Intensivmed 44:37–42 (2007)
DOI 10.1007/s00390-007-0740-7

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Endovascular cooling improves neurological short-term outcome after prehospital cardiac arrest

Endovaskuläre Kühlung verbessert das frühe neurologische Ergebnis nach prähospitalem Herz-Kreislauf-Stillstand

▶ **Zusammenfassung** Der Einsatz milder Hypothermie nach prähospitalem Herz-Kreislauf-Stillstand verbessert das neurologische Ergebnis dieser Patienten. Ein gängiges Verfahren zur Induktion milder Hypothermie ist die Oberflächenkühlung mittels Eispacks. Eine neuere Methode stellt die endovaskuläre Kühlung dar, die sich als sicher und praktikabel erwiesen hat. Ob sich aufgrund präziserer Temperaturkontrolle unter klinischen Alltagsbedingungen mit diesem Verfahren bessere neurologische Frühergebnisse erzielen lassen, untersuchten wir retrospektiv an 39 Patienten nach prähospitalem Herz-Kreislauf-Stillstand.

Die Kühlung erfolgte entweder mit Hilfe eines endovaskulären Systems (n = 19, Gruppe 1) oder mittels Applikation von Eispacks (n = 20, Gruppe 2) für jeweils 24 h. Die Zieltemperatur betrug 33 °C in Gruppe 1 und 32–34 °C in Gruppe 2. Verglichen wurden die Effektivität der Kühlung sowie das neurologische Ergebnis anhand der cerebral performance category (CPC) zum Zeitpunkt der Krankenhausentlassung.

Die Basischarakteristika der Patientengruppen waren vergleichbar. Während der Hypothermiephase wurde die Zieltemperatur bei allen Patienten in Gruppe 1 erzielt, jedoch nur bei zwei Patienten in Gruppe 2 ($p < 0{,}001$). Die mittlere Körperkerntemperatur betrug $32{,}9 \pm 0{,}1$ °C in Gruppe 1 und $36{,}1 \pm 1{,}3$ °C in Gruppe 2 ($p < 0{,}001$). Bei Krankenhausentlassung hatten mehr Patienten in Gruppe 1 ein gutes neurologisches Ergebnis (47,4% CPC 1/2 in Gruppe 1 vs. 20,0% CPC 1/2 in Gruppe 2; $p = 0{,}08$). In der Subgruppe der Nicht-Diabetiker war dieser Unterschied noch deutlicher (63,6% CPC 1/2 in Gruppe 1 vs. 23,1% CPC 1/2 in Gruppe 2; $p = 0{,}007$).

Verglichen mit der Applikation von Eispacks zur Induktion milder Hypothermie nach prähospitalem Herz-Kreislauf-Stillstand verbessert die endovaskuläre Kühlung unter klinischen Alltagsbedingungen das frühe neurologische Ergebnis, insbesondere bei Nicht-Diabetikern. Dieser Effekt ist vornehmlich auf die deutlich verbesserte Effektivität dieses neueren Verfahrens zurückzuführen.

▶ **Schlüsselwörter**
Milde Hypothermie – Herz-Kreislauf-Stillstand – Endovaskuläre Kühlung – Retrospektive Studie

▶ **Abstract** Mild hypothermia following successful resuscitation from prehospital cardiac arrest has shown to improve patient's short-term neurological outcome. Usually, extracorporal methods are performed to achieve a core temperature of 32–34 °C. Recently, an endovascular cooling device has proven to be safe and feasible to induce mild hypothermia. Because of precise target temperature control in daily clinical routine, the endovascular method might lead to more favorable neurological outcomes than extracorporal cooling using cold packs.

Received: 18 May 2006
Accepted: 16 June 2006

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We retrospectively studied 39 patients after prehospital cardiac arrest from various causes, who were treated with mild hypothermia for 24 h either by an endovascular cooling device (group 1; n = 19) or by an extracorporal method (group 2; n = 20) using cold packs. Target temperature was 33 °C in group 1 and 32-34 °C in group 2. The efficiacy of the cooling procedure and patient's neurological outcome (classified by cerebral performance category CPC) at the time of hospital discharge were compared between both groups.

Patient's baseline characteristics were comparable between both groups. During hypothermia, the target temperature was reached in all cases in group 1 but only in two cases in group 2 ($p < 0.001$). Mean core temperature was 32.9 ± 0.1 °C in group 1 and 36.1 ± 1.3 °C in group 2 ($p < 0.001$). At the time of hospital discharge, more patients in group 1 had a good neurological outcome (group 1 vs group 2, 47.4% CPC 1/2 vs 20.0% CPC 1/2; $p = 0.08$). In the subgroup of non-diabetic patients, this difference was even more pronounced (group 1 vs group 2, 63.6% CPC 1/2 vs 23.1% CPC 1/2; $p = 0.007$).

Compared to an extracorporal method using cold packs, endovascular cooling can improve neurological short-term outcome after prehospital cardiac arrest, especially in non-diabetics. This effect results from better target temperature control in daily clinical routine.

▶ **Key words** mild hypothermia – cardiac arrest – endovascular cooling – retrospective study

Introduction

Prehospital cardiac arrest is a frequent event with an incidence of 0.04 to 0.13% of the total population per year in Europe [1, 2]. Despite some significant improvement of survival until hospital admission, the neurological outcome of these patients remains poor [3–5], depending on the duration of global brain ischemia caused by cardiac arrest and on the magnitude of reperfusion injury after return of spontaneous circulation [6, 7]. The application of therapeutic mild hypothermia following cardiopulmonary resuscitation (CPR) has clearly shown to improve patients neurological recovery [8, 9], presumably by mechanisms that mitigate reperfusion injury [10, 11]. Various methods for the induction of mild hypothermia have been described [8, 9, 12, 13]. A procedure generally used is the application of cold packs to the patients head and torso [9] to achieve a core temperature of 32 to 34 °C. This method has been shown to be feasible in the setting of clinical trials [9, 14]. However, it is laborious and time-consuming and therefore, it may not be as effective for target temperature control in daily clinical routine. Recently, an endovascular cooling device has proven to be safe and feasible to induce mild hypothermia after prehospital cardiac arrest [15]. Because of precise target temperature control with a minimal amount of work, this endovascular cooling method might lead to more favorable short-term neurological outcomes in the setting of daily clinical routine than the use of cold packs. Therefore, we undertook an observational clinical trial to analyze the effectiveness of both cooling methods and to assess their impact on neurological short-term outcome in patients after prehospital cardiac arrest.

Materials and methods

We retrospectively analyzed 39 patients following successful resuscitation from prehospital sudden cardiac arrest, who were treated with mild hypothermia.

Endovascular cooling group

We studied 19 patients admitted to our intensive care unit between January 1 and September 30, 2005, who were scheduled to be treated with mild hypothermia using an endovascular cooling device (CoolGard™ system with the Icy™ catheter, Alsius Corporation, Irvine, CA, USA). All patients met the following criteria for treatment with mild hypothermia: 18 years of age or older, suspicion of primary cardiac arrest and return of spontaneous circulation (ROSC) without regained conciousness (Glasgow Coma Scale [GCS] < 9). All patients were treated regarding the cause of cardiac arrest as per standard care, including medical therapy or percutaneous coronary intervention [PCI] with or without implantation of coronary stents, if indicated. Thereafter, therapeutic mild hypothermia was applied using the CoolGard™ Temperature Control System with the Icy™ catheter. The function of this device has recently been described elsewhere, and its safety has been proven [15]. In principle, the system consists of a temperature control unit connected to a heat-exchange catheter placed in the inferior vena cava via the femoral route. Cold saline pumped through the catheter serves as the heat-exchanging medium to reduce body core temperature. The target temperature was set at 33 °C with maximum cooling rate. Hypothermia was maintained for 24 h following

a rewarming phase of another 24 h with a rewarming rate of 0.15 °C/h. After reaching the target rewarming temperature of 37 °C, the catheter was removed. All patients were intubated and mechanically ventilated for at least 48 h. Sedation was performed with midazolam and fentanyl. Cisatracurium was used for pharmacological paralysis to prevent shivering. Core body temperature was measured continuously using a temperature probe placed in the rectum. Patients received volume expansion or vasopressors/inotropics, if appropriate, to maintain a mean arterial pressure (MAP) >65 mmHg. Early enteral feeding was performed via a nasogastric tube. Elevated blood glucose levels were treated with continuous intravenous insulin infusion. Patients received deep venous thrombosis prophylaxis and stress ulcer prophylaxis, if indicated. All further treatment and management of complications were performed according to standard procedures.

Extracorporal cooling group

The extracorporal cooling group consisted of 20 patients admitted to our intensive care unit within the year 2004, who were treated with mild hypothermia using an extracorporal method. The criteria for the implementation of mild hypothermia were the same as in the endovascular cooling group. Mild hypothermia was induced using cold packs applied on the patientś neck and torso, aiming for a target temperature of 32–34 °C. After 24 h, the cold packs were removed and passive rewarming was allowed. Except for the method of cooling, standard care as well as the therapeutic principles and procedures in the extracorporal cooling group did not differ from those in the endovascular cooling group.

Data acquisition

Data were collected retrospectively by chart review in both patient groups. Baseline characteristics consisted of the following: age, sex, initial rhythm (as documented by the emergency doctor), cause of sudden cardiac arrest, bystander CPR, time from cardiac arrest to the beginning of CPR (in time intervals of each 5 min) and known diabetes or arterial hypertension, respectively. To compare the effectiveness of both cooling procedures, minimal temperatures, time to reach target temperatures (calculated from the time of admission to the intensive care unit) and duration of effective hypothermia were recorded. Any serious adverse events related to the cooling procedures were documented. Outcome parameters were neurological status, classified according to the cerebral performance category [16], at the time of hospital discharge, or in-hospital death. Cerebral performance categories (CPC) 1 or 2 were regarded as good neurological outcome, and CPCs 3 or 4 were regarded as impaired neurological outcome.

Statistics

Statistical analyses were performed using a statistical software package (SPSS Version 11.0, SPSS Inc., Chicago, USA). Continuous variables are presented as mean ± standard deviation. One-sample Kolmogorov-Smirnoff tests were performed to test continuous variables for normal distribution. For comparisons between the groups, Students t-tests or Mann-Whitney U-tests were performed, as appropriate. Ordinal data were compared using chi-square tests. A test giving a p value of <0.05 was considered statistically significant.

Results

Baseline characteristics

Baseline characteristics of both patient groups are presented in Table 1. There were no significant differences between the groups. However, in the subgroup of non-diabetic patients (n = 24), more patients in the extracorporal cooling group presented with asystole as the initial rhythm (n = 0 in the endovascular cooling group vs n = 3 in the extracorporal cooling group). In the same subgroup, more patients in the extracorporal cooling group had received bystander CPR (n = 0 in the endovascular cooling group vs n = 6 in the extracorporal cooling group). No further differences in baseline parameters could be observed between the both patient groups divided into diabetic and non-diabetic patients.

Effectiveness of cooling procedures

In the endovascular cooling group, the target temperature of 33 °C was reached in all (100%) patients, whereas in the extracorporal cooling group, an effective hypothermia of 32–34 °C could be achieved only in 2 (10%) patients ($p<0.01$). Minimal temperatures were 32.9 ± 0.1 °C in the endovascular cooling group and 36.1 ± 1.3 °C in the extracorporal cooling group (Fig. 1). The target temperatures were reached at 8.7 ± 4.3 h in the patients cooled by the endovascular method, and in 4 and 2 h, respectively, in the two

Table 1 Baseline characteristics

	Endovascular cooling (n = 19)	Extracorporal cooling (n = 20)	P value
Age, Mean ± SD	61 ± 13	63 ± 13	0.55
Sex, Male/Female	14/5	12/8	0.37
Cause of CA			0.44
CAD with AMI	11 (57.9%)	10 (50%)	
CAD without AMI	3 (15.8%)	7 (35%)	
DCM	3 (15.8%)	1 (5%)	
Others	2 (10.5%)	2 (10%)	
Initial rhythm			0.19
VF	17 (89.5%)	16 (80%)	
Asystole	1 (5.3%)	4 (20%)	
PEA	1 (5.3%)	0 (0%)	
Bystander CPR			0.17
Yes	3 (15.8%)	7 (35%)	
No	16 (84.2%)	13 (65%)	
Time to CPR (min)			0.41
0–5	0 (0%)	0 (0%)	
6–10	11 (57.9%)	10 (52.6%)	
11–15	5 (26.3%)	8 (42.1%)	
16–20	3 (15.8%)	1 (5.3%)	
Diabetes mellitus			0.65
Yes	8 (42.1%)	7 (35%)	
No	11 (57.9%)	13 (65%)	
Arterial hypertension			0.42
Yes	12 (63.2%)	15 (75%)	
No	7 (36.8%)	5 (25%)	

SD standard deviation, *CA* cardiac arrest, *CAD* coronary artery disease, *AMI* acute myocardial infarction, *DCM* dilated cardiomyopathy, *VF* ventricular fibrillation, *PEA* pulseless electrical activity, *CPR* cardiopulmonary resuscitation

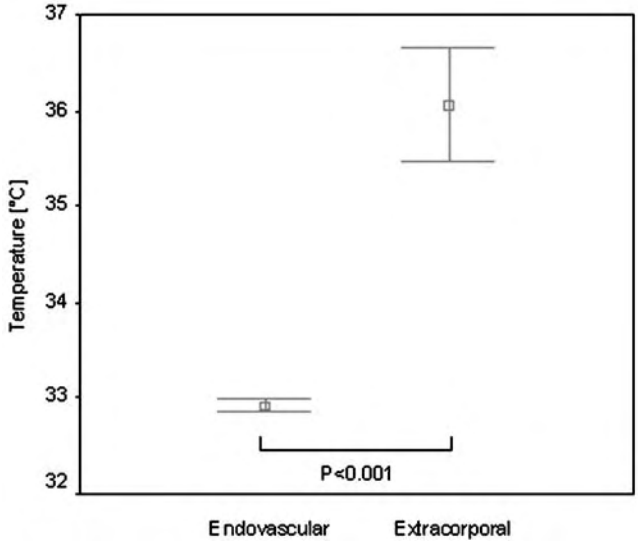

Fig. 1 Minimal temperatures during the cooling procedures in the two patient groups

patients of the extracorporal cooling group. In these two patients, the duration of effective hypothermia was 4 and 1 hour, respectively. In the endovascular cooling group, effective hypothermia was maintained for 24.6 ± 3.3 h. No serious adverse events related to the cooling procedure could be observed in the patient group cooled by the extracorporal method. One patient of the endovascular cooling group suffered from serious bradycardia (< 30/min) during hypothermia, which required the application of a temporary transvenous pacemaker. No further serious procedure-related adverse events could be observed.

Outcome

Mean length of hospital stay was 20.2 ± 12.6 days in the endovascular cooling group and 24.2 ± 23.4 days in the extracorporal cooling group (p = 0.52). At the time of hospital discharge, there was a trend toward a more favorable neurological outcome in the endovascular cooling group (Fig. 2). This difference became significant in the subgroup of non-diabetic patients (Fig. 3). No difference in survival at hospital discharge could be observed between the treatment groups (endovascular cooling group vs extracorporal cooling group, 59.9% vs 55%, p = 0.86).

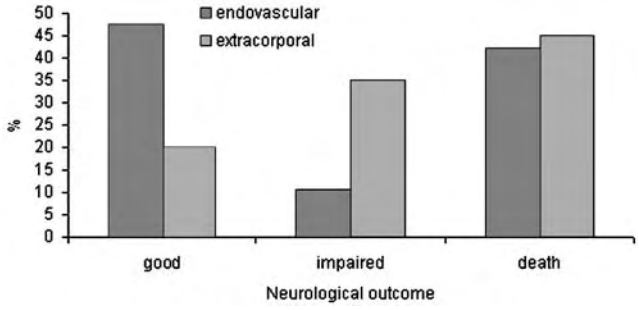

Fig. 2 Neurologic outcome and death of patient groups cooled by the endovascular and extracorporal method, respectively (p = 0.08 for comparison between groups; chi-square test)

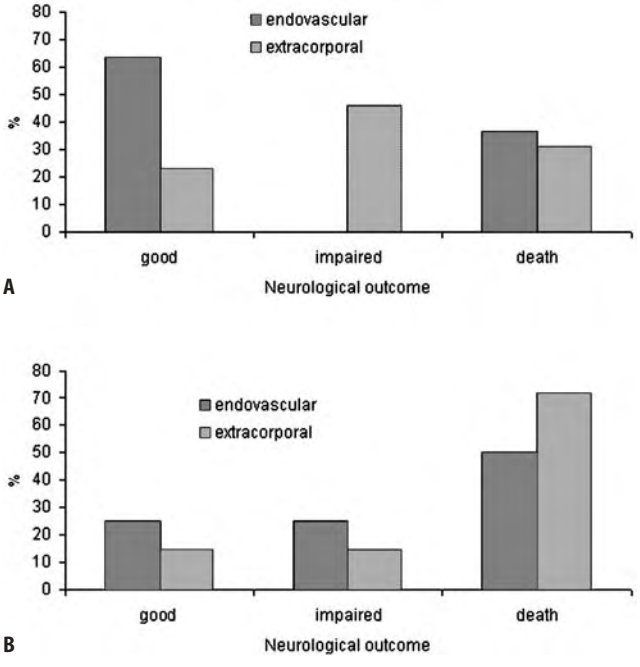

Fig. 3 Neurologic outcome and death of patient groups cooled by the endovascular and extracorporal method, respectively, **A** Non-diabetics (p = 0.007 for comparison between groups; chi-square test). **B** Diabetics (p = 0.70 for comparison between groups; chi-square test)

Discussion

To date, mild therapeutic hypothermia is the only evidence based neuroprotective procedure for patients after successful resuscitation from prehospital sudden cardiac arrest. Its beneficial effect on neurological outcome and on survival has been shown in two randomized, controlled trials [8, 9], and its use in patients after sudden cardiac arrest has recently been recommended by the International Liaison Committee on Resuscitation [17]. To make the most of the neuroprotective effect of mild hypothermia, it is important to apply it in a way that offers precise target temperature control and simple performance in daily clinical routine. The aim of this study was to compare an extracorporal cooling procedure using cold packs with an endovascular cooling method using the CoolGard^{TM} System with the Icy^{TM} catheter under daily clinical routine conditions.

We could clearly demonstrate that the endovascular cooling device was superior to the extracorporal method in achieving and maintaining target temperatures under these conditions. Only two patients in the extracorporal cooling group reached effective temperatures of 32–34 °C during the hypothermia phase, and they reached them only for a short time. However, all patients of the endovascular cooling group were effectively cooled down for more than 24 h. The disappointing results in the patients cooled by the extracorporal method are in contrast to the findings of Bernard and coworkers [9], who achieved effective target temperatures in 43 patients after prehospital cardiac arrest and maintained them for about 12 h by using cold packs applied to the patientś head and torso. However, these results were achieved in a randomized, controlled trial, which may not reflect daily clinical routine. Extracorporal cooling using cold packs is labor-intensive and requires significant nursing attention. Moreover, many patients after prehospital cardiac arrest develop febrile temperatures [18, 19], which further complicates the procedure of effective extracorporal cooling. Thus, our observations concerning the effectiveness of extracorporal cooling using cold packs may represent a more realistic scenario than a prospective trial.

The most important result of our study was the difference in short term neurological outcome between the patient groups. At the time of hospital discharge, about 27% more good neurological results (CPC 1/2) could be observed in the patient group cooled by the endovascular device. Although previous studies comparing hypothermia with normothermia after prehospital cardiac arrest reported similar results [8, 9], it is surprising to find such a difference in neurological outcomes when comparing two methods of applying hypothermia. However, extracorporal cooling using cold packs was not effective in achieving target temperatures of 32–34 °C in our study. We could demonstrate, that in daily clinical routine, applying mild therapeutic hypothermia to patients after prehospital cardiac arrest is much more effective using an endovascular cooling device than using cold packs, resulting in better short term neurological outcomes.

Interestingly, we could observe this beneficial effect especially in non-diabetic patients, whereas diabetics showed no differences in neurological short-

term outcome with respect to the cooling procedure. Although a recent study showed lower survival rates in diabetic patients after prehospital cardiac arrest [20], it is not clear why we could not find improved neurological results in diabetics treated with effective mild hypothermia. A known side effect of hypothermia is insulin resistance and a decrease in insulin levels [21], which might have led to more elevated glucose levels despite insulin therapy in the patient group cooled by the endovascular device, especially in the subgroup of diabetics. As hyperglycemia is associated with neurological complications in critically ill patients [22], the beneficial effect of effective mild hypothermia on neurological recovery may have been diminished by the difficulty to treat insulin resistance in diabetics. However, more studies are needed to confirm this hypothesis.

Our study has two major limits. First, due to the retrospective nature of this analysis, potential confounders cannot be excluded. However, this type of study may reflect the true benefit of endovascular cooling in daily clinical routine better than prospectively aquired data. Second, the sample size was small, explaining the borderline significance of the differences observed. Nevertheless, we believe that these data gathered in a single center are highly supportive of a clinically relevant benefit of endovascular as opposed to external cooling after prehospital cardiac arrest.

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