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Therapeutic hypothermia in comatose patients after out-of-hospital cardiac arrest*

A. W. Hay,[1] D. G. Swann,[1] K. Bell,[2] T. S. Walsh[1] and B. Cook[1]

1 Consultants, Critical Care, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh, EH16 4SB, UK
2 Medical Student, College of Medicine and Veterinary Medicine, The University of Edinburgh, The Chancellor's Building, 49 Little France Crescent, Edinburgh, EH16 4SB, UK

Summary

Our intensive care unit has been treating comatose patients, following an out-of-hospital cardiac arrest, with therapeutic hypothermia since 2002. In all, 139 out-of-hospital cardiac arrest patients were admitted in the 4-year period 2002–5. Of these, 27% had a favourable outcome (discharged home or to rehabilitation). Forty-one per cent of patients presenting with ventricular fibrillation (VF) and 7% of non-VF patients had a favourable outcome. No patient with an estimated time from collapse to first attempt at cardiopulmonary resuscitation over 12 min survived to hospital discharge. Twenty-two per cent of patients over 70 years were discharged home, suggesting age was not a barrier to surviving out-of-hospital cardiac arrest. The introduction of a therapeutic hypothermia clinical pathway, at the end of 2003 improved the efficiency of cooling. The percentage of patients cooled to below 34 °C within 4 h increased from 15 to 51% and those cooled for more than 12 h increased from 30 to 83%.

Correspondence to: Dr Alasdair Hay
E-mail: alasdairwhay@gmail.com
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In 2002, two clinical trials were published which demonstrated that therapeutic hypothermia improved both neurological outcome and survival in unconscious patients resuscitated from out-of-hospital cardiac arrest (OHCA) [1, 2]. These findings have been confirmed in recent systematic reviews and a meta-analysis [3, 4]. Therapeutic hypothermia in the two trials involved active cooling to 32–34 °C for between 12 and 24 h. Trial patients were a selected group resuscitated from OHCA. In the largest trial, only patients with an initial rhythm of ventricular fibrillation (VF), aged less than 70 years and with a downtime, defined as an estimated time from collapse to first attempt at cardiopulmonary resuscitation (CPR), of less than 15 min were recruited [1]. In 2003, the International Liaison Committee on Resuscitation (ILCOR) advised that unconscious patients post OHCA should be cooled when the initial rhythm is VF. The statement also suggested the cooling may be beneficial after non-VF arrests [5].

Since 2003, surveys of clinical practice from the UK, Germany and the USA suggest that the majority of intensive care units (ICUs) do not routinely cool patients post OHCA and have no immediate plans to do so [6–8]. Overall, OHCA is perceived to have a very poor outcome, such that intensive care clinicians may be unwilling to admit patients for ongoing treatment [6]. Reasons cited for not using therapeutic hypothermia include scepticism regarding the ability to reach cooling targets in the clinical environment and availability of ICU beds [6]. However, published data show that outcomes for patients surviving to hospital admission are good. The Scottish Heart Start investigators showed that 48% of patients who sustained an OHCA of primary cardiac aetiology and who survived to hospital admission were subsequently discharged home [9]. These data were collected prior to the hypothermia publications. The Termination of Resuscitation investigators found that although 91.9% of patients after OHCA were

pronounced dead in the emergency department, 3.1% (39% of emergency department survivors) were discharged home [10]. These data suggest that implementation of evidence-based measures that could improve outcomes for patients surviving to hospital admission are potentially worthwhile.

Prior to the publication of the therapeutic hypothermia trials in 2002 our ICU had a policy of considering admission of unconscious patients successfully resuscitated from OHCA. Following publication of the therapeutic hypothermia randomised control trials, we implemented cooling on an ad-hoc basis. Local audit showed inconsistent use and variable success. A therapeutic hypothermia clinical pathway was therefore introduced at the end of 2003.

The aim of this retrospective audit was to answer four questions:

1 What was the case mix of admissions and what factors predicted a favourable outcome?
2 Did the introduction of a clinical pathway improve the efficiency of cooling?
3 Did the patients we treated who would have been excluded from the clinical trials have good clinical outcomes?
4 What were the ICU and hospital stays of these patients and thus the potential burden on resources?

Methods

The study had prior ethics committee approval as a clinical audit. The study population consisted of all patients admitted to our ICU following an OHCA, between 1 January 2002 and 31 December 2005.

Data collection

Data were collected from a computerised ICU patient database (WardWatcher®; Critical Care Audit, London, UK), and review of the medical notes. The following characteristics of the patients were obtained from WardWatcher: age, sex, APACHE II score from the first 24 h following ICU admission, length of ICU stay, hospital outcome and discharge destination. Details of the cardiac arrest were collated from available medical notes. These included the initial cardiac rhythm, occurrence of bystander cardiopulmonary resuscitation (CPR) and downtime. Information regarding cooling was extracted from the ICU clinical charts.

Cooling technique

A therapeutic hypothermia clinical pathway was introduced at the end of 2003 (Fig. 1).

Cooling was achieved by means of an external cooling device. The two devices used were the Arctic Sun® (Medivance, Inc., Louisville, CO, USA) and the Blanketrol II® (Cincinnati Sub-Zero, Cincinnati, OH, USA). When both were available, the Arctic Sun was used in preference. The Arctic Sun works by circulating chilled water into pads that are wrapped around the patient's body. The Blanketrol consists of two water-filled blankets placed below and above the patient.

Primary outcomes

A favourable outcome was defined as discharge home or to rehabilitation and an unfavourable outcome was death or discharge to a nursing home [2].

Statistical analysis

Statistical analyses were performed using SPSS, Version 14.0. Data were expressed as median rather than mean when visual inspection suggested the data were clearly not normally distributed. Statistical significance was taken as $p = 0.05$, all tests were two-sided. Proportions were compared using Chi-squared test or Fisher's exact test. Binary logistic regression modelling used forward stepwise variable selection (including all variables with $p = 0.05$ and excluding all variables with $p > 0.1$). The following binary variables were used: sex, VF presenting rhythm, bystander CPR, downtime < 5 min and primary cardiac aetiology. APACHE II score and age were entered as continuous variables. Odds ratios were presented with 95% confidence intervals.

Results

In all, 139 OHCA patients were admitted to our ICU between January 2002 and December 2005. Of these, 27% (37/139) patients had a favourable outcome (36 discharged home and one discharged to rehabilitation).

1 What was the case mix of admissions and what factors predicted a favourable outcome?

Case notes were available for 100 patients (72%). Table 1 shows that the patients with case notes available were a representative sample in terms of age, sex, severity of illness and outcome. Of these 100 patients, 56 had an initial rhythm of VF, 21 had pulseless electrical activity (PEA) and 23 asystole. The median estimated downtime was 6 min (range 0–62) and 66% had bystander CPR. Outcomes for these groups are shown in Fig. 2.

Low APACHE II score (OR 1.17, 95% CI 1.06–1.30) and downtime < 5 min (OR 1.22, 95% CI 1.02–1.44) remained as independent predictors of a favourable outcome. The model was repeated without the APACHE II score as this data is not available until after the first 24 h. The independent predictors of favourable outcome

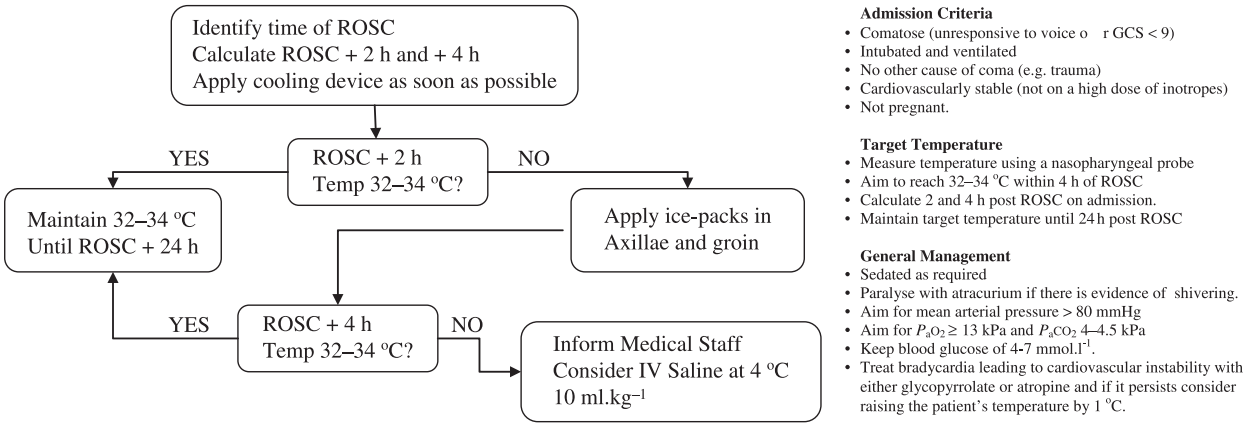

Figure 1 Therapeutic hypothermia clinical pathway, Royal Infirmary of Edinburgh, December 2003. ROSC, return of spontaneous circulation; GCS, Glasgow Coma Scale.

Table 1 Demographic data. A comparison between the patients where case note review was possible and all the patients identified from the computerised database as being admitted after OHCA. Values are median (range) or percentage (number).

	Notes available (n = 100)	All patients (n = 139)
Age; years	68.5 (18–87)	68 (18–87)
Sex; female	23% (23/100)	29% (40/139)
APACHE II	26 (9–51)	26 (4–51)
Favourable outcome	26% (26/100)	27% (37/139)

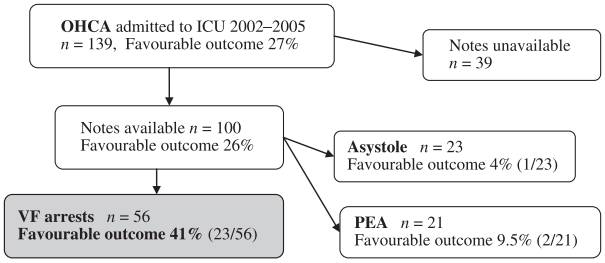

Figure 2 Outcome stratified by presenting rhythm. VF, ventricular fibrillation; PEA, pulseless electrical activity.

on the repeat model were an initial rhythm of VF (OR 4.37, 95% CI 1.27–15.02) and downtime < 5 min (OR 1.12, 95% CI 1.04–1.42). Outcome in relation to downtime are shown in Table 2.

2 Did the introduction of a clinical pathway improve the efficiency of cooling?

The introduction of the clinical pathway at the end of 2003 resulted in a statistically significant increase in the proportion of OHCA patients being cooled (Table 3).

Table 2 Outcome stratified by downtime (n = 84).

Downtime	Favourable outcome
< 5 min	44% (12/27)
5–10 min	32% (6/19)
10–15 min	31% (4/13)
> 15 min	0% (0/25)

Table 3 Percentage of OHCA actively cooled and reaching the two cooling targets. ROSC, return of spontaneous circulation.

	2002–3	2004–5	Chi squared
Therapeutic hypothermia	44% (20/45)	75% (41/55)	p = 0.04
< 34 °C within 4 h of ROSC	15% (3/20)	51% (21/41)	p = 0.001
32–34 °C for > 12 h	30% (6/20)	83% (34/41)	p < 0.001

The proportion of patients achieving cooling targets also increased dramatically.

By 2004–5, all OHCA patients appropriate for cooling received this treatment. The most common reasons patients were not cooled were cardiovascular instability (6/14) and withdrawal of active treatment due to poor prognosis (5/14). Other reasons were bleeding (1/14), septic shock (1/14) and a rapid rise in conscious level (1/14). The main reasons for patients not being cooled for over 12 h in the first 24 h post return of spontaneous circulation (ROSC) were withdrawal of active treatment (3/7), death (1/7), withdrawal due to rapid increase in conscious level (1/7) and a long delay in reaching target temperature (1/7).

3 Did the patients we treated who would have been excluded from the clinical trials have good clinical outcomes?

The large European clinical trial included only patients with an initial VF rhythm, downtime less than 15 min and age less than 70 [1]. In our sample of 100 patients with case note review, we identified only 16 patients who met these criteria. Eight (50%) of these patients had a favourable outcome. Adherence to these trial entry criteria would have excluded from ICU admission 69% (18/26) of all our surviving patients. Survival with a favourable outcome was 21% (18/84) in those patients not meeting trial criteria. No patient with a downtime over 12 min survived.

Of 139 patients in the database, 60 (43%) were aged over 70 years. Thirteen (22%) of them survived with a favourable outcome. This compared with 24 (30%) of the 79 patients aged $\leq$ 70 years ($p = 0.333$)

4 What were the ICU and hospital stays of these patients and thus the potential burden on resources?

Data on length of stay were available for all patients ($n = 139$). The median length of ICU stay was 1.9 days (range 0.1–30) and the median length of total hospital stay was 2.4 days (range 0.1–99). For patients with a favourable outcome the median length of ICU stay was 2 days and of hospital stay 22 days. In the non-survivors the median length of ICU stay was 1.65 days. Only three (3%) of 102 patients with an unfavourable outcome had an ICU length of stay of greater than 7 days. Ninety-three per cent (96/103) of deaths were in ICU. Only one patient, who made a good recovery in ICU, died later in the wards (after 23 days). The other six deaths, occurring after ICU discharge, were in patients with severe hypoxic brain injury. These patients died between 0 and 33 days after ICU discharge.

Discussion

We have reviewed ICU admissions of patients with OHCA where evidence from clinical trials was translated into clinical practice. Our data show that 27% of all patients treated, irrespective of presenting rhythm or demographics, had a favourable outcome. For patients with an initial rhythm of VF, 41% had a favourable outcome. Only 16% of the patients we treated would have been eligible for inclusion in the published randomised controlled trials; there was a favourable outcome in 50% of this subgroup. These outcomes are comparable with the two cooling randomised controlled trials. In these studies a favourable outcome occurred in the intervention groups in 55% [1] and 49% [2] of cases.

Our data confirmed the findings of others that patients presenting to the emergency department with a lowered conscious level and a presenting rhythm of asystole or PEA have an extremely poor prognosis [9, 11, 12]. PEA, in the context of a non-cardiac cause for the arrest, was a subgroup with a better prognosis. Two out of four of these patients survived: one had taken a drug overdose and the other had a primary respiratory arrest. No patient with a downtime over 12 min had a favourable outcome, confirming the known strong correlation between long downtime and poor outcome. These data suggest that admission of patients with downtime >15 min and/or asystole as presenting rhythm is futile. However, we observed favourable outcomes for patients aged over 70 years, suggesting that age alone should not exclude active management after cardiac arrest. In addition, age was not independently associated with a higher probability of poor outcome in our regression model.

It was not possible to examine whether cooling per se improved outcome. The decision to cool individual patients was influenced by other clinical factors such as cardiovascular stability. Our data do clearly show that implementation of a therapeutic hypothermia clinical pathway can significantly improve clinical practice. Following the introduction of the clinical pathway all suitable patients were cooled, 51% reached the target temperature within 4 h of return of circulation (ROSC) and 83% were cooled for more than 12 h. These data show that the clinical trial protocol can be achieved in a busy clinical environment; we achieved the 4-h cooling target more quickly than in the European therapeutic hypothermia trial [1]. We did not systematically document the factors that were most important to successful implementation, but these included a close working relationship with the emergency department and education and support of nursing staff.

We were unable to establish in each individual case which cooling system was used (Arctic Sun or Blanketrol II). Therefore, we were unable to compare the two systems. There are numerous methods used to induce and maintain mild hypothermia: cheap simple methods such as the infusion of ice-cold fluids or surface cooling using ice packs; commercial surface cooling systems which circulate either cold air (Deltatherm, Kinetic Concepts Inc., San Antonio, TX, USA) or cold water through blankets (Blanketrol II) or pads (Arctic Sun); and invasive methods such as intravascular cooling catheters (Celcius Control [Innercool Therapies, San Diego, CA, USA], CoolLine [Alsius, Irvine, CA, USA], SetPoint [Radiant Medical, Redwood City, CA, USA]) [13, 14]. There are no trials demonstrating that use of a particular system improves clinical outcome, although certain methods may result in a more rapid induction of hypothermia and a

more accurate maintenance of the target temperature [13, 14].

Only 16% of patients in our cohort met the entry criteria to the therapeutic hypothermia trials. This suggests that strict adherence to the entry criteria of the trials would result in very low rates of admission for therapeutic hypothermia, at least in our population. International Liaison Committee on Resuscitation (ILCOR) guidelines suggested that consideration be given to cooling all OHCA patients. The favourable outcome recorded in 22% of patients aged >70 years supports this suggestion, although we cannot prove that therapeutic hypothermia explains this. We had no detailed data on cognitive outcomes for any of the patients as this is difficult to measure out with a trial setting.

Implementation of a therapeutic hypothermia policy did not result in a large pressure on ICU beds. Our hospital receives emergency admissions from a population of over 500 000 and the Scottish population has a high incidence of coronary heart disease. However, despite a broad OHCA admission policy, only around 35 of these patients were admitted per year to ICU. This represents less than 3% of our ICU admissions. These patients had a short ICU stay, particularly the non-survivors. Between 2002 and 2005, treating 139 patients involved 437 ICU days and 1137 hospital days, which in our cohort translates to 11.8 days of ICU care and 30.7 days of hospital care per favourable outcome. One reason for the short ICU stay is our policy of withdrawal of active treatment in patients who remain comatose at 72 h. This policy is in line with the Australian therapeutic hypothermia trial [2].

Conclusion

Clinician scepticism regarding the external validity of clinical trial results is the most common reason that potentially beneficial treatments are under-used [15]. Two randomised controlled trials confirmed the efficacy of therapeutic hypothermia [1, 2]. We obtained comparable outcomes to these studies with benefit extending to more elderly patients, a group excluded from the trials. This audit therefore supports the use of a 'therapeutic hypothermia package' as a clinically effective treatment which does not require major additional critical care resources.

References

1 Holzer M. The Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurological outcome after cardiac arrest. *New England Journal of Medicine* 2002; **346**: 549–56.

2 Bernard S, Gray T, Buist M, et al. Treatment of comatose survivors of out of hospital cardiac arrest with induced hypothermia. *New England Journal of Medicine* 2002; **346**: 557–63.

3 Cheung KW, Green RS, Magee KD. Systematic review of randomised controlled trials of therapeutic hypothermia as a neuroprotectant in post cardiac arrest patients. *Journal of the Canadian Association of Emergency Physicians* 2006; **8**: 329–37.

4 Holzer M, Bernard SA, Hachimi-Idrissi S, Roine RO, Sterz F, Mullner M. Hypothermia for neuroprotection after cardiac arrest: Systematic review and individual patient data meta-analysis. *Critical Care Medicine* 2005; **33**: 415–8.

5 Nolan JP, Morley PT, Vanden Hoek TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Circulation* 2003; **108**: 118–21.

6 Laver SR, Padkin A, Atalla A, Nolan JP. Therapeutic hypothermia after cardiac arrest: a survey of practice in intensive care units in the United Kingdom. *Anaesthesia* 2006; **61**: 873–7.

7 Merchant RM, Soar J, Skrifvars MB, et al. Therapeutic hypothermia utilisation among physicians after resuscitation from cardiac arrest. *Critical Care Medicine* 2006; **34**: 1935–40.

8 Sander M, von Heymann C, Spies C. Implementing the International Liaison Committee on Resuscitation guidelines on hypothermia after cardiac arrest. The German experience: still a long way to go? *Critical Care* 2006; **10**. http://ccforum.com/content/10/2/407.

9 Pell JP, Sirel JM, Marsdel AK, et al. Presentation, management, and outcome of out of hospital cardiopulmonary arrest: comparison by underlying aetiology. *Heart* 2003; **89**: 839–42.

10 Morrison LJ, Visentin LM, Kiss A, et al. Validation of a rule for termination of resuscitation in out-of-hospital cardiac arrest. *New England Journal of Medicine* 2006; **355**: 478–87.

11 Grubb NR, Elton RA, Fox KA. In-hospital mortality after out-of-hospital cardiac arrest. *Lancet* 1995; **346**: 417–21.

12 Herlitz J, Bang A, Gunnarsson J, et al. Factors associated with survival to hospital discharge among patients hospitalised alive after out of hospital cardiac arrest: change in outcome over 20 years in the community of Goteborg, Sweden. *Heart* 2003; **89**: 25–30.

13 Polderman KH. Application of therapeutic hypothermia in the intensive care unit. Opportunities and pitfalls of a promising treatment modality – Part 2. Practical aspects and side effects. *Intensive Care Medicine* 2004; **30**: 757–67.

14 Polderman KH. Keeping a cool head: How to induce and maintain hypothermia. *Critical Care Medicine* 2004; **32**: 2558–60.

15 Rothwell PM. External validity of randomised controlled trials: 'To whom do the results of this trial apply?'. *Lancet* 2005; **365**: 82–93.