A review of the pre-ROSC intranasal cooling effectiveness study

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Guidelines for ambulance services and prehospital care are continuously under review. Now that our profession is embracing evidence-based practice, we as practitioners on the road find that what we do and how we do it are constantly under scrutiny and frequently changes as a result of new findings.

The Coalition Government has introduced new means for assessing the quality and performance of all ambulance trusts (Department of Health (DH), 2010). In April 2011, the 'Category B' target was to be replaced with a collection of clinical indicators and outcome measures that will, for the first time, attempt to look at the actual 'care' delivered to our patients in a very real way.

These new outcome measures are forcing ambulance trusts to look at maximizing the impact that the services provided have on their local populations and the local health economy, rather than just how fast an ambulance or response vehicle with a qualified member of staff can arrive at a patient's door.

One of the biggest challenges is the addition of monitoring survival to discharge from out-of-hospital cardiac arrest, as well as a return of spontaneous circulation (ROSC) by the time of handover in an accident and emergency unit. This new requirement comes at a timely moment, when the treatment of out-of-hospital cardiac arrest is undergoing dramatic changes and advances, with ROSC rates rising for ambulance services throughout the world.

Therapeutic hypothermia

With the publication of the 2010 European Resuscitation Council Guidelines (Nolan et al, 2010) late last year, the use of therapeutic hypothermia was recommended for the first time as part of the treatment algorhythm for cardiac arrest. One of the highlighted changes in the 2010 summary was the:

Abstract

With the publication of the 2010 European Resuscitation Council Guidelines, therapeutic hypothermia has been recommended as part of the treatment algorhythm for the management of adult cardiac arrest. As ambulance services around the world struggle to decide on the best method of cooling a patient at the time of the return of spontaneous circulation (ROSC), the ground-breaking 'PRINCE' study has been published describing the novel approach of 'trans-nasal' evaporative cooling during the peri-arrest period. This study describes a significant difference found on arrival at hospital between the mean tympanic temperatures of the two groups (cooled *vs* control) following a period of cooling (34.2 °C [SD 1.5 °C] *vs* 35.5 °C [SD 0.9 °C], $P<0.001$). In addition, when looking at survival to discharge following out-of-hospital (OOH) cardiac arrest, there was a statistically significant difference in a subgroup of patients where CPR was commenced within 10 minutes of cardiac arrest (56.5% of trans-nasally cooled patients survived to discharge compared with 29.4% of control patients ($P=0.04$, relative risk =1.9)). This article examines the PRINCE study and considers the implication of this method of inducing therapeutic hypothermia in the out-of-hospital cardiac arrest patient within the UK.

Key words

- Advanced Life Support (ALS) • Cardiac arrest • Therapeutic hypothermia • Trans-nasal evaporative cooling

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'Use of therapeutic hypothermia to include comatose survivors of cardiac arrest associated initially with non-shockable rhythms as well as shockable rhythms' (Nolan et al, 2010).

Therapeutic hypothermia gained widespread recognition following two landmark randomized control trials (Bernard, 2002; Holzer et al, 2002) that displayed improved neurological outcome following application of cooling post ROSC after an out-of-hospital ventricular fibrillation (VF) Arrest. Following this, in 2003, the Advanced Life Support Task Force for the International Liaison Committee

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Figure 1. If the patient was randomized into the cooling group, hypothermia was commenced using the Rhino Chill System

on Resuscitation (ILCOR) recommended cooling for unconscious patients after out-of-hospital VF cardiac arrest (Nolan et al, 2003).

Published literature in the field of therapeutic hypothermia has mostly concentrated on its use in the post-arrest patient who has had a ROSC, either in or out of hospital (Merchant et al, 2006; Oddo et al, 2006; Annopoulos et al, 2007). Evidence from these studies has been used to develop the use of the technique in the prehospital environment.

Current methods for cooling

Common methods of cooling patients that are already in use in various service environments around the world include the use of ice cold Ringers Lactate solution, cooling blankets and ice packs. While these methods have all been used effectively to initiate hypothermia, many of them have proven limitations. Ice packs have been shown to be unpopular with some groups of nursing staff (Bernard, 2002) and the rate of cooling has been recorded as slow in comparison to other methods (<0.9 °C per hour).

‘The treatment of out-of-hospital cardiac arrest is undergoing dramatic changes and advances’

Cold air blankets appear to cool core temperature even more slowly (Holzer et al, 2002), and with both methods it has been described that frequent over-cooling of patients has occurred (Kupchick, 2009).

In one study, 28% of respondents believed that the cooling of patients was technically too difficult or too slow when used within their department (Abella et al, 2005). However, even though the methods have been troublesome, the benefit to patient outcome is clear.

As early as 1991, Sterz et al showed improved outcomes in dog models when hypothermia was initiated prior to the return of oxygenated blood. This ultimately led to researchers speculating on the effect that earlier induction of hypothermia could have on the patient suffering from a cardiac arrest. Boddicker et al (2005) postulated that ‘intra-arrest’ hypothermia might very well improve survival to discharge and increase neurologically positive outcome compared with the ‘standard’ post-ROSC treatment. However, she concluded that:

> ***‘Intra-arrest hypothermia via external cooling is at present impractical in large animals or humans because of the prolonged time required to achieve cooling. In the future, however, intra-arrest cooling may become feasible in a clinical setting as new techniques are developed.’ (Boddicker et al, 2005)***

Trans-nasal evaporative cooling

The years have passed and the novel ‘trans-nasal evaporative’ cooling method has been developed for use during the intra-arrest period. It has generated significant interest following the publication of the PRINCE study last year (Castren et al, 2010).

The pre-ROSC intranasal cooling effectiveness (PRINCE) study is a significant step towards understanding the improvements that the early application of therapeutic hypothermia in the prehospital setting can make to the mortality and morbidity rates of patients suffering from an out-of-hospital cardiac arrest.

Importantly, for the first time, a large scale randomized trial was undertaken to look at the effects of therapeutic hypothermia during the intra-arrest period, rather than after the return of spontaneous circulation.

The study was conducted over a period of 8 months between November 2008 and June 2009 and included a total of fifteen sites in five European countries. All systems enrolled in the trial offered ALS facilities and a prehospital physician service.

Randomization took place at the patient's side once the ALS providers on scene had deemed them suitable for inclusion in the study. If the patient was randomized into the cooling group, hypothermia was commenced using the RhinoChill intranasal cooling system (BeneChill, Inc, San Diego, Calif) at the earliest opportunity during the resuscitation efforts. Cooling was continued until transition to systemic cooling in the hospital.

The RhinoChill system

The RhinoChill System is fully portable, weighing approximately 12 kg when fully outfitted. It contains a disposable nasal catheter, the control unit, a 1 litre bottle of coolant liquid and an oxygen cylinder (which can be replaced by the crews' normal oxygen supply, thus reducing weight) (*Figure 1*).

The nasal catheter is approximately 10 cm long (*Figure 2*) and delivers the coolant directly to the base of the nasal cavity (*Figure 3*). The nasal cavity and nasopharynx act as a heat exchanger which removes heat both haematogenously in the presence of a circulation, but importantly, via conduction across the base of the skull in the absence of a circulation.

This technique was effectively demonstrated in swine studies (Boller et al, 2007) and was further researched and proven as an effective method during cardiopulmonary resuscitation in porcine models by Yu et al (2010).

Although trans-nasal evaporative cooling cools the body at roughly the same rate as cold intravascular fluid, it has been shown to produce a quicker core cooling rate than the slower systemic methods of hypothermia induction, such as endovascular cooling, cold fluids, ice packs and surface cooling (1.4˚C/hr (Busch et al, 2010) compared to 1.1˚C/hr (Arrich, 2007).

Additionally, rapid cooling of the target organ, the brain, is achieved and a brain–body temperature gradient is produced (Wolfson et al, 2008). This is achieved by the phase change of the coolant from liquid to gas (as occurs when the nebulized liquid coolant hits the warm tissues inside the nasal cavity) that removes much more heat than does simply circulating a cold fluid.

Other studies have demonstrated that the recommended temperature for the best results following cardiac arrest is that of mild hypothermia, i.e. 33–34 ˚C (Holzer et al, 2002; Bernard et al, 2002; Nolan et al, 2003). Improved survival and neurological outcome in those patients resuscitated from both VF and non-VF arrest have been shown when the patient is cooled to the target temperature (Haschimi-Idrissi et al, 2001; Holzer et al, 2005; Nielsen et al, 2009).

Inclusion criteria for the PRINCE study warrented that patients be over the age of 18 and experiencing cardiac arrest, irrespective of rhythm, where cardiopulmonary resuscitation had been commenced by EMS within 20 minutes of the collapse. The services taking part in the study excluded patients based on their usual criteria for not commencing CPR, along with those who had


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Figure 2. Nasal catheter for dispersal of coolant into the nasal cavity and nasopharynx

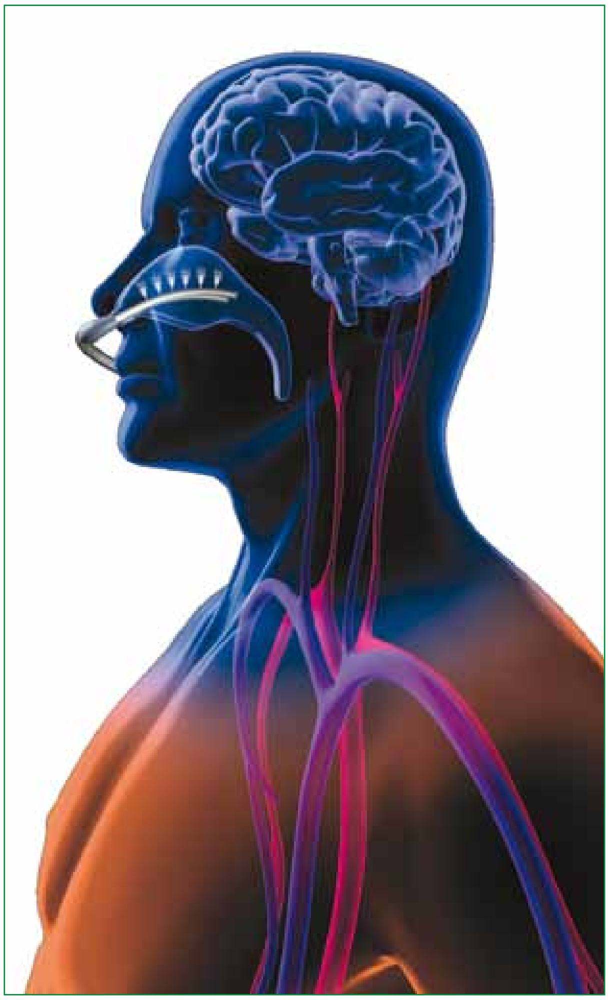
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Figure 3. Rapid brain cooling and creation of brain-body temperature gradient

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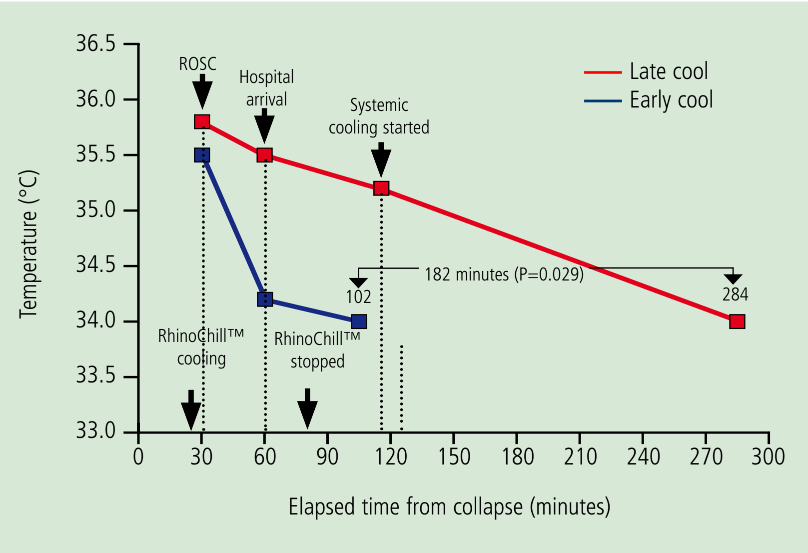

Figure 4. Comparison of time to target tympanic temperature

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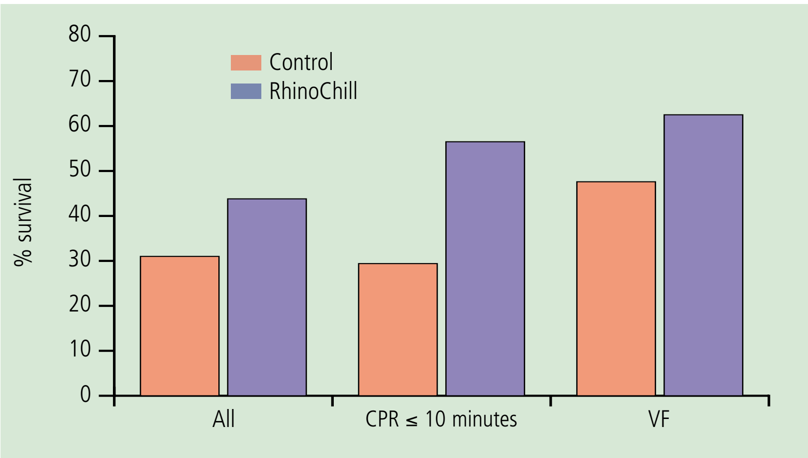

Figure 5. Rates of survival in the treatment and control groups among those patients admitted to the hospital for the entire group, those who recieved rescuer CPR within 10 minutes, and those with a presenting rhythm of VF

achieved ROSC before randomization and those with an intranasal obstruction that prevented the insertion of the nasal catheter.

If a ROSC was achieved and the patient remained unconscious, then cooling continued throughout the transfer to hospital and handover to the emergency room teams. If possible, trans-nasal cooling was continued until the receiving units' own systemic cooling methods were introduced to maintain the reduction in body temperature.

The patient's temperature was measured at the time of ROSC and then again on admission to hospital using a tympanic thermometer (at hospital admission, both core and tympanic were measured; core was typically rectal or bladder).

Results

Throughout the trial period, 93 patients received the trans-nasal cooling intervention and 101 served as controls, receiving the standard advanced cardiac life support (ACLS) treatment without prehospital cooling.

The median time for the commencement of cooling was 23 minutes from the time of collapse. Mean tympanic temperatures between the two groups were similar at the time of ROSC (35.5˚C [SD 0.9˚C] for the intervention group compared with 35.8˚C [SD 1.5˚C] in the control group). However, on arrival at the hospital there was a significant difference between the mean tympanic temperatures of the two groups following a period of cooling (34.2˚C [SD 1.5˚C] *vs* 35.5°C [SD 0.9°C], $P < 0.001$). There was also a significant difference between the core temperatures in the two groups of patients.

Overall, after continuation of hospital-based systemic cooling of the patient, the median time for achievement of the target temperature of 34˚C was 155 minutes (interquartile range 124 to 315 minutes) *vs* 284 minutes (interquartile range 172 to 471 minutes) in control patients (*Figure 4*).

The result of the study provides the reader with a tantalizing glimpse at the possible improvement in clinical outcome following cardiac arrest when utilising prehospital therapeutic hypothermia during the intra-arrest period.

Rate of ROSC was not statistically different between the treatment group and the control group (35 [37.6%] of 93 in the treatment group and 43 [42.6%] of 101 control subjects, $P=0.48$). However, this is to be expected as the ROSC is achieved very early on in the cooling period, at which time there may well be no significant difference in brain temperature between the two groups.

Survival to discharge

When the authors looked at survival-to-discharge data from the group of patients admitted alive to the hospital there was a statistically non-significant, but meaningful, difference between the treatment and control groups (43.8% of treated patients and 31.0% of control patients, $P=0.26$, relative risk=1.4). There was, however, a statistically significant difference in the subgroup of patients where CPR was commenced within 10 minutes of cardiac arrest (56.5% of trans-nasally cooled patients survived to discharge compared with 29.4% of control patients $P=0.04$, relative risk =1.9) (*Figure 5*).

When looking at survival of patients neurologically intact, the authors also noted a significant improvement in the subgroup of patients who received CPR within 10 minutes of collapse (43.5% *vs* 17.6%, $P=0.03$, relative risk =2.5). Positive differences were also observed in the study group as a whole, and in those patients presenting with VF when cooled intra-arrest via the nasal route. However, these again were deemed not to be significant (*Figure 6*). Even in the groups where significance was not achieved, it is encouraging to see a trend toward improvement in the groups that have been cooled during the arrest phase instead of following a ROSC.

An interesting and important additional finding of the study was the improvement of the treatment group in respect to the amount of time spent in intensive care and on a ventilator (8 days in the intensive care unit for treated patients *vs* 11 days for control patients; and 4.2 days on a ventilator for treated patients *vs* 8.8 days for control patients).

Discussion

Use of therapeutic hypothermia in survivors of cardiac arrest is now seen as the standard of care (Bernard, 2006). It is also widely acknowledged that reaching and maintaining the moderate hypothermia level of 34˚C is beneficial to survivors of cardiac arrest. However, the speed and efficiency of reaching the target temperature also has a direct effect on patient outcome and neurological function post ROSC (Holzer et al, 2005; Bayegan, 2008; Holzer, 2008; Varon and Acosta, 2008).

Current methods used to cool patients are wide and varied and have an equally diverse rate of cooling. Some of these are obviously unsuitable for the prehospital or critically ill patient, but when looking for a means to compare the efficiency of these devices and techniques, an examination of either the rate of cooling in ˚C/hr, or the overall mean time for patients to attain the target temperature of 34˚C can be used.

As the trans-nasal evaporative cooling selectively targets the brain for rapid cooling to increase the effect of moderate hypothermia to the target organ, the best method of comparison is to look at the rate of cooling.

Polderman and Herold (2009) completed a systematic analysis on the current methods used for the induction of therapeutic hypothermia. Data taken from this review along with data from other papers (Kliegel et al, 2005; Hoedemaekers et al, 2007; Holzer, 2008; Bayegan et al, 2008) is summarized in *Table 1* to provide a direct comparison of cooling rates of devices and methods in use now, and also in the experimental phase.

During the initial rapid cooling phase of the Rhino Chill system, a tympanic temperature drop of 1.3˚C on average occurred from ROSC to hospital arrival (mean time of 26 mins). This equates to a mean cooling rate for the brain of 3.0˚C/hr. The overall time to core hypothermia

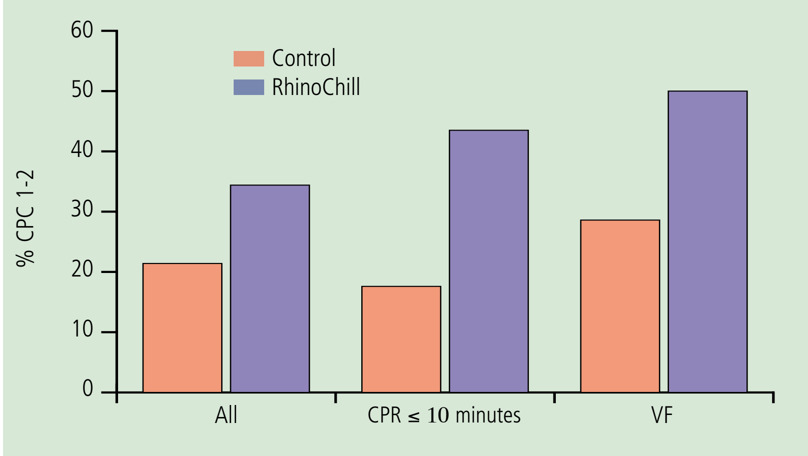

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Figure 6. Rates of neurologically intact survival (defined as having a cerebral performance category (CPC) of 1 or 2) in the treatment and control groups among those patients admitted to the hospital for the entire group, those who recieved rescuer CPR within 10 minutes, and those with a presenting rhythm of VF

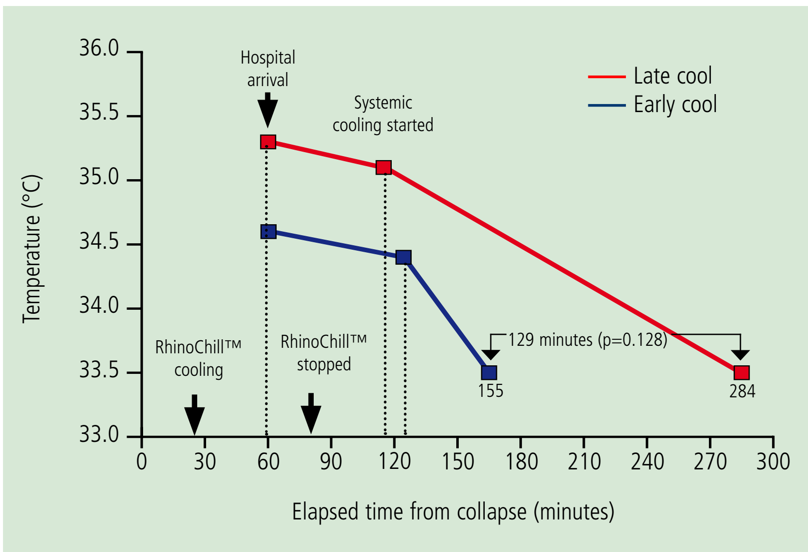

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Figure 7. Comparison of time to target core temperature

was at a slower rate due to the use of conventional cooling methods once the patient was transferred to standard in-hospital care, and the effect of the brain–body temperature gradient, but was still significantly faster than the standard in-hospital cooling methods used in the study (*Figure 7*).

Conclusion

There are various methods that can be used to cool the patient to the target mild hypothermic temperature of 34˚C. The PRINCE study, however, introduces a method that can be used rapidly within the prehospital environment, with relatively little training impact on the workforce.

All EMS staff who were involved in the study across the 15 European sites received just 2 hours of training to ensure that they were competent

Table 1. Comparison of cooling rates of alternative methods for induction of hypothermia

Method	Cooling rate
Air exposure to skin	0.5 ˚C/hr
Air blankets	0.5 ˚C/hr
Cooling helmet	0.5 ˚C/hr
Bladder lavage	0.8 ˚C/hr
Fans	1.0 ˚C/hr
Air exposure with water/alcohol sprays	1.0 ˚C/hr
Water circulating blankets	1.0–1.5 ˚C/hr
Water circulating wrapping garments	1.5 ˚C/hr
Hydrogel coated water circulating pads	1.5–2.0 ˚C/hr
Infusion of ice cold fluids	2.5–3.5 ˚C/hr
Intravascular catheters	2.0–4.5 ˚C/hr
Precooled matresses (latex/water/ graphite glued to the skin)	3.3 ˚C/hr
Extra corporeal circulation	4.0–6.0 ˚C/hr
Complete immersion in water	8.0–10.0 ˚C/hr
Experimental	
Cold metal plates	4.1 ˚C/hr
Thermosuit system	24.0 ˚C/hr
IV neurotensin	Very rapid/ undetermined rate
Large volume ice cold Intra Pulmonary perflurocarbon	Very rapid/ undetermined rate

in the use of the system. Also, for the first time, a method is available that requires no additional cooling facilities be built into the ambulance and can easily be taken to the patient's side to start the cooling process at a time when most other methods would not even have been considered.

It is important to remember, however, that the PRINCE study is the first large-scale trial looking at the feasibility and efficiency of intra-arrest cooling, and as such should be the starting point for more work in the prehospital field. The UK was unfortunately not one of the sites participating in the trial, so there is clearly a gap in the knowledge and application of the findings to the UK setting.

Evidence-based practice is driving our profession forward. Paramedic training is evolving into higher education and providers are becoming aware of innovation and development in their specialized fields. Cardiac arrest care continues to be an area of development and improvement. The RhinoChill System can be used along with other products to maximize the potential for recovery. Together with the introduction of mechanical assist devices such as the LUCAS and the AUTOPULSE, and the emergent field of prehospital fast ultrasound scanning and the use of capnography in cardiac arrest, a 'package of care' is rapidly forming for our patients.

As we progress and await the introduction into practice of the new recommendations from the 2010 ERC guidelines, we remain hopeful that the routine use of therapeutic hypothermia will be introduced to the UK ambulance services and look forward to using the latest developments in technology to ensure that our patients receive the best possible chance of survival to discharge with good neurological function.

Conflict of interest
The authors have received honoraria from BeneChill, Inc.

Abella B, Rhee J, Huang K et al (2005) Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey. *Resuscitation* **64**(2): 181–6

Annopoulos D, Kotsifas K, Aufderheide T et al (2007) Cardiac arrest, mild therapeutic hypothermia, and unanticipated cerebral recovery. *Neurologist* **13**(6): 369–75

Arrich J (2007) Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* **35**(4): 1041–7

Bayegan K, Janata A, Frossard M et al (2008) Rapid non-invasive external cooling to induce mild therapeutic hypothermia in adult human-sized swine. *Resuscitation* **76**(2): 291–8

Bernard S, Gray T, Buist M et al (2002) Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* **346**(8): 557–63

Bernard S (2006) Therapeutic hypothermia after cardiac arrest: now a standard of care. *Crit Care Med* **34**(3): 923–924

Boddicker K, Zhang Y, Zimmerman M et al (2005) Hypothermia improves defibrillation success and resuscitation outcomes from ventricular fibrillation. *Circulation* **111**(24): 3195–3201

Boller M, Lampe J, Becker L (2007) Feasibility of selective brain cooling during cardiac arrest: a novel nasopharyngeal approach. *Circulation* **116**: II_944 Abstract

Busch H, Eichwede F, Födisch M et al (2010) Safety and feasibility of nasopharyngeal evaporative cooling in the emergency department setting in survivors of cardiac arrest. *Resuscitation* **81**(8): 943–9

Castren M, Norberg P, Svensson L et al (2010) Intra-arrest trans-nasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness) *Circulation* **122**(7): 729–36

Department of Health (2010. *Equity and Excellence: Liberating the NHS*. http://tinyurl.com/2a8ljeo (accessed 6 April 2011)

Hachimi-Idrissi S, Corne L, Ebinger G et al (2001) Mild hypothermia induced by a helmet device: a clinical feasibility study. *Resuscitation* **51**(3): 275–81

Hoedmaekers C, Ezzahti M, Gerritsen A et al (2007) Comparison of cooling methods to induce and maintain normo-and hypothermia in intensive care unit patients: a prospective intervention study. *Critical Care* **11**(4): R91

Holzer, M et al (2002) The hypothermia after cardiac arrest study group: mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* **346**(8): 549–56

Key points

- Therapeutic hypothermia is now recommended as part of the treatment algorhythm for adult cardiac arrest in the 2010 European Resuscitation Council Guidelines.
- Trans-nasal evaporative cooling is a novel and safe way for the prehospital practitioner to achieve rapid cooling of the brain in out-of-hospital cardiac arrest prior to ROSC.
- Trans-nasal evaporative cooling has been shown to be both faster and more effective at achieving target hypothermia temperatures than other, more standard methods (average tympanic temp on arrival to hospital—34.2 °C [SD 1.5°C]).
- In certain groups of patients (e.g. CPR commenced within 10 minutes of collapse), trans-nasal evaporative cooling produced significant improvements in survival to discharge following OOH cardiac arrest (56.5% of trans-nasally cooled patients survived to discharge compared with 29.4% of control patients (*P*=0.04, relative risk =1.9).
- Further research is required into the use of the RhinoChill® intranasal cooling system by the UK ambulance services to verify the results within the UK prehospital care system.

Holzer M, Bernard S, Hachimi-Idrissi S et al (2005) Collaborative Group on Induced Hypothermia for Neuroprotection After Cardiac Arrest. Hypothermia for neuroprotection after cardiac arrest: systematic review and individual patient data meta-analysis. *Crit Care Med* **33**(2): 414–18

Holzer M, Behringer W, Janata A et al (2005) Extracorporeal venovenous cooling for induction of mild hypothermia in human-sized swine. *Crit Care Med* **33**(6): 1346–50

Holzer M (2008) Devices for rapid induction of hypothermia. *European Journal of Anaesthesiology* **25**(Suppl 42): 31–38

Kliegel A, Losert H, Sterz F et al (2005) Cold simple intravenous infusions preceding special endovascular cooling for faster induction of mild hypothermia after cardiac arrest—a feasibility study. *Resuscitation* **64**(3): 347–51

Kupchick L (2009) Development and Implementation of a therapeutic hypothermia protocol. *Crit Care Med* **37**(7 Suppl): S279-84

Merchant R, Soar J, Skrifvars M et al (2006) Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. *Crit Care Med* **34**(7): 1935–40

Nielsen N, Hovdenes J, Nilsson F et al (2009) Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. *Acta Anaesthesiol Scand* **53**(7): 926–34

Nolan J, Morley P, Vanden Hoek T et al (2003) Therapeutic hypothermia after cardiac arrest: an advisory statement by the Advanced Life Support Task Force of the International Liaison Committee on Resuscitation. *Circulation* **108**(1): 118–21

Nolan J, Soar J, Zideman D et al (2010) European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. *Resuscitation* **81**(10): 1219–76

Oddo M, Schaller M, Feihl F et al (2006) From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. *Crit Care Med* **34**(7): 1865–73

Polderman K, Herold I, (2009) Therapeutic hypothermia and controlled normothermia in the intensive care unit: Practical
Sterz F, Safar P, Tisherman S et al (1991) Mild hypothermic
considerations, side effects, and cooling methods. *Crit Care Med* **37**(3): 1101–20
cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Crit Care Med* **19**(3): 379–89

Varon J, Acosta P (2008) Therapeutic Hypothermia, Past Present and Future. *Chest* **133**(5): 1267–74

Wolfson M, Malone D, Wu J, et al (2008) Intranasal perfluorochemical spray for preferential brain cooling in sheep. *Neurocrit Care* **8**(3) 437–47

Yu T, Barbut D, Ristagno G et al (2010) Survival and neurological outcomes after nasopharyngeal cooling or peripheral vein cold saline infusion initiated during cardiopulmonary resuscitation in a porcine model of prolonged cardiac arrest. *Crit Care Med* **38**(3): 916–21