Efficacy and Safety of Endovascular Cooling After Cardiac Arrest
Cohort Study and Bayesian Approach

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Background and Purpose—Recently 2 randomized trials in comatose survivors of cardiac arrest documented that therapeutic hypothermia improved neurological recovery. The narrow inclusion criteria resulted in an international recommendation to cool only a restricted group of primary cardiac arrest survivors. In this retrospective cohort study we investigated the efficacy and safety of endovascular cooling in unselected survivors of cardiac arrest.

Methods—Consecutive comatose survivors of cardiac arrest, who were either cooled for 24 hours to 33°C with endovascular cooling or treated with standard postresuscitation therapy, were analyzed. Complication data were obtained by retrospective chart review.

Results—Patients in the endovascular cooling group had 2-fold increased odds of survival (67/97 patients versus 466/941 patients; odds ratio 2.28, 95% CI, 1.45 to 3.57; \( P < 0.001 \)). After adjustment for baseline imbalances the odds ratio was 1.96 (95% CI, 1.19 to 3.23; \( P = 0.008 \)). When discounting the observational data in a Bayesian analysis by using a sceptical prior the posterior odds ratio was 1.61 (95% credible interval, 1.06 to 2.44). In the endovascular cooling group, 51/97 patients (53%) survived with favorable neurology as compared with 320/941 (34%) in the control group (odds ratio 2.15, 95% CI, 1.38 to 3.35; \( P = 0.0003 \); adjusted odds ratio 2.56, 1.57 to 4.17). There was no difference in the rate of complications except for bradycardia.

Conclusion—Endovascular cooling improved survival and short-term neurological recovery compared with standard treatment in comatose adult survivors of cardiac arrest. Temperature control was effective and safe with this device. (Stroke. 2006;37:1792-1797.)

Key Words: brain ■ cardiopulmonary resuscitation ■ heart arrest ■ hypoxia

In industrial countries, per year 36 to 128 per 100 000 inhabitants experience a sudden out-of-hospital cardiac arrest. Fortunately, survival with favorable neurological recovery is still a rare event after resuscitation. Recently, 2 randomized trials documented that reducing the body temperature to 32°C to 34°C after successful restoration of spontaneous circulation could substantially improve neurological recovery. Based on these 2 trials international recommendations to cool comatose patients after cardiac arrest attributable to ventricular fibrillation have been formulated. A further small randomized trial included only patients after asystole or pulseless electrical activity and found a nonsignificant increase in survival and improvement of neurological recovery, indicating that there might be also some beneficial effect in these patients. Because of narrow inclusion criteria, the generalizability of these trials to an unselected population was limited. The second drawback was the partly insufficient cooling, especially in the European multicenter trial, where patients were cooled with cold air. Delays in cooling diminish or even abrogate the beneficial effects of hypothermia in experimental models.

Endovascular cooling is a routine rapid-cooling technique. A balloon catheter is inserted in a central vein and with a “closed loop” internal cooling circuit, the catheter cools the patient’s blood as it circulates past the catheter. The newer devices have also the advantage of automatic feedback control of patient’s temperature and provide controlled active rewarming.

The aim of this cohort study was to investigate the efficacy and safety of endovascular cooling in consecutively admitted survivors of cardiac arrest. We used a Bayesian approach to discount nonrandomized evidence.

Methods

Patients
We evaluated comatose patients after witnessed cardiac arrest and successful restoration of spontaneous circulation who were consec-
To be corrected for multiple testing.

Cooling we rewarmed the patients with a rate of 0.5°C/hour to 36°C.

Served as controls.

With an endovascular cooling device (Icy catheter and CoolGard

first 24 hours.

Hypothermia with a method other than endovascular cooling, if it

lasted longer than 240 minutes from restoration of spontaneous

circulation until the initiation of cooling, and if they died within

the first 24 hours.

The hypothermia group consisted of patients who were cooled

with an endovascular cooling device (Icy catheter and CoolGard

3000; Alsius Corp) with or without the administration of cold fluids

in the induction phase of therapeutic hypothermia. All other patients

served as controls.

General Management

The resuscitation therapy and postresuscitation care was according to

established guidelines. We used a standardized treatment protocol

for all patients after cardiac arrest at our institution. Besides

analgesia and sedation in all patients, we paralyzed the patients in the

endovascular cooling group with rocuronium 0.5 mg/kg initially and

for all patients after cardiac arrest at our institution. Besides

analgesia and sedation in all patients, we paralyzed the patients in the

endovascular cooling group with rocuronium 0.5 mg/kg initially and

used a continuous infusion of 0.5 mg/kg per hour thereafter.

Cooling Procedure

Without delay in patients of the endovascular cooling group, we

introduced the cooling device (Icy and CoolGard 3000; Alsius Corp)

into the inferior vena cava via a femoral vein and used a foley-

catheter with a temperature probe (Ruesch Sensor; Ruesch) for

automatic feed-back control of the patient’s temperature at 33°C. A

number of the patients received 50 mL/kg ice-cold Ringer’s lactate

during the induction phase of hypothermia. Some of these patients

are presented in detail elsewhere. Twenty-four hours after start of

cooling we rewarmed the patients with a rate of 0.5°C/hour to 36°C.

After the patients had reached normothermia, we kept the tempera-
ture below 37°C with usual clinical methods.

Definition of the End Points

As outcome parameter we recorded survival until 30 days after

cardiac arrest. We also recorded the neurological performance at 30

days with the cerebral performance category score (CPC). Good

neurological recovery was defined as CPC 1 or 2 (the patient is at

least alert and has sufficient cerebral function to live independently

and work part-time).

For the safety analysis, adverse events for the endovascular

cooling group were predefined and recorded prospectively. Controls

were selected by frequency matching. Matching criteria were wit-

nessed out-of-hospital ventricular fibrillation cardiac arrest of pre-

sumed cardiac cause with duration of cardiac arrest longer than 1

minute. In the control group a chart review was conducted to identify

all adverse events. Arrhythmias and bleeding events were recorded

between admission and 32 hours. Pneumonia, sepsis, acute renal

failure and pancreatitis were recorded within the first 7 days.

Statistical Methods

Continuous variables are given as mean±SD if they were normally

distributed or as median and the range between the 25th and 75th

quartile if they were not. Nominal data are given as counts and

percent of total number. We performed univariate comparisons

between groups with a X² test or Fisher exact test when indicated. For

safety analyses we used contingency tables and Fisher exact tests.

We did not correct for multiple testing.

Logistic Regression for Observational Data

We used a logistic regression model providing an approximate

normal likelihood for the odds ratio while adjusting for baseline

imbbalances. We entered the following baseline variables in the

model: age, history of diabetes, New York Heart Association score

before arrest, location out-of-hospital arrest, presumed cardiac cause,

ventricular fibrillation or ventricular tachycardia as primary rhythm,

basic life-support, no-flow, low-flow. We used standard procedures

to check proportionality of odds and model-fit.

Bayesian Analysis

In a retrospective Bayesian analysis the observed data (the likelihood)

modify a defined presudy probability (the prior distribution) to obtain

an updated probability (the posterior distribution) of the possible values

for the variable of interest. This represents a powerful mechanism for

incorporating information from previous studies and for controlling

confounding. Additionally, randomization is incidental, and it is

possible to assess any magnitude of therapeutic response with this

method.

From the posterior probability distributions, means and 95% credible

intervals were calculated. A 95% credible interval includes the true value of

the variable of interest with 95% probability. We discounted the cohort study data by assuming that the observed
effect was actually 0 and probability of exceeding the observed
effect was 5%.

The formulas used to calculate the posterior mean and variance of

the ln(OR) were:

\[ M_i = M_0 \frac{1}{V_0} + \frac{1}{V} \]

\[ V_i = \frac{1}{1 + \frac{1}{V}} \]

where \( M_i \) indicates posterior mean; \( M_0 \), data mean; \( V_0 \), prior variance; \( V_i \), posterior variance; \( V \), data variance.

We calculated also the magnitude of therapeutic response for a threshold of benefit of 10%, 20% and 30% using the skeptical prior
to discount the observational data. This magnitude of therapeutic
response gives the respective probability that the risk reduction
exceeds a putative “threshold of benefit” given the observational
data.

For all statistical calculations we used Stata, release 8.2 (StataCorp) and MS Excel 2002 (Microsoft). A P<0.05 was considered statistically
significan.

Results

Patients

Between August 1991 and November 2004, 1038 patients

fulfilled the inclusion and exclusion criteria and were in-
cluded in the analysis. Of the included patients, 97 were

treated with endovascular cooling and 941 served as controls

(supplemental Figure I, available online at http://stroke. ahajournals.org). The baseline demographic information of

all patients is given in Table 1.

Cooling Procedure

Continuous temperature and cooling data were available

only for the endovascular cooling group. Admission tym-
panic temperature was 35.4±1.1°C at 40 (interquartile range [IQR] to 58) minutes after cardiac arrest. Of the 97

patients who were cooled with endovascular cooling, 41 received additional cold Ringer’s lactate during induction

of hypothermia. Because this might influence the calculated

cooling rate of endovascular cooling, we restricted the following analysis to patients who received endovas-
cular cooling exclusively.

The bladder temperature at start of cooling 95 (IQR 67 to

156) minutes after restoration of spontaneous circulation was

35.3±1.0°C. It lasted 253 (IQR 170 to 345) minutes from
The cooling rate was 1.2 (IQR 0.7 to 1.5)°C/hour with endovascular cooling. The patients were cooled for 24.3 (IQR 22.0 to 25.5) hours. Thereafter, they were rewarmed within 388 (IQR 313 to 579) minutes to a temperature of 36°C (Figure 1).

In 14 of the 97 patients, cooling was terminated after median 11.7 (min 5.7; max 19.1) hours after start of cooling attributable to hemodynamic instability (n=2), bleeding at the catheter insertion site (n=2), transfer to the operation theater (n=2), obvious signs of brain death (n=1) and various other causes (n=7) including multiple organ failure and subarachnoid hemorrhage.

**Outcome**

Regardless of treatment, 533 of 1038 patients (51%) survived for 30 days and 371 of 1038 patients (36%) survived for 30 days and had favorable neurological recovery (CPC 1 or 2).

**Survival to 30 Days**

In the univariate analysis patients in the endovascular cooling group had 2-fold increased odds of survival (67 of 97 patients versus 466 of 941 patients; odds ratio 2.28, 95% CI, 1.45 to 3.57; P<0.001). After adjustment for baseline imbalances in a multivariate model the odds ratio was only slightly attenuated (odds ratio 1.96, 95% CI, 1.19 to 3.23; P=0.008). The model had an acceptable fit (Hosmer-Lemeshow χ²=7.39, df=8; P=0.495). When discounting the observational data in a Bayesian analysis by using a skeptical prior the posterior odds ratio was 1.61 (95% credible interval, 1.06 to 2.44; Figure 2). The calculated magnitude of therapeutic response for a threshold of benefit of 10%, 20% and 30% using the skeptical prior to discount the observational data is shown in Table 2.

**Survival to 30 Days or Until Discharge and Good Neurological Recovery**

In the univariate analysis 51/97 patients (53%) in the endovascular cooling group survived with favorable neurology as compared with 320/941 (34%) in the control group (odds ratio 2.15, 95% CI, 1.38 to 3.35; P=0.001). After adjustment for baseline imbalances in a multivariate model, the odds ratio was further increased (odds ratio 2.56, 95% CI, 1.57 to 4.17; P=0.001). The model had an acceptable fit (Hosmer-Lemeshow χ²=8.22, df=8; P=0.413).

**Safety of Endovascular Cooling**

There were no statistically significant differences in adverse events between the frequency-matched groups except for the occurrence of transient bradycardia (Table 3). In most cases the rate of adverse events was comparable. Transient increases in renal (n=11) and pancreatic enzymes (n=4) attended the period of cooling and resolved with rewarmin.

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**TABLE 1. Demographic and Resuscitation Data of the Patients in the Endovascular Cooling and Control Group**

<table>
<thead>
<tr>
<th></th>
<th>Endovascular Cooling (n=97)</th>
<th>Control (n=941)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>30 (31)</td>
<td>329 (35)</td>
<td>0.426</td>
</tr>
<tr>
<td>Age, y (IQR)</td>
<td>52 (42–62)</td>
<td>60 (50–70)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>9 (9)</td>
<td>179 (19)</td>
<td>0.018</td>
</tr>
<tr>
<td>New York Heart Association Class</td>
<td>1 (1–1)</td>
<td>1 (1–2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Out-of-hospital cardiac arrest, n (%)</td>
<td>89 (92)</td>
<td>608 (65)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cardiac cause of cardiac arrest, n (%)</td>
<td>82 (85)</td>
<td>600 (64)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ventricular fibrillation, n (%)</td>
<td>69 (71)</td>
<td>435 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BLS, n (%)</td>
<td>41 (42)</td>
<td>240 (26)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to initiation of BLS (no flow), min (IQR)</td>
<td>5 (1–9)</td>
<td>0 (0–5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time from initiation of BLS to ROSC (low flow), min (IQR)</td>
<td>15 (9–25)</td>
<td>13 (5–22)</td>
<td>0.0734</td>
</tr>
<tr>
<td>Rearrest within 24 h, n (%)</td>
<td>12 (12)</td>
<td>153 (16)</td>
<td>0.319</td>
</tr>
<tr>
<td>Survival at 1 mo, n (%)</td>
<td>67 (69)</td>
<td>466 (50)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Survival and Good Neurology (CPC 1 or 2) at 1 mo, n (%)</td>
<td>51 (53)</td>
<td>320 (34)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

IQR indicates range between the 25th and 75th quartile; No flow, time interval from cardiac arrest to first resuscitation attempts; ROSC, restoration of spontaneous circulation; BLS, basic life-support.

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restoration of spontaneous circulation to reach the target temperature of 33°C. The cooling rate was 1.2 (IQR 0.7 to 1.5)°C/hour with endovascular cooling. The patients were cooled for 24.3 (IQR 22.0 to 25.5) hours. Thereafter, they were rewarmed within 388 (IQR 313 to 579) minutes to a temperature of 36°C (Figure 1).

In 14 of the 97 patients, cooling was terminated after median 11.7 (min 5.7; max 19.1) hours after start of cooling attributable to hemodynamic instability (n=2), bleeding at the catheter insertion site (n=2), transfer to the operation theater (n=2), obvious signs of brain death (n=1) and various other causes (n=7) including multiple organ failure and subarachnoid hemorrhage.

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**Figure 1.** Bladder temperature course. Median, 25th and 75th quartile of bladder temperature after return of spontaneous circulation in patients, who were exclusively cooled with the endovascular cooling device (n=56). Target temperature, 33°C; cooling duration, 24 hours.
Dialysis or other clinical interventions were not required. Attributable to bleeding at the insertion site of the endovascular cooling catheter, cooling was terminated in 2 cases (5 and 14 hours after start of cooling). One of the 2 cases received thrombolysis, the other underwent coronary angioplasty. However, the total number of bleeding events was not different between the groups.

**Discussion**

Treatment of unselected patients after resuscitation from cardiac arrest with the Icy-CoolGard3000 cooling device significantly reduced mortality and improved favorable neurological recovery at 30 days or discharge as compared with controls from our resuscitation database. Therapeutic hypothermia with endovascular cooling was not associated with a higher rate of adverse events.

Based on 2 randomized controlled trials, mild therapeutic hypothermia both reduced neurological damage and improved survival in primary survivors of cardiac arrest. The discounted odds ratio obtained in the Bayesian analysis of 1.61 (95% credible interval, 1.06 to 2.44) found in our study compared well to the calculated odds ratios of 1.77 (95% CI, 1.07 to 2.94) and 2.00 (95% CI, 0.71 to 5.69) in the 2 large randomized trials. In contrast to these studies, consecutive patients with various causes of arrest and with other primary rhythms than ventricular fibrillation or ventricular tachycardia were included in our trial. This makes the results obtained by our study more generalizable and suggests that hypothermia will be the therapy of choice for all comatose patients who are successfully resuscitated from cardiac arrest.

The cooling rate of 1.2°C/hour in our study compared well with reported cooling rates of endovascular cooling in stroke, subarachnoid hemorrhage, myocardial infarction and cardiac arrest, which was between 0.8°C/hour and 4.8°C/hour. This rate was much faster than external cooling with a water-filled cooling blanket or with cold air where 14% of the patients never reached target temperature, 70% required additional ice packs and the mean time to target temperature was 480 minutes.

Recently, a rapid method of induction of hypothermia was studied by Bernard et al. The infusion of 30 mL/kg of ice-cold (4°C) intravenous lactated Ringer’s solution over 30 minutes achieved a rapid decrease in median core temperature from 35.5°C to 33.8°C (cooling rate 3.4°C/hour) in 22 comatose survivors of out-of-hospital cardiac arrest. The combination of these 2 techniques would induce hypothermia.

| **TABLE 2. Posterior Probability of Benefit of Empirical Data Discounted With a Skeptical Prior** |
|---|---|---|
| Threshold of Benefit, % | Posterior Probability of Benefit of Empirical Data Discounted With a Skeptical Prior |
| 10 | 0.96 |
| 20 | 0.92 |
| 30 | 0.84 |

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**Figure 2.** Discounted odds ratio of observational data. Odds ratio (log-scale) for observational data by applying a skeptical prior (assuming that the observed effect is actually 0 and probability of exceeding the observed effect was 5%). Dotted line, skeptical prior; dashed line, observational data; continuous line, posterior odds ratio (discounted data).
rapidly and then allows a convenient control of the temperature over the selected time by endovascular cooling. A further advantage of endovascular cooling is the possibility of an individual rewarming speed which could be adapted to various etiologies of ischemic damage.

There was no statistically significant difference in adverse events between the endovascular cooling group and the control group except for bradycardia (Table 3). The elevated number of minor bleedings at the cooling catheter insertion site could be explained by the use of anticoagulation in patients who had a myocardial infarction and underwent thrombolysis or angioplasty. Pneumonia and sepsis might be a further problem as suggested by the European multicenter trial of therapeutic hypothermia after cardiac arrest.4 These complications did not occur more frequently in the endovascular cooling group in our study. If this was caused by the more precise temperature management attributable to feedback, control of bladder temperature is not known, but there was virtually no overshoot during induction of hypothermia (Figure 1).

There are several limitations to mention. This trial was not blinded for the assessment of neurological outcome, which might have lead to information bias. This is not an issue, however, for the end point of survival. Furthermore, only few patients with unfavorable neurological recovery survive hospital discharge,4 and “Do Not Resuscitate” orders might also have an impact on outcome. Because this was a retrospective cohort study, selection bias might have occurred. Although there has been a department policy of cooling all patients after cardiac arrest, who fulfilled the inclusion and exclusion criteria, the final decision to cool a patient was left to the discretion of the attending physician. Therefore, it is possible that a higher proportion of patients with expected bad outcome have not been cooled. There were imbalances in prognostic baseline variables. We tried to adjust for these imbalances by using standard multivariate analyses. We like to point out that the outcome was only moderately confined by the baseline imbalances. A further problem might be that the exact course of the resuscitation can only be estimated.25 We tried to reduce this problem by thoroughly interviewing all involved individuals immediately after resuscitation and entering all data in a central database. All of these limitations could have led to an overestimation of effect size. This was accounted for by further discounting the result by a skeptical prior in a Bayesian analysis. We like to point out that the outcome was only moderately confined by the baseline imbalances. A further problem might be that the exact course of the resuscitation can only be estimated.25 We tried to reduce this problem by thoroughly interviewing all involved individuals immediately after resuscitation and entering all data in a central database. All of these limitations could have led to an overestimation of effect size. This was accounted for by further discounting the result by a skeptical prior in a Bayesian analysis.

Endovascular cooling via the Icy-CoolGard cooling device improved survival and short-term neurological recovery compared with standard treatment in adult survivors of cardiac arrest. Temperature control was effective and safe with this device.

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Disclosures
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M.M., A.Z. and A.N.L. have no conflicts of interest to declare.

References


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