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CLINICAL PAPER

# Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest<sup>☆</sup>

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## KEYWORDS

Cardiac arrest;  
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## Summary

**Aim of the study:** Cold infusions have proved to be effective for induction of therapeutic hypothermia after cardiac arrest but so far have not been used for hypothermia maintenance. This study investigates if hypothermia can be induced and maintained by repetitive infusions of cold fluids and muscle relaxants.

**Material and methods:** Patients were eligible, if they had a cardiac arrest of presumed cardiac origin and no clinical signs of pulmonary oedema or severely reduced left ventricular function. Rocuronium (0.5 mg/kg bolus, 0.5 mg/kg/h for maintenance) and crystalloids (30 ml/kg/30 min for induction, 10 ml/kg every 6 h for 24 h maintenance) were administered via large bore peripheral venous cannulae. If patients failed to reach  $33 \pm 1$  °C bladder temperature within 60 min, endovascular cooling was applied.

**Results:** Twenty patients with a mean age of 57 ( $\pm 15$ ) years and mean body mass index of 27 ( $\pm 4$ ) kg/m<sup>2</sup> were included (14 males). Mean temperature at initiation of cooling (median 27 (IQR 16; 87) min after admission) was 35.4 ( $\pm 0.9$ ) °C. In 13 patients (65%) the target temperature was reached within 60 min, 7 patients (35%) failed to reach the target temperature. Maintaining the target temperature was possible in three (15%) patients and no adverse events were observed.

**Conclusion:** Cold infusions are effective for induction of hypothermia after cardiac arrest, but for maintenance additional cooling techniques are necessary in most cases.

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## Introduction

Mild hypothermia improves survival and neurological outcome after out-of-hospital cardiac arrest.<sup>1–3</sup> According to the results of two large randomised controlled trials the European Resuscitation Council Guidelines 2005 recommend treating comatose survivors of out-of-hospital cardiac arrest due to a shockable rhythm with mild hypothermia for 12–24 h.<sup>4</sup> The ideal method for induction and maintenance of therapeutic hypothermia is not known. As experimental results suggest that the effect of hypothermia on neurological outcome might be most beneficial when applied as early as possible after return of spontaneous circulation<sup>5,6</sup> recent research focused on methods for fast induction of hypothermia.<sup>7–13</sup> So far, five feasibility trials have investigated the efficacy and safety of large volume infusions of cold infusions in more than 200 adult cardiac arrest survivors (9–13). Those studies showed that hypothermia could be induced very effectively with cooling rates up to  $-4.0^{\circ}\text{C}/\text{h}$  and no clinically relevant adverse effects of the infusions, especially no pulmonary oedema, were observed. Although the target temperature ( $32\text{--}34^{\circ}\text{C}$ ) could be reached in most patients, hypothermia was then maintained by additional more resource demanding cooling techniques. To our knowledge no study has investigated, if hypothermia can be induced and also maintained by repetitive infusions of cold crystalloid fluids and complete muscle relaxation with deep sedation.

## Methods

This was a prospective, observational case series of a convenience sample of patients after cardiac arrest admitted to an emergency department of a tertiary care hospital between October 2005 and February 2006. The study procedures were approved by the responsible committee on human experimentation. According to our study protocol there was no need for patient's consent to be included in our study but patients or their relatives received detailed information about the trial.

Inclusion and exclusion criteria are presented in Table 1. As with previous feasibility trials a total of 20 participating patients was considered to be sufficient. Data documentation was performed according to Utstein Style.<sup>14</sup> Cardiac arrest data of out-of-hospital cardiac arrests were obtained through interviews with the ambulance physicians, paramedics, bystanders and families. The interval from the time of collapse to the first sustained

perfusing rhythm was termed time to return of spontaneous circulation. Acute care included basic and advanced cardiac life support performed by the ambulance service personnel or in-hospital emergency physicians per standard protocol according to current guidelines.<sup>4,15</sup>

At the emergency department, after initial neurological evaluation, assessment of respiratory and haemodynamic function, patients received the following standardised treatment. Foley catheters with incorporated temperature probes, arterial catheters, central venous catheters, intubation and mechanical ventilation were used. Sedation and analgesia with midazolam ( $0.2\text{--}0.25\text{ mg/kg/h}$ ) and fentanyl ( $0.01\text{ mg/kg/h}$ ) was given to facilitate respiratory management, to avoid stress induced by invasive procedures and to allow continuous muscle relaxation.

## Study interventions (also see Figure 1)

Neuromuscular blockade was induced by rocuronium with a bolus infusion ( $0.5\text{ mg/kg}$ ) and a subsequent continuous infusion ( $0.5\text{ mg/kg/h}$ ) to prevent shivering until patients reached normothermia again. If patients showed any signs of shivering or gooseflesh the dose of muscle relaxation was gradually increased until these symptoms ceased. The target temperature was monitored via a bladder temperature probe.

As soon as patients were included they received an intravenous bolus infusion of  $30\text{ ml/kg}$  crystalloid fluid at  $4^{\circ}\text{C}$  over 30 min via two peripheral cubital large bore intravenous catheters. Usually normal saline or lactated Ringer's solution was selected, depending on serum electrolytes revealed in the first blood gas analysis on admission. If no laboratory values were available normal saline was used. Central venous application was not used to avoid any delay and to reduce the risk of arrhythmias. If the temperature dropped below  $33^{\circ}\text{C}$  or clinical signs of pulmonary oedema emerged the infusion was stopped. Further management of therapeutic hypothermia with cold fluids and/or other cooling techniques after the bolus infusion is presented in Figure 1. This cooling procedure differed from our clinical routine, where comatose cardiac arrest survivors receive cold fluids ( $30\text{ ml/kg}/30\text{ min}$ ) immediately after admission for the induction of hypothermia and an additional cooling technique (e.g. endovascular or surface cooling devices) is applied simultaneously if it does not delay immediate coronary angiography.

To avoid fluid overload, repetition of cold infusions was limited to every 6 h and the dose was

**Table 1** Inclusion and exclusion criteria

## Inclusion criteria

Age 18–85

Witnessed, normothermic cardiac arrest of presumed cardiac aetiology

Return of spontaneous circulation with systolic blood pressure &gt;90 within 60 min of initiation of advanced cardiac life support

Comatose upon enrollment (Glasgow Coma Scale &lt;8)

## Exclusion criteria

Clinical signs of pulmonary oedema

Severely reduced left ventricular function

Coma possibly due to cerebrovascular accident or head trauma

Patients receiving any form of renal replacement therapy

Patients with a diagnosed terminal illness

Patients with known hypersensitivity to any of the drugs used

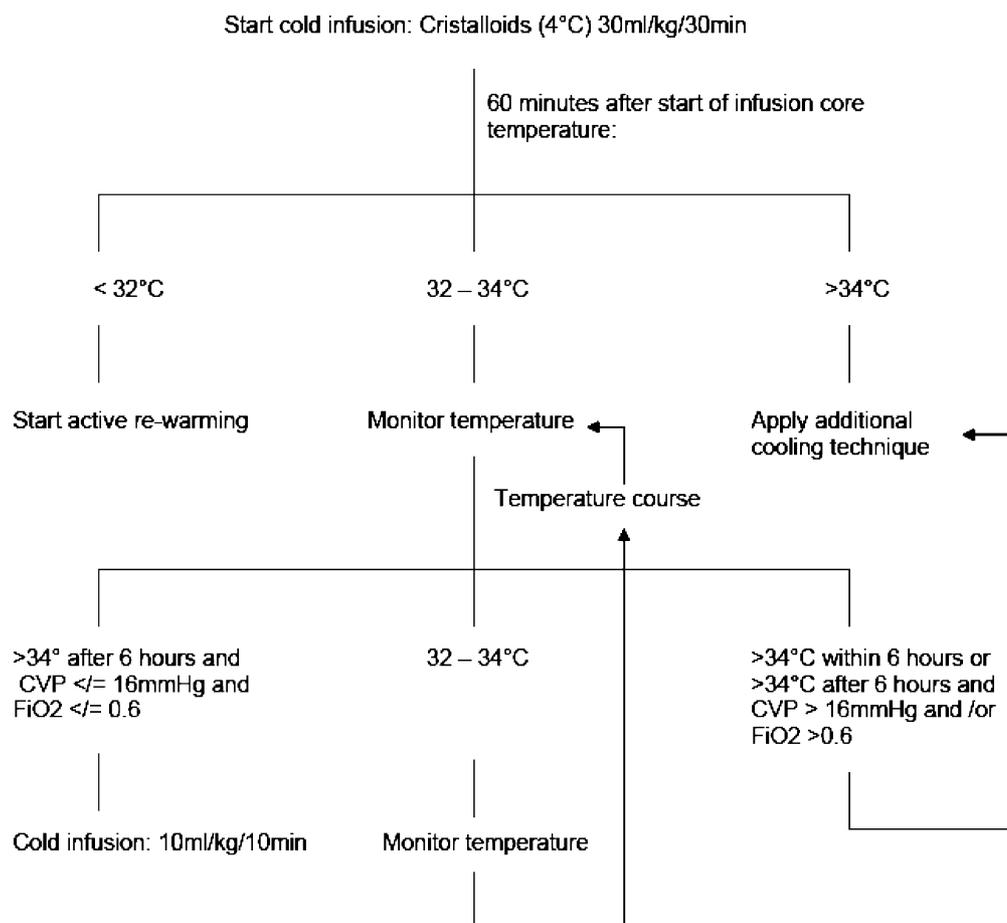
Known coagulopathy or thrombocytopenia

Possible pregnancy (females &lt;50 years were tested for pregnancy)

reduced to 10 ml/kg for the additional applications. If possible, the target temperature was maintained for 24 h with cold infusions. If the temperature rose above 34 °C after 12 or more hours no additional cooling technique was applied as current guidelines recommend a cooling period of 12–24 h.<sup>4</sup>

**Monitoring**

Temperature was monitored continuously in the bladder. For cardiovascular monitoring, catheters were placed in the radial or femoral artery and the upper vena cava as soon as possible. Arterial

**Figure 1** Treatment algorithm after inclusion. CVP: central venous pressure, FiO<sub>2</sub>: fraction of inspired oxygen.

(ABP) and central venous pressure (CVP) were displayed on a multichannel monitor (HP Series 600 Monitor, Hewlett-Packard, Palo Alto, CA, USA). Special attention was paid to potential adverse effects of hypothermia and fluid overload such as abnormal bleeding, haemodynamic instability, arrhythmias, electrolyte disturbances and signs of acute heart failure.

If the patient's core temperature dropped below the target temperature ( $33 \pm 1^\circ\text{C}$ ) we provided a light weight mattress with tiny holes with constant warm air flow (Bair Hugger®, Augustin Medical, Inc., Eden Prairie, MN) for warming. If these methods failed to rewarm the patient effectively, they could be rewarmed with an endovascular heat exchange catheter (Icy catheter, CoolGard 3000, Alsius, Irvine, CA, USA).

### Outcome measurements

The primary endpoint was the achievement of the target temperature 60 min after start of the first bolus infusion and maintenance of hypothermia over 24 h. As a secondary only descriptive endpoint, survival to discharge and neurological outcome were assessed and are reported in terms of cerebral performance categories (CPC).<sup>16</sup> The best CPC score achieved between 3 days and within 6 months was used for calculation. A CPC score of 1 or 2 was considered as good, and a score of 3–5 as poor neurological outcome.

### Statistical analysis

Data were tested for normal distribution using the Kolmogorov–Smirnov test. Parametric data are presented as mean and standard deviation, non-parametric data are presented as median and interquartile range (IQR). For comparison of pre- and post-infusion values parametric data were tested using paired *t*-tests. Non-normally distributed variables were analysed using Chi-square or Mann–Whitney-*U*-tests, respectively. *p*-Values were two-tailed, and values of  $p < 0.05$  were considered significant. All statistical analyses were performed using SPSS 11.5 for Windows.

### Results

The demographics and cardiac arrest data of the 20 patients studied are presented in Table 2. Bladder temperature on admission was  $35.2 (\pm 1.1)^\circ\text{C}$ . A total amount of 2465 ( $\pm 536$ ) ml of cold infusions was given commencing 93 ( $\pm 62$ ) min after return of spontaneous circulation and 27 (16; 87) min after admission. Cold infusions were started at a mean patient temperature of  $35.4 (\pm 0.9)^\circ\text{C}$  which dropped to  $34.4 (\pm 1.1)^\circ\text{C}$  after 30 min ( $p < 0.001$ ) and to  $34.2 (\pm 1.0)^\circ\text{C}$  after 60 min ( $p < 0.001$ ), respectively (Figure 2).

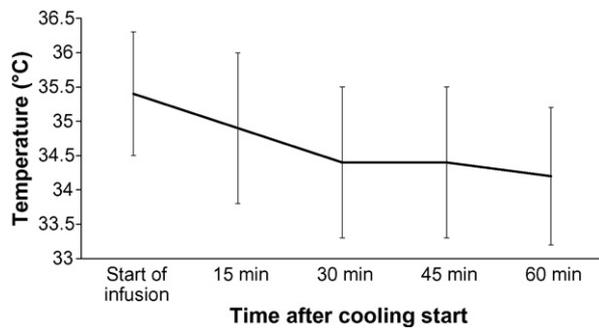
Of all 20 patients, 13 (65%) reached the target temperature within the required 60 min in a mean time of 30 ( $\pm 16$ ) min. The other seven patients (35%) received additional endovascular cooling 1 h

**Table 2** Demographic and cardiac arrest data

Age (years)	57 ( $\pm 15$ )
Male, <i>n</i> (%)	14 (70%)
Body mass index ( $\text{kg}/\text{m}^2$ )	27 ( $\pm 4$ )
Body surface area ( $\text{m}^2$ )	1.93 ( $\pm 0.22$ )
Time from collapse until ROSC (min)	20 ( $\pm 9$ )
BLS, <i>n</i> (%)	8 (40%)
First recorded ECG rhythm	
VF or VT, <i>n</i> (%)	14 (70)
PEA, <i>n</i> (%)	2 (10)
Asystole, <i>n</i> (%)	4 (20)
Cardiac arrest due to cardiac cause, <i>n</i> (%)	15 (75%)
Defibrillations ( <i>n</i> )	2 ( $\pm 1.5$ )
Amount of adrenaline (epinephrine) during CPR (mg)	1.9 ( $\pm 1.6$ )
Serum lactate on admission (mmol/l)	9.4 ( $\pm 5.6$ )
pH-value on admission	7.20 ( $\pm 0.21$ )

Data are given as numbers (percentages) and mean values ( $\pm$  standard deviation). ROSC: return of spontaneous circulation; BLS: basic life support; ECG: electrocardiography; VF: ventricular fibrillation; VT: ventricular tachycardia; PEA: pulseless electrical activity; CPR: cardiopulmonary resuscitation.

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**Figure 2** Temperature course within 60 min after the start of the first bolus infusion ( $n = 33$ ).

after start of the initial bolus infusion. Of those 13 patients who had reached the target temperature 9 patients (69%, i.e. 45% of all patients) required additional endovascular cooling for hypothermia maintenance as their temperature increased to  $>34^{\circ}\text{C}$  199 ( $\pm 72$ ) min after start of infusions. In only three patients (23% of those who had reached the target temperature, i.e. 15% of all patients) could the target temperature be maintained successfully by cold infusions, sedation and muscle relaxation (Figure 3). Of those three patients, only one received an additional cold infusion 10 h after inclusion. One patient who had disseminated breast cancer (which had not been known by the investigators at the time of the inclusion) died 5 h after the start of cooling.

There was a trend towards a higher probability of cooling success with cold infusions in younger patients (54 years versus 65 years,  $p = 0.06$ ) and for patients with a lower body mass index ( $26\text{ kg/m}^2$  versus  $29\text{ kg/m}^2$ ,  $p = 0.08$ ) whereas body surface area ( $1.90\text{ m}^2$  versus  $1.99\text{ m}^2$ ,  $p = 0.38$ ) seemed to have no influence.

The total infusion amount could be given without complications in all cases. No patient developed clinical signs of pulmonary oedema and haemodynamic measurements, oxygenation and other

laboratory variables showed no relevant changes during and after cold infusions (Table 3).

Of all patients, eight (40%) survived to discharge (seven of those had ventricular fibrillation as first recorded ECG rhythm) and seven (35%) had a favourable neurological outcome (six of those had ventricular fibrillation as first recorded ECG rhythm).

## Discussion

In most patients who achieve return of spontaneous circulation after cardiac arrest hypothermia can be successfully induced by cold infusions. Although large amounts of fluid were administered within 30 min, no serious side effects occurred. Once the target temperature was reached few patients remained within the temperature range of  $32\text{--}34^{\circ}\text{C}$  but the majority rewarmed within several hours and required additional endovascular cooling. No patient required active rewarming during the induction or maintenance period as temperature never dropped below  $32^{\circ}\text{C}$ .

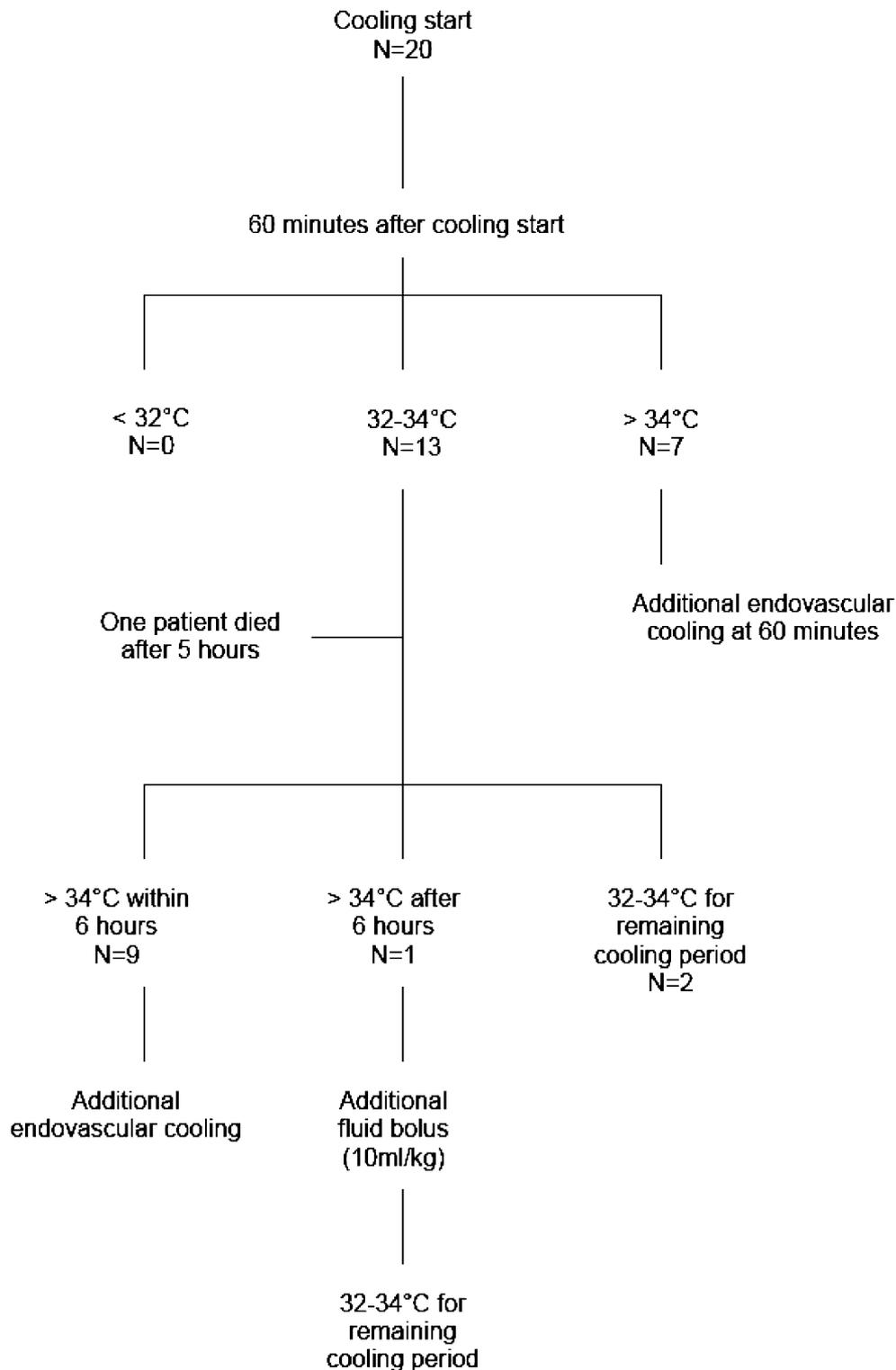
Our study is the first to investigate if patients who are treated with therapeutic hypothermia after cardiac arrest can be kept in mild hypothermia by repeated administrations of cold infusions, sedation and complete muscle relaxation. To avoid cardiac decompensation due to fluid overload, the volume of the 2nd, 3rd or 4th infusion was reduced to  $10\text{ ml/kg}$  and repetitive cold infusions were allowed only every 6 h (Figure 1). Therefore, we do not know if continuous cold infusions or larger volumes of repeated cold infusions within shorter time intervals might be more effective for maintenance of mild hypothermia. According to our former experience<sup>11</sup> a slow infusion rate of cold fluids leads to less effective cooling. If the combination of cheap and easy applicable cooling techniques such as cold fluids followed by external cooling with ice packs or fans would be sufficient for hypothermia

**Table 3** Haemodynamic, respiratory and laboratory data before and after the first bolus infusion

	Before cold infusion	After cold infusion	<i>p</i> -Value
Mean arterial pressure (mmHg)	75 ( $\pm 18$ )	81 ( $\pm 19$ )	0.08
Heart rate ( $\text{min}^{-1}$ )	93 ( $\pm 27$ )	87 ( $\pm 23$ )	0.02
Sodium (mmol/l)	137 ( $\pm 5$ )	137 ( $\pm 4$ )	0.53
Potassium (mmol/l)	3.9 ( $\pm 0.6$ )	3.9 ( $\pm 0.6$ )	0.87
Haemoglobin (g/dl)	12.6 ( $\pm 2.5$ )	11.8 (2.2)	0.04
Platelet count (G/l)	207 ( $\pm 62$ )	191 ( $\pm 50$ )	0.22
$\text{PaO}_2/\text{FiO}_2$ (mmHg)	511 ( $\pm 343$ )	352 ( $\pm 166$ )	0.09

Data are given as mean values ( $\pm$  standard deviation);  $\text{PaO}_2$ : partial pressure of oxygen in arterial blood;  $\text{FiO}_2$ : fraction of inspired oxygen.

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**Figure 3** Number of patients within the target temperature range (32–34 °C) treated only with cold infusions, sedation and muscle relaxation.

induction and maintenance, this might save costs compared to the use of cooling devices. This matter has still to be investigated.

Previous studies have already reported the effectiveness of cold infusions for induction of

hypothermia.<sup>9–13</sup> Those studies reported cooling rates between 2.2 and 4.0 °C/h but in some cases simultaneous additional cooling techniques were applied.<sup>11,12</sup> We achieved a cooling rate of only 2 °C/h during the active cooling period, although

we left the patient uncovered, turned off all heating equipment in ventilators and beds, and the infusion bags were stored at 4 °C until just before the fluid was given. The reason why our cooling rate was less than the previously reported is not clear. Similar to previously reported data,<sup>9–11</sup> not all of our patients reached the target temperature soon after the infusion, but nevertheless at 60 min 65% ( $n=13$ ) had reached a temperature below 34 °C. Patients with a lower body mass index and younger patients were more likely to reach target temperature.

After the induction of hypothermia with cold infusions all previous studies<sup>9–13</sup> used additional cooling techniques for maintenance of hypothermia. Kim et al.<sup>13</sup> reported that some patients who received no active cooling for maintenance had a rapid rise in temperature after successful induction. In contrast to our patients these patients received only sedation with midazolam but no muscle relaxants. This anaesthesia management probably has influenced the temperature course as shivering contributes considerably to rewarming in hypothermic patients. To exclude shivering all our patients received continuous muscle relaxation. However, 77% ( $n=10$ ) of our patients who initially had reached target temperature after the first cold infusion rewarmed within 199 ( $\pm 72$ ) min after start of infusions and needed further active cooling by endovascular cooling. Only three patients (23% of those who had reached target temperature) remained in mild hypothermia. These data suggest that sedation and muscle relaxation is not enough to prevent rewarming during therapeutic hypothermia and that other mechanisms, such as non-shivering thermogenesis, might contribute substantially to the rewarming process.

Other previous studies have not revealed any serious side effects of cold infusions<sup>9–13</sup> especially pulmonary oedema and only slight increases of central venous pressures were reported. In our patients we did not observe infusion or cooling related side effects either (Table 3).

## Conclusion

In the majority of patients after cardiac arrest, therapeutic hypothermia can be induced by rapid infusion of cold fluids. However, most patients rewarm after 3–4 h and require additional cooling. As most therapeutic and diagnostic interventions can be performed within this period (e.g. coronary angiography or computed tomography) the induction of hypothermia with cold infusions will allow

a rapid induction of hypothermia in this first critical phase after the arrest while more resource demanding cooling procedures can be applied afterwards.

## Conflict of interest statement

There are no conflicts of interest.

## References

1. Bernard SA, Gray TW, Buist MD, Jones BM, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002;346:557–63.
2. 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.
3. Holzer M, Bernard SA, Hachimi-Idrissi S, et al. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med* 2005;33:414–8.
4. Nolan JP, Deakin CD, Soar J, Böttiger BW, Smith G. European Resuscitation Council guidelines for resuscitation 2005. Section 4. Adult advanced life support. *Resuscitation* 2005;67(Suppl. 1):S39–86.
5. Sterz F, Safar P, Tisherman S, Radovsky A, et al. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Crit Care Med* 1991;19:379–89.
6. Markarian GZ, Lee JH, Stein DJ, Hong SC. Mild hypothermia: therapeutic window after experimental cerebral ischemia. *Neurosurgery* 1996;38:542–51.
7. Holzer M, Müllner M, Sterz F, et al. Efficacy and safety of endovascular cooling after cardiac arrest: cohort study and bayesian approach *stroke* 2006;37:1792–7.
8. Al-Senani FM, Graffagnino C, Grotta JC, et al. A prospective, multicenter pilot study to evaluate the feasibility and safety of using the coolgard system and icy catheter following cardiac arrest. *Resuscitation* 2004;62:143–50.
9. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003;56:9–13.
10. Virkkunen I, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer's solution: a pilot study. *Resuscitation* 2004;62:299–302.
11. Kliegel A, Losert H, Sterz F, et al. Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest—a feasibility study. *Resuscitation* 2005;64:347–51.
12. Polderman K, Rijnsburger E, Peerdeman S, Girbes A. Induction of hypothermia in patients with various types of neurologic injury with use of large volumes of ice-cold intravenous fluid. *Crit Care Med* 2005;33:2744–51.
13. Kim F, Olsufka M, Carlbom D, et al. Pilot study of rapid infusion of 2 L of 4 °C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation* 2005;112:715–9.
14. Jacobs I, Nadkarni V, The ILCOR Task Force on Cardiac Arrest and Cardiopulmonary Resuscitation Outcomes. Cardiac arrest and cardiopulmonary resuscitation outcome

- reports update and simplification of the Utstein templates for resuscitation registries. A statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation. *Resuscitation* 2004;63:233–49.
15. de Latorre F, Nolan J, Robertson C, Chamberlain D, Baskett P. European Resuscitation Council Guidelines 2000 for Adult Advanced Life Support—a statement from the Advanced Life Support Working Group 1 and approved by the Executive Committee of the European Resuscitation Council. *Resuscitation* 2001;48:211–21.
  16. Recommended guidelines for uniform reporting of data from out-of-hospital cardiac arrest: the 'Utstein style'. Prepared by a Task Force of Representatives from the European Resuscitation Council, American Heart Association, Heart and Stroke Foundation of Canada, Australian Resuscitation Council. *Resuscitation* 1991; 22:1–26.