Mild hypothermia treatment in patients resuscitated from non-shockable cardiac arrest

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Accepted 9 January 2011
Published Online First
1 March 2011

ABSTRACT

Objective Therapeutic hypothermia has proved effective in improving outcome in patients after cardiac arrest due to ventricular fibrillation (VF). The benefit in patients with non-VF cardiac arrest is still not defined.

Methods This prospective observational study was conducted in a university hospital setting with historical controls. Between 2002 and 2010 387 consecutive patients have been admitted to the intensive care unit (ICU) after cardiac arrest (control n=186; hypothermia n=201). Of those, in 175 patients the initial rhythm was identified as non-shockable (asystole, pulseless electrical activity) rhythm (control n=88; hypothermia n=87). Neurological outcome was assessed at ICU discharge according to the Pittsburgh cerebral performance category (CPC). A follow-up was completed for all patients after 90 days, a Kaplan–Meier analysis and Cox regression was performed.

Results Hypothermia treatment was not associated with significantly improved neurological outcome in patients resuscitated from non-VF cardiac arrest (CPC 1–2: hypothermia 27.59% vs control 18.20%, p=0.175). 90-Day Kaplan–Meier analysis revealed no significant benefit for the hypothermia group (log rank test p=0.82), and Cox regression showed no statistically significant improvement.

Conclusions In this cohort patients undergoing hypothermia treatment after non-shockable cardiac arrest do not benefit significantly concerning neurological outcome. Hypothermia treatment needs to be evaluated in a large multicentre trial of cardiac arrest patients found initially to be in non-shockable rhythms to clarify whether cooling may also be beneficial for other rhythms than VF.

In 2002, randomised controlled trials demonstrated that therapeutic hypothermia is an effective measure to improve neurological outcome in patients after cardiac arrest.[1 2] Based on the patient groups included in these trials the International Liaison Committee on Resuscitation recommended this treatment in 2003 for all comatose survivors after out-of-hospital cardiac arrest due to ventricular fibrillation (VF). In addition, the International Liaison Committee on Resuscitation stated that patients with other rhythms might also benefit from therapeutic hypothermia.[3] Consequently, many published hypothermia protocols used in daily clinical practice include patients after cardiac arrest independently of the initial rhythm and report no relevant side effects.[4 5]

It is well known that patients resuscitated from non-VF share a poor prognosis.[6] At present there is little knowledge on whether therapeutic hypothermia improves outcomes in patients resuscitated from non-shockable (asystole, pulseless electrical activity; PEA) cardiac arrest as it does in patients resuscitated from shockable rhythm (VF).[7] Therefore we conducted a single centre prospective observational database including patients after cardiac arrest admitted to our intensive care unit (ICU) between 2002 and 2010. This is a subanalysis of patients with non-shockable initial rhythm. Due to the implementation of mild therapeutic hypothermia in recent years we compared controls (non-hypothermia group) included before the era of hypothermia with cardiac arrest patients undergoing cooling treatment (hypothermia group).

METHODS

The study protocol was approved by the local ethics committee on human research. Written informed consent to the use of routine clinical data is part of the standard contract between patients and the University Hospital Charité Berlin and was obtained from patients or their legal representatives, if available. Due to our local standard procedures all patients after out-of-hospital cardiac arrest were directly admitted to the ICU. Between 2002 and 2010 387 consecutive patients have been admitted to our ICU after cardiac arrest (control n=186; hypothermia n=201). Of those, in 175 patients the initial rhythm was identified as non-shockable (asystole, PEA) rhythm (control n=88; hypothermia n=87). After implementation of hypothermia treatment in January 2007 all patients regardless of initial rhythm have been cooled over 24 h as a result of current guidelines. None of the cardiac arrest survivors admitted to ICU has been excluded from hypothermia treatment. Detailed characteristics of the study population are given in table 1. During the admission procedure therapeutic hypothermia was initiated in all patients with the infusion of cold saline (1000 ml sodium chloride 0.9% over 30 min) and circulating water blankets (ArcticSun, Medivance Louisville, USA) following our local standard operating procedure. The target temperature of 33°C was reached in a range of 180–320 min and was maintained for 24 h. No major complications (malignant arrhythmia: VF or Torsades des points) or serious adverse events (potassium imbalance) that would have made it necessary to stop cooling were observed during the hypothermia procedure. Sedation was induced in all patients by intravenous midazolam (0.125 mg/kg per hour) and fentanyl (0.002 mg/kg per hour) with dose adjustment as needed. Paralysis was induced with pancuronium (0.1 mg/kg) during hypothermia treatment to prevent shivering. In addition, all patients received standard post-resuscitation care. In none of the patients was hypothermia treatment stopped prematurely. Controlled re-warming was performed with a temperature increase of 0.25°/h.

Table 1 Baseline characteristics, n=175

Variable	Non-hypothermia (n=88)	Hypothermia (n=87)	p Value
Age, years	63 (52–73)	65 (53–75)	0.82
Female sex, n/total n (%)	29/88 (33)	34/87 (39)	0.40
APACHE score	25 (19–32)	31 (25–35)	**0.02**
Location of cardiac arrest			
Out-of-hospital, n/total n (%)	61 (69.3)	66 (75.9)	0.33
In-hospital, n/total n (%)	27 (30.7)	21 (24.1)	
Cause of cardiac arrest			
AMI, n/total n (%)	28 (31.8)	12 (13.8)	0.25
Primary arrhythmia, n/total n (%)	20 (22.7)	26 (29.9)	
Respiratory, n/total n (%)	36 (40.9)	44 (50.6)	
Other, n/total n (%)	4 (4.5)	1 (1.1)	
Initial rhythm			
Asystole, n/total n (%)	64 (72)	63 (72)	
PEA, n/total n (%)	24 (28)	24 (28)	
Time to ROSC, min	20 (12–30)	16 (12–25)	**0.02**
Total epinephrine dose, mg	3 (2–5)	2 (1–4)	**0.01**
Length of ICU stay, days	11.5 (6–22)	8 (4–27)	0.05
Time on ventilator, h	193 (93–340)	149 (80–407)	0.16
PCI, n/total n (%)	25 (28)	27 (31)	0.74

Data are presented as medians (25th and 75th percentiles) or as absolute numbers (relative frequencies).
A value of $p<0.05$ was considered to be statistically significant.
AMI, acute myocardial infarction; APACHE II, Acute Physiology and Chronic Health Evaluation II; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ICU, intensive care unit; PEA, pulseless electrical activity; PCI, percutanous coronary intervention, ROSC, return of spontaneous circulation.

Neurological outcome was defined at the time of discharge from the ICU according to the Pittsburgh cerebral performance category (CPC) while the defining physician on duty was blinded to the study.[8] CPC 1 and 2 were classified as a favourable neurological outcome, whereas CPC 3, 4 and 5 were regarded as an unfavourable outcome. A follow-up concerning mortality was completed for all patients after 90 days.

SPSS software (version 17.0) was used for statistical analysis. Descriptive parameters are given as median and IQR (25th–75th percentiles). Univariate analysis of differences between hypothermia patients and the control group was performed by using the Mann–Whitney U test for non-parametric unpaired data and Fisher's exact test for dichotomous variables. Survival data were analysed by the Kaplan–Meier analysis and comparison between groups was performed by the log rank test, Cox regression was used to adjust for confounders.

RESULTS

Figure 1 shows patient recruitment. The results of univariate analysis are given in table 1. Hypothermia treatment was associated with improved neurological outcome without reaching a level of significance in patients resuscitated from non-VF cardiac arrest (CPC 1–2: hypothermia 27.59% vs control 18.20%, p=0.175). Differences between unfavourable outcome and death were only minor (CPC 3–5: hypothermia 72.41%, control 81.80%; CPC 5: hypothermia 58.62%, control 63.64%, p=1.00) (table 2).

Patients in the hypothermia group tended to have a shorter duration of ventilator treatment (hypothermia 149 h, 80–407 IQR; non-hypothermia 193 h, 93–340 IQR, p=0.16) and a shorter stay in the ICU (hypothermia 8 days, 4–27 IQR; non-hypothermia 11.5 days, 6–22 IQR, p=0.05) without reaching a level of significance, whereas time to return of spontaneous circulation (ROSC; hypothermia 16 min, 12–25 IQR; non-hypothermia 20 min, 12–30 IQR, p=0.02) and epinephrine dosage (hypothermia 2 mg, 1–4 IQR; non-hypothermia 3 mg, 2–5 IQR, p<0.01) was significantly lower in patients undergoing hypothermia treatment.

Kaplan–Meier analysis after 90 days revealed no significant benefit for the hypothermia group (log rank test p=0.82), and Cox regression showed no statistically significant improvement for survival (figure 2 and table 3).

DISCUSSION

Only a minority of published data are concerned with the role of mild therapeutic hypothermia in patients with initially non-shockable rhythm.[9] Published guidelines from the Clinical Practice Committee of the Scandinavian Society of Anaesthesiology for Hypothermia recommend hypothermia also after

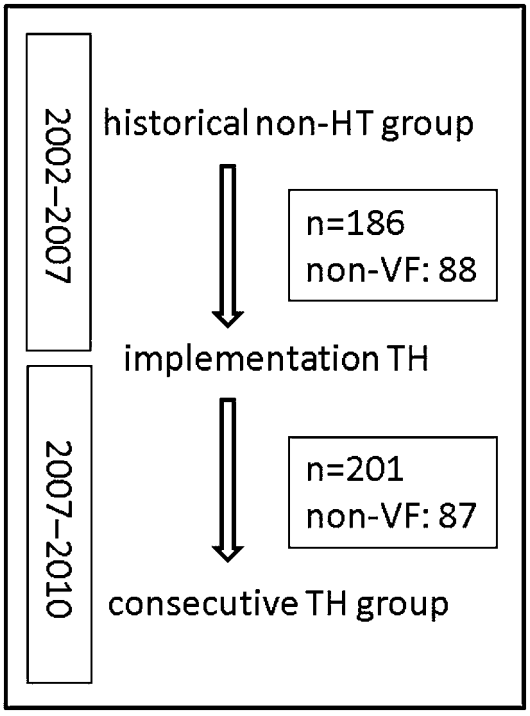

Figure 1 Chart of study design. HT, hypothermia treatment; TH, therapeutic hypothermia; VF, ventricular fibrillation.

Table 2 Neurological outcome at ICU discharge given as CPC 1–5

Neurological outcome n/total n (%)	Non-hypothermia (n=88)	Hypothermia (n=87)	p Value
CPC 1	6 (6.8)	15 (17.2)	0.25
CPC 2	10 (11.4)	9 (10.3)	
CPC 3	2 (2.3)	2 (2.3)	
CPC 4	14 (15.9)	10 (11.5)	
CPC 5	56 (63.6)	51 (58.6)	
CPC 1–2	16 (18.2)	24 (27.6)	0.17
CPC 3–5	72 (81.8)	63 (72.4)	1.00

Data are presented as absolute numbers and relative frequencies (%).
CPC, cerebral performance category; ICU, intensive care unit.

non-VF rhythms.[7] In a recent study the initial rhythm (VF vs non-VF) was not a predictor for survival in logistic regression analysis in survivors after out-of-hospital cardiac arrest.[10] A case series published by Foedisch *et al*[11] including 49 survivors after cardiac arrest (31/49 presenting with VF/ventricular tachycardia, 17/49 presenting with asystole) reported favourable neurological outcomes in seven patients with asystole as the initial rhythm (41%). The authors concluded that therapeutic hypothermia might be beneficial in patients after non-VF cardiac arrest.[11] However, data published by Hay *et al*[12] reported a favourable neurological outcome in only 7% of the non-VF patients in a study of 139 survivors after out-of-hospital cardiac arrest. Another current study revealed a 16.7% survival rate, 8.3% with good outcome, in 74 patients treated with hypothermia after non-shockable cardiac arrest.[10]

Based on our results, hypothermia failed to improve significantly the number of patients with favourable outcomes at ICU discharge (survival rate 41.3%; good outcome 27.6%). In Kaplan–Meier analysis and Cox regression no statistically significant benefit concerning mortality was observed either.

Some limitations of our study have to be emphasised. First of all the results presented were generated in an observational fashion using historical controls. Although ICU treatment did not change substantially, in general the possibility that in some cases treatment differed over the years cannot be fully excluded. As an example, time on ventilator was shorter in our hypothermia group. Obviously this result may not only be attributed to hypothermia itself but also to the increased use of lung protective strategies. Furthermore, patients with initially non-shockable cardiac arrest represent a very heterogeneous patient

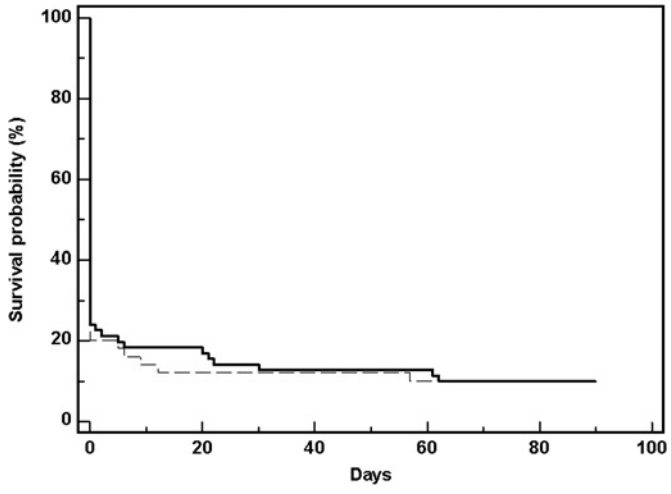

Figure 2 Kaplan–Meier survival analysis of both groups. A dashed line indicates the hypothermia group and the solid line the non-hypothermia group. A 90-day period was analysed in follow-up time. The difference between the two groups was not significant (log rank test p=0.82).

Table 3 Regression coefficients, HR, 95% CI and p values of Cox regression model

Variable	Coefficient	HR	95% CI	p Value
Epinephrine	0.16	1.02	0.93 to 1.11	0.73
tROSC	0.00	1.00	0.97 to 1.02	0.86
Rhythm	0.37	1.04	0.70 to 1.60	0.87
Location of CA	0.20	1.22	0.72 to 2.07	0.46
Hypothermia	−0.12	0.98	0.53 to 1.50	0.63
Age	0.00	1.00	0.98 to 1.01	0.55
Gender	−0.20	0.82	0.50 to 1.40	0.45
APACHE	−0.01	1.00	1.00 to 1.02	0.53
ICU stay	−0.02	1.00	1.00 to 1.00	0.13

Sign (−) indicates a negative effect on the dependent variable.
APACHE, Acute Physiology and Chronic Health Evaluation; CA, cardiac arrest; ICU stay, duration of intensive care unit treatment; tROSC, time to return of spontaneous circulation.

group.[10] In addition, the time to ROSC and epinephrine dosage was significantly shorter in the hypothermia group, whereas the Acute Physiology and Chronic Health Evaluation (APACHE) score was higher compared with the control group. In order to compensate for this heterogeneity, studies with larger patient groups are required. When using historical controls there may be effects due to the fact that the introduction of therapeutic hypothermia itself has focused the physicians in charge to more sophisticated post-resuscitation care in general. Another limitation may be that we cannot provide follow-up data regarding the CPC score after 90 days. Although recent studies show that CPC does not change significantly in the first months after discharge, it might possible that even minor changes may have an important impact on patients' quality of life.[9 13]

Nevertheless, our data suggest no statistically significant beneficial effects of therapeutic hypothermia in this patient group. Of course, data from different centres are hardly comparable as a result of different standard operating procedures or local conditions, therefore in the future only a multicentre randomised controlled trial can identify the possible benefit of hypothermia for non-shockable cardiac arrest patients and can provide adequate control for confounders. Because of the trend towards a better neurological outcome (non-significant) in the hypothermia group (CPC 1–2: hypothermia 27.59% vs control 18.20%, p=0.175) the ethical component of a randomised study design needs to be discussed. On the basis of our results a sample size of 670 patients (1β 0.80; α 0.05) is needed to test the hypothesis appropriately concerning neurological outcomes between hypothermia and non-hypothermia-treated patients.

In summary, there was no statistically significant benefit but only a trend towards a more favourable neurological outcome for the hypothermia group. There was no benefit in short-term 90-day mortality.

Following our results hypothermia treatment needs to be evaluated in a large multicentre trial for cardiac arrest survivors with initially non-shockable rhythms to clarify whether cooling may also be beneficial for other rhythms than VF.

Acknowledgements The authors would like to thank the study nurse, Astrid Caemmerer, for assistance and support throughout the study.

Competing interests None.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethics committee of the Charité-Universitätsmedizin Berlin, Germany.

Contributors CS and DH designed and supervised the data from acquisition to analysis. JN, MR and AJ participated in data collection and revised the manuscript for important intellectual content. All authors have read and approved the final version of the manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **The Hypothermia After Cardiac Arrest Study Group.** Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002;**346**:549–56.
2. **Bernard SA,** Gray TW, Buist MD, *et al*. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;**346**:557–63.
3. **Nolan JP,** Morley PT, Hoek TL, *et al*. Therapeutic hypothermia after cardiac arrest. An advisory statement by the Advancement Life support Task Force of the International Liaison Committee on Resuscitation. *Resuscitation* 2003;**57**:231–5.
4. **Storm C,** Schefold JC, Nibbe L, *et al*. Therapeutic hypothermia after cardiac arrest—the implementation of the ILCOR guidelines in clinical routine is possible! *Crit Care* 2006;**10**:425.
5. **Sunde K,** Pytte M, Jacobsen D, *et al*. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007;**73**:29–39.
6. **Pepe PE,** Levine RL, Fromm RE Jr, *et al*. Cardiac arrest presenting with rhythms other than ventricular fibrillation: contribution of resuscitative efforts toward total survivorship. *Crit Care Med* 1993;**21**:1838–43.
7. **Castren M,** Silfvast T, Rubertsson S, *et al*; Task Force on Scandinavian Therapeutic Hypothermia Guidelines, Clinical Practice Committee Scandinavian Society of Anaesthesiology and Intensive Care Medicine. Scandinavian clinical practice guidelines for therapeutic hypothermia and post-resuscitation care after cardiac arrest. *Acta Anaesthesiol Scand* 2009;**53**:280–8.
8. **Jennett B,** Bond M. Assessment of outcome after severe brain damage. *Lancet* 1975;**1**:480–4.
9. **Arrich J**; European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007;**35**:1041–7.
10. **Oddo M,** Ribordy V, Feihl F, *et al*. Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. *Crit Care Med* 2008;**36**:2296–301.
11. **Foedisch M,** Viehoefer A, Richling N, *et al*. Good neurological recovery at ICU discharge of asystole patients treated with induced mild hypothermia. *Crit Care* 2008;**12**(Suppl 2):P373.
12. **Hay AW,** Swann DG, Bell K, *et al*. Therapeutic hypothermia in comatose patients after out-of-hospital cardiac arrest. *Anaesthesia* 2008;**63**:15–19.
13. **Cronberg T,** Lilja G, Rundgren M, *et al*. Long-term neurological outcome after cardiac arrest and therapeutic hypothermia. *Resuscitation* 2009;**80**:1119–23.

Images in emergency medicine

‘Scurvy’: presentation and skin manifestations of a not so uncommon condition

An 84-year-old man attended our emergency department with a 5-month history of poor oral intake since the death of his wife. He complained of lethargy, dyspnoea, epistaxis and myalgic pains. He was severely thin with purpuric skin lesions over his knuckles, elbows and shins (figures 1 and 2).[1]

Scurvy was suggested and confirmed by dermatology. The patient was started on ascorbic acid (400 mg/24 h) and initially improved, but died later of a nosocomial infection.

Scurvy is a state of vitamin C (ascorbic acid) deficiency. Ascorbic acid is used in the synthesis of collagen, neurotransmitters and helps in dietary iron absorption. Deficiency results in poor wound healing, defective capillary walls and anaemia.

The UK incidence of clinical scurvy is unknown, but the prevalence of vitamin C deficiency is estimated at 25% in men and 16% in women and is associated with low income, poor diet and smoking.[1] Symptoms/signs include lethargy, purpura, epistaxis, myalgia, dyspnoea, spongy gums and tooth loss. Complications include haemorrhage, neuropathies, immunocompromise and hepatic and renal failure.

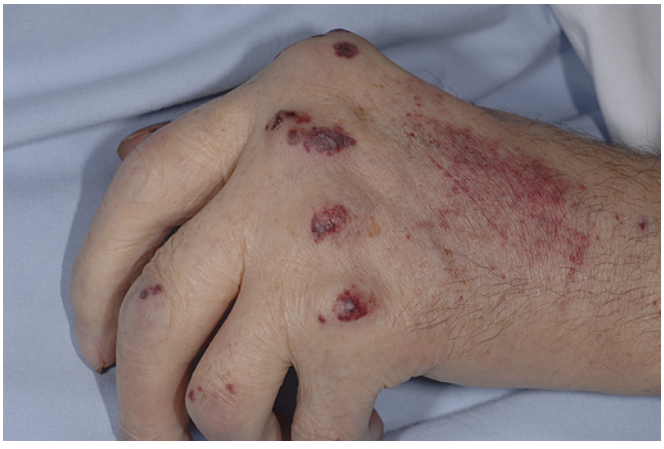

Figure 1 Skin lesions on the left hand (symmetrical on the right hand).

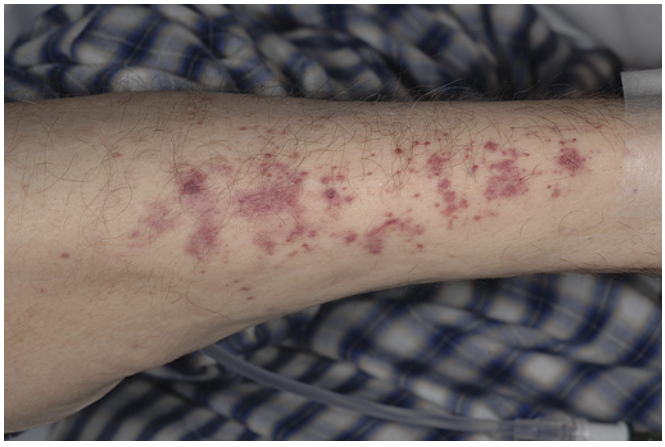

Figure 2 Skin lesions on the forearm and also present on the shins.

Scurvy is believed to be historical or a diagnosis of developing countries. However, it is more common than perceived. Patients can easily be treated with dietary input and ascorbic acid supplementation. Symptoms often resolve in 1–2 weeks.

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Competing interests None.

Patient consent Obtained.

Contributors Under the care of authors and Dr K Amsha (Consultant).

Provenance and peer review Not commissioned; internally peer reviewed.

Accepted 24 June 2011
Published Online First 2 August 2011

Emerg Med J 2012;**29**:103. doi:10.1136/emermed-2011-200417

REFERENCE

1. **Mosdol A,** Erens B, Brunner EJ. Estimated prevalence and predictors of vitamin C deficiency within the UK’s low-income population. *J Public Health (Oxf)* 2008;**30**:456–60.

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Emerg Med J 2012 29: 100-103 originally published online March 1, 2011
doi: 10.1136/emj.2010.105171