 patients versus 5 placebo patients survived with a Glasgow Outcome Scale of 4 or 5. Mean serum S100 protein 24 hours after CPR was significantly lower in the CoQ10 group (0.47 versus 3.5 ng/mL).

Conclusions—Combining CoQ10 with mild hypothermia immediately after CPR appears to improve survival and may improve neurological outcome in survivors. (Circulation. 2004;110:3011-3016.)

Key Words: heart arrest ■ metabolism ■ brain ■ free radicals

Cardiopulmonary resuscitation (CPR) is attempted in ≈375 000 cases of cardiac arrest per year in Europe1 but restores spontaneous perfusion in only one third of cases; less than 10% of survivors can return to their former lifestyles, mainly because of brain damage.2,3 Neuronal death occurs both during ischemia as well as after the return of blood flow, and inflammation, mitochondrial dysfunction, oxidative stress, altered signal transduction and programmed cell death are implicated in delayed injury.4 Two recent trials demonstrated that therapeutic hypothermia after CPR improves survival and reduces neuronal damage.5,6 By contrast, clinical trials of neuroprotective drugs after cardiac arrest have been unsuccessful. Coenzyme Q10 (CoQ10) is an essential mitochondrial cofactor that has been shown to confer neuroprotection in neurodegenerative disorders7–10 and may also have a cardioprotective effect in cardiosurgery.11 We investigated whether CoQ10 can provide additional benefit in patients receiving mild hypothermia after out-of-hospital cardiac arrest.

Methods

Patients

The study was performed between January 2000 and June 2001 at the University of Dresden, Germany, which provides emergency care for an area with ≈1 million inhabitants. The following patients were eligible: age, 18 to 80 years; witnessed out-of-hospital cardiac arrest of presumed cardiac origin; coma with response to pain no better than flexion despite restored spontaneous perfusion; absence of previous neurological disease, pregnancy, or heart failure greater than New York Heart Association class II; and admission within 6 hours of cardiac arrest. Patients were included as soon as possible, but revascularizing procedures and stabilization took precedence.

Study Design

The trial was randomized and controlled, with blinded assessment of the outcome. Protocol and consent procedures were approved by the ethics review committee of the Dresden University of Technology, in accordance with European guidelines for Good Clinical Practice. The next of kin were informed about the trial before inclusion, and written consent was obtained within 24 hours. The protocol specified that patients would not be included if the family raised any objections; however, there were none. Assignment to treatment or placebo groups was randomly generated by a computer in blocks of 25; all personnel involved in treatment and assessment were blinded to the assignment until the end of the study.

Treatment

The treatment protocol prescribed a systolic blood pressure between 120 and 140 mm Hg, sedation with adjusted doses of propofol and sufentanil, pancuronium if needed to prevent shivering, and strict...
adherence to normal ranges for serum sodium, colloid osmotic pressure, hemoglobin, glucose, and arterial PCO₂. Nimodipine was prohibited because of cerebral Ca²⁺ antagonism, sodium nitroprusside because of cerebral vasodilation, as well as barbiturates, corticosteroids, or other potentially neuroprotective drugs. Temperature was measured with a bladder-temperature probe. Cooling started on admission with the use of the Medutek Blanketrol surface cooling mattress aiming at a core temperature between 35° and 36°C. Rewarming at a rate of 0.2°C/h began after 24 hours, or earlier if hemodynamic instability or cardiac dysrhythmia were attributed to hypothermia, but temperatures were kept strictly below 37° in all cases.

Liquid CoQ10 or placebo was administered immediately after inclusion by nasogastric tube flushed with tea. Patients in the CoQ10 group were given a loading dose of 250 mg CoQ10, followed by 150 mg TID, using a novel lipophilic emulsion of CoQ10 (Sanomit, MSE Pharma). Placebo patients were given a corresponding amount of colored water of identical appearance.

**Neurological Assessment**

Neurological assessments were carried out on days 0, 1, 3, and 5, as well as 90 days after CPR by intensive care neurologists, included clinical examination, 4-channel EEG, and somato sensory evoked potentials (SSEP); the first examination was performed as soon as emergency cardiological intervention permitted. Survivors underwent neuropsychological testing, including the Mini-Mental State Examination, a German version of the Trailmaking Test, and a vocabulary test. SSEP and EEG studies were performed by research assistants using the Viking IV device (Nicolet), according to standard protocols, and evaluated by one clinical neurophysiologist. Median nerve SSEP amplitude ratios were calculated between averaged N20 potentials with electrodes over C3 and C4, and N13 potentials with electrodes over C2.

**Laboratory Tests**

Blood was drawn for assessment of serum S100 protein as an indicator of acute neuronal damage. Samples were taken on inclusion, exactly 24 hours afterward and on day 5, then frozen and assayed after the end of the study, before unblinding, to prevent any bias to treatment.

**Outcome**

The outcome variables were (1) survival to discharge from the intensive care unit (ICU); (2) 3-month survival rate; (3) Glasgow Outcome Scale (GOS) ratings after 3 months; and (4) S100 protein serum levels in treatment and placebo groups on days 0, 1, and 5.

**Statistical Evaluation**

From previous neuroprotective studies, ~50 patients were estimated to provide sufficient power in a parallel design. Cardiac arrest data were documented according to the Utstein style. Statistical analysis was performed with the SPSS 10.0 statistical software (Advanced Analysis package); t tests for independent samples were used as appropriate. We used a Kaplan-Meier analysis of survival with a log rank test. For the contingency that patients might have incomplete follow-up, a sensitivity analysis was convened, by which they would be declared “survivors” if they were in the untreated group, and “fatalities on day 6” if they were in the treatment group, thus stacking the analysis against significance. Significance was defined as a level of P<0.05.

**Results**

**Patient Collective**

Fifty consecutive patients were included; there was one dropout, a patient who was included, but whose study medication was not administered by mistake. Thus, 49 patients were available for intention-to-treat analysis, 25 in the CoQ10, and 24 in the placebo group. Twenty-three patients in the CoQ10 group and 22 in the placebo group were available for complete follow-up after discharge. Two patients in each group died after day 5 but before day 90, with incomplete data, due to discharge to distant institutions. In accord with the sensitivity analysis principle, the 2 in the treatment group were classed as “dead on day 6” and the 2 placebo patients as “survivors” for the survival analysis. Baseline characteristics in the 2 groups are compared in Table 1. There were no significant differences at admission (unpaired t test).

**Treatment Administration**

There was no significant difference in treatment in the 2 groups apart from the study medication, and there were no significant breaches of protocol in the 49 patients accepted for analysis. In the CoQ10 group, the first dose of study medication was administered on average 8.9 hours after arrest (SD±4.6 hours) and in the placebo group 8.4 hours (±3.9). No side effects were attributable to study medication. Table 2 shows physiological variables in the ICU. The average temperature in both groups lay between 35°C and 36°C at inclusion, so mild hypothermia was more a matter of maintaining low temperature than of cooling down. Seven patients in the CoQ10 group (28%) were rewarmed prematurely because of circulatory instability, and 6 in the placebo group (25%) were rewarmed prematurely. CK levels were higher in the placebo group but did not differ significantly between survivors and nonsurvivors, which argues against its prognostic importance (20.41±34.2 versus 27.42±57.45 μkat/L).

**TABLE 1. Baseline Characteristics of CoQ10 and Placebo Groups**

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>CoQ10</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No.</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Age (SD)</td>
<td>60.6 (16.0)</td>
<td>62.5 (14.7)</td>
</tr>
<tr>
<td>Male sex, No. (% of total)</td>
<td>17 (68)</td>
<td>20 (83)</td>
</tr>
<tr>
<td>Average BMI (SD)</td>
<td>26.1 (3.6)</td>
<td>25.4 (2.2)</td>
</tr>
<tr>
<td>Diabetes, No. (% of total)</td>
<td>8 (32)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>IHD, No. (% of total)</td>
<td>11 (44)</td>
<td>8 (33)</td>
</tr>
<tr>
<td>Statin treatment before CPR, No. (% of total)</td>
<td>1 (4)</td>
<td>5 (21)</td>
</tr>
<tr>
<td>Delay to CPR after collapse, min (SD)</td>
<td>6.3 (5.5)</td>
<td>6.1 (6.9)</td>
</tr>
<tr>
<td>CPR initiated by lay person, No. (% of total)</td>
<td>7 (28)</td>
<td>6 (25)</td>
</tr>
<tr>
<td>VF or pulseless tachycardia, No. (% of total)</td>
<td>13 (52)</td>
<td>17 (70)</td>
</tr>
<tr>
<td>Asystole, No. (% of total)</td>
<td>9 (36)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>Minutes of CPR to restore spontaneous circulation (SD)</td>
<td>37.1 (22.5)</td>
<td>42.5 (32.0)</td>
</tr>
</tbody>
</table>

| Serum glucose on admission, mmol/L (SD) | 15.2 (4.4) | 14.0 (4.9) |

BMI indicates body mass index; IHD, ischemic heart disease; and VF, ventricular fibrillation.

Patients were divided into 2 groups, the CoQ10 group and the placebo group. The CoQ10 group had a higher dopamine dose on day 3 in the CoQ10 group. There was no difference in dopamine and dobutamine doses, except for a higher dopamine dose on day 3 in the CoQ10 group. Additional epinephrine was necessary on the first day in 6 patients of each group and more in the placebo group (1.88 mg/h versus 18.70 mg/h average dose; P=0.003). The GOS rating increased more rapidly in the CoQ10 group to an average of 5.6 versus 4.0 after 24 hours. There was no...
significant difference between the 2 groups in coronary status on emergency cardiac catheterization or in indicators of left ventricular function. The ejection fraction was established by transesophageal echocardiography in all patients during the ICU stay and averaged 43.0% (SD 16.1%) in the CoQ10 group and 41.0% (SD 11.1%) in the placebo group (not significant).

**Primary Outcome Measure**
The 3-month survival rate was significantly higher in the CoQ10 group: 17 of 25 (68%) in the CoQ10 group survived, but only 7 of 24 (29.2%) in the placebo group survived (P=0.0413; log rank test) (Figure 1).

**Other Outcome Measures**
Twenty-one of the 25 patients in the CoQ10 group (85%) survived until discharge from the ICU, compared with 17 of 24 (70.8%) patients in the placebo group (t test, not significant). The neurological status after 3 months according to GOS did not differ significantly. However, in the CoQ10 group, 9 of 25 patients (36%) had a good neurological outcome (GOS 4 or 5) versus only 5 of 24 (20%) in the placebo group (Figure 2). Only a single patient who was still comatose and unresponsive to pain on day 5 of ICU achieved GOS better than 2 after 3 months (CoQ10 group; GOS, 4). Conversely, only one of the patients who survived the ICU

<table>
<thead>
<tr>
<th>TABLE 2. Physiological Variables During ICU Treatment</th>
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<tbody>
<tr>
<td>Physiological/Treatment Variable</td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td><strong>Temperature, °C (SD)</strong></td>
</tr>
<tr>
<td>CoQ10</td>
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<tr>
<td>Placebo</td>
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<tr>
<td><strong>MAP, mm Hg (SD)</strong></td>
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<tr>
<td>CoQ10</td>
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<tr>
<td>Placebo</td>
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<tr>
<td><strong>CVP, mm Hg (SD)</strong></td>
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<td>Placebo</td>
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<tr>
<td><strong>Lactate, mmol/L (SD)</strong></td>
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<tr>
<td>CoQ10</td>
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<tr>
<td>Placebo</td>
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<td><strong>PH (SD)</strong></td>
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<td>CoQ10</td>
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<td>Placebo</td>
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<td><strong>Hemoglobin, mmol/L (SD)</strong></td>
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<tr>
<td>CoQ10</td>
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<tr>
<td>Placebo</td>
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<tr>
<td><strong>Creatinine, μmol/L (SD)</strong></td>
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<tr>
<td>CoQ10</td>
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<tr>
<td>Placebo</td>
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<tr>
<td><strong>CK, μkat/L (SD)</strong></td>
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<td>CoQ10</td>
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<tr>
<td>Placebo</td>
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<tr>
<td><strong>Dopamine, mg/h (SD)</strong></td>
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<td>CoQ10</td>
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<td>Placebo</td>
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<tr>
<td><strong>Dobutamine, mg/h (SD)</strong></td>
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<td>CoQ10</td>
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<td>Placebo</td>
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<tr>
<td><strong>Average GCS rating (SD)</strong></td>
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<tr>
<td>CoQ10</td>
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<tr>
<td>Placebo</td>
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<tr>
<td><strong>Serum S100, μg/L(SD)</strong></td>
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<tr>
<td>CoQ10</td>
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<tr>
<td>Placebo</td>
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</tbody>
</table>

*Significant difference between CoQ10 and placebo groups (unpaired t test). CK indicates creatine kinase; GCS, Glasgow Coma Scale rating (3–15). SD may exceed mean values in skewed groups. Serum S100 protein normal level: <0.15 μg/L.
but died within 3 months, a patient in the placebo group who
died of a recurrent cardiac disorder, was neurologically intact; 9 of the 12 late fatalities (3 in the CoQ10 group and 6 in the
placebo group) were patients who were discharged comatose
and ventilator-dependent. S100 protein levels in serum were
significantly lower in the CoQ10 group on day 1 (Table 2).

Other Variables
There was no significant difference in overall SSEP ampli-
tudes or N20/N13 amplitude ratios in the 2 groups or in the
bad outcome patients of both groups. However, in good
outcome survivors the average N20/N13 amplitude ratio on
day 5 was twice as high in the CoQ10 group (3.42 versus
1.55, P=0.019; t test), suggesting a possible prolongation of
the potential for improvement past the first 72 hours. There
was no significant difference in psychometric test results
between the 2 groups, but these were only performed in a
minority of survivors (n=7 in the CoQ10 group, n=5 placebo
patients).

Discussion
These data show a significant increase in 3-month survival
after out-of-hospital cardiac arrest for patients given CoQ10
in addition to mild hypothermia, compared with patients
treated with hypothermia alone. Both patients with ventricu-
lar fibrillation and with asystole as cause of arrest were
included. There was no significant difference between the
groups regarding conditions or duration of initial CPR. A
difference regarding the degree of initial cardiac damage
cannot be excluded given the difference in initial total CK
(Table 2), but the two patient groups were well matched with
regard to other initial demographic and physiological param-
eters, and we could not identify a relevant difference in any
other recognized predictors of outcome.1,3,12 In particular,
echocardiographic measures of left ventricular performance
in the ICU were similar and thus cannot explain any differ-
ence in survival or response to treatment.

Hypothermia has a well-established neuroprotective effect.
A large body of experimental evidence suggests that hypo-
thermia after hypoxemic cardiac arrest can reduce oxygen
consumption and slow the release of excitotoxic neurotrans-
mitters and reactive oxygen species.13–16 Bernard et al5
reported survival to hospital discharge in 21 of 49 (49%) patients treated with hypothermia at 33°C for 12 hours versus
9 of 34 (26%) patients treated with normothermia after CPR.
The HACA study group maintained hypothermia for 24 hours
after CPR for ventricular fibrillation and reported a good
Cerebral Performance Category rating in 75 of 136 hypother-
mia patients (55%) versus 54 of 137 (39%) normothermia
patients, as well as reduced mortality rates at 6 months.6
Neither study showed significant side effects, although ex-
periments with more profound hypothermia report decreased
cardiac output and dysrhythmia. We used only mild hypo-
and allowed for an early transition to normothermia by the treating team, which was done in almost a third of cases. Whereas the optimal temperature for hypothermia treatment remains to be established, tight temperature control is clearly crucial for neuroprotection, and body temperature must be closely observed in any neuroprotective drug study. Older drug trials may have failed to take this into account, which may have contributed to their failure to show any benefit.

Reperfusion injury and neuronal damage after a severe hypoxic-ischemic event are due to a range of mechanisms, including inflammation and excitotoxicity. Neurotransmitter release overstimulates metabotropic and ionotropic receptors and causes calcium and reactive oxygen species to accumulate. However, clinical studies with steroids, glutamate receptor antagonists, and calcium antagonists have been negative, with side effects including CNS and cardiodepression.\(^{27}\) Caspase activation, which can initiate programmed cell death after ischemia, may be modulated by metabotropic glutamate receptors,\(^ {23}\) but no clinical trials have targeted this pathway after cardiac arrest. Caspase activation also alters mitochondrial permeability, and the importance of mitochondrial dysfunction in reperfusion injury is gaining recognition.\(^ {24}\) Mitochondrial disruption causes ATP depletion, collapse of the electrochemical gradient, intracellular acidification, and failure of oxygen free radical detoxification.\(^ {25,26}\) Apoptosis is fueled by Cytochrome c release through mitochondrial permeability transition pores and release of apoptogenic molecules in a delayed process over many hours.\(^ {27}\)

Mitochondrial metabolism has not yet been targeted in treatment of severe hypoxia; however, mitochondrial intermediates can confer neuroprotection in neurodegenerative disorders. Recent studies suggest that CoQ10 is a potent neuroprotective agent that inhibits glutamate release and calcium influx, preserves the electrochemical gradient and reduces oxidative stress.\(^ {8}\) It improves oxidative metabolism in Huntington’s disease and has recently been shown to slow the progression of Parkinson’s disease.\(^ {7,9,10}\) In addition, CoQ10 improved bioenergetics in Friedreich ataxia,\(^ {28}\) confirming earlier experimental data demonstrating that CoQ10 protects mitochondrial metabolism from toxic damage.\(^ {29}\) After published human data, we used 450 mg CoQ10 daily and a loading dose of 250 mg; although Shults et al\(^ {10}\) have since demonstrated that 1200 mg/d is more effective than 600 mg/d in Parkinson’s disease, the optimal dose remains unclear. We did not measure serum CoQ10 levels because their relevance with respect to intracellular levels and under the extreme conditions of CPR is uncertain. Statins are the most commonly used medication with an influence on CoQ10; there was no significant difference between the groups (Table 1).

The difference in serum S100 protein levels between the two groups strongly suggests that the CoQ10 patients had less acute neuronal damage, and, together with the improved SSEP amplitude ratios, suggests that a neuroprotective effect primarily improves survival. A cardioprotective potential further supports combination of CoQ10 with hypothermia,\(^ {11}\) but we cannot determine what role it might have played here. Despite an increase of survival rate by 75%, the number of survivors in a persistent vegetative state was concerning (Figure 2). However, more patients in the CoQ10 group had an excellent neurological outcome (11 versus 5), too, although this did not reach statistical significance because of the small sample size. Thus, combined treatment may improve outcome in all grades of severity, leaving some who would otherwise have died alive but dependent but also allowing some survivors to recover completely who would otherwise have sustained severe hypoxic brain damage. The fact that the most striking difference in survival developed after CoQ10 treatment was terminated is no surprise, as delayed deaths almost always occurred in patients who emerged from ICU treatment with coma or severe neurological dysfunction. Thus, reduced early brain injury may correlate with improved long-term survival, whereas failure to improve in the first days makes for delayed death.

In conclusion, CoQ10 administration together with mild hypothermia appears to increase survival after cerebral hypoxia and may improve neurological outcome in survivors. This pilot study raises a number of questions that need to be addressed in larger trials. First, the mechanism by which CoQ10 may be effective needs to be elucidated; similarly, the optimal timing and dosage of CoQ10 remain undecided. Earlier treatment, possibly even before revascularization, should be considered, especially given the lack of side effects in our study. There are potential differences in efficacy between CoQ10 formulations; possibly lipophilic derivatives may be more effective due to better mitochondrial targeting.\(^ {30}\) Finally, the benefit of combining CoQ10 with other neuroprotective agents, for instance, targeting caspase activation, lipid peroxidation,\(^ {31}\) or inflammatory pathways, should be investigated, and neuroimaging data should be included in future studies.

Acknowledgments

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References


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