Review Article

Mild Therapeutic Hypothermia in Out-of-Hospital Cardiac Arrest Survivors

Nikolaos I. Nikolaou, Apostolos H. Christou, Emmanouil C. Papadakis, Athanasios I. Marinakos, Sotirios P. Patsilinakos

Cardiology Department, Konstantopoulio General Hospital, Athens, Greece

Key words:
Spontaneous circulation, neuroprotection, cooling.

Manuscript received:
November 9, 2011;
Accepted:
June 19, 2012.

Address:
Apostolos H. Christou

20 Argiroupoleos St.
142 31 Nea Ionia
Athens, Greece
e-mail: christouapostolos@yahoo.com

Cardiac arrest is a major cause of death in the industrialized world.[1] More than 275,000 out-of-hospital cardiac arrests are treated annually by the emergency medical services in European countries.[2] The global incidence of out-of-hospital cardiac arrest (OHCA) ranges from 35 to 125 cases per 100,000 people, with 25% of these being less than 65 years of age.[3,4] Despite recent advances in resuscitation science and practice, survival from OHCA remains far from satisfactory.[5,6]

Severe post anoxic brain damage is an important cause of morbidity and mortality in patients who initially undergo successful resuscitation. The induction of mild therapeutic hypothermia (TH) in selected patients surviving out-of-hospital sudden cardiac arrest and return of spontaneous circulation (ROSC) has a major impact on long-term neurologically intact survival and may prove to be one of the most promising clinical advances in the field of resuscitation.

History

The utility of hypothermia in medicine has been recognized since antiquity. Hippocrates, the world's first modern doctor, advocated the packing of wounded soldiers' limbs in snow and ice.[7] Historical evidence from later years refers to the records of Napoleonic surgeon Barron Larrey, who observed that injured officers who were kept closer to a fire after being operated upon survived less often than infantrymen who were left in a cold environment.[7]

The first medical article concerning hypothermia was published in 1945 and focused on the effects of hypothermia on patients suffering from severe head injury.[7] In the 1950's, hypothermia received its first medical application, being used in intracerebral aneurysm surgery to create a bloodless field.[7] Most of the early research, however, focused on the applications of deep hypothermia, defined as a body temperature between 20-25°C. Such an extreme drop in body temperature is accompanied by a whole host of side effects, which made the use of deep hypothermia impractical in most clinical situations.

During this period, sporadic reports of the therapeutic use of mild hypothermia appeared, with body temperature being kept between 32-34°C. In the 1950s, Rosomoff demonstrated the positive effects of mild hypothermia after brain ischemia and traumatic brain injury in dogs. In the 1980s further animal studies indicated the ability of mild hypothermia to act as a general neuroprotectant following a blockage of blood flow to the brain.[8]

In 1999, during a skiing accident, An-

na Bagenholm's heart stopped for more than three hours and her body temperature dropped to 13.7°C before she was successfully resuscitated.[9]

After studies of safety and feasibility had been conducted,[10,11] 2 randomized studies, published in February 2002 in the New England Journal of Medicine,[12-13] provided the evidence base for the establishment of TH as a means of improvement of patient outcomes in comatose survivors of cardiac arrest.

The Hypothermia After Cardiac Arrest (HACA) study[12] was a randomized multicenter trial that included 274 patients who remained comatose after being resuscitated from ventricular fibrillation (VF) cardiac arrest. These patients were randomized to be treated with either mild hypothermia (cooling to 32-34ºC with an external cooling device for 24 hours) or standard post-resuscitation treatment. At six months, 75/136 patients (55%) in the hypothermia group had a favorable neurologic outcome as compared with 54/137 (39%) in the standard treatment group (risk ratio, RR, 1.40; 95% confidence interval, CI, 1.08-1.81, estimated number needed to treat, NNT=6). Mortality at six months was also lower in the hypothermia group (56/137=35% of patients died), as compared with 55% in the normothermia group (76/138 patients; RR 0.74; 95% CI 0.58-0.95, NNT=7).[12] The NNT is very low and comparable to other important emergent treatments, such as cardiac catheterization for acute coronary syndromes.

In the second trial, 77 OHCA patients with VF were randomized to either 12 hours of hypothermia (followed by active rewarming) or to normothermia during post-resuscitation treatment. TH was associated with a higher frequency (21/43, 49%) of good patient outcome (survival to hospital, discharge to home or a rehabilitation facility) compared with 9/34 (26%) in the normothermic group.[13]

Definition and pathophysiology

Hypothermia is a condition in which an organism's temperature drops below that required for normal metabolism and body functions. There is a continuum regarding the effects of increasing hypothermia on human metabolism and clinical status. For treatment of cardiac arrest mild TH (32-34°C) is employed. Cardiac arrest and ROSC represent a case of whole body ischemia-reperfusion injury that may cause enormous biochemical structural and functional insults, leading to progressive cell destruction, multi-organ dysfunction, and death.[14,15]

Most early hypotheses suggested that hypothermia reduces the harmful effects of ischemia by merely decreasing the body's need for oxygen.[7] For every Celsius degree drop in body temperature, cellular metabolism slows by 5-7%.[16] Thus initial therapeutic attempts were based on the application of deep hypothermia, because it is more effective than milder degrees of hypothermia in reducing metabolic rhythm and energy demands.[17]

Recent data, however, suggest that even a modest reduction in temperature can function as a neuroprotectant.[18] Therefore, hypothermia may offer organ protection, not only by decreasing cellular metabolic needs, but also by inhibiting temperature-sensitive pathways of the ischemia reperfusion cascade.

Mechanisms of protection

Neuronal ischemia may culminate in cell death because of excessive calcium influx into the neuron cells through stimulation of the *N*-methyl *D*-aspartate (NMDA) receptor.[19] The receptor is activated by glycine and stimulated by excitatory neurotransmitters such as aspartate and glutamate, which increase during ischemia and cause neurological damage in proportion to their concentration.[20-23] The release of these neurotransmitters during ischemia is temperature-dependent, and even mild hypothermia is effective in reducing their levels.[24,25]

Apart from protection of neuronal cells from calcium overload, hypothermia can minimize ischemic cell damage by avoiding the activation and transformation of astroglial cells to phagocytes, thus reducing cell damage caused by the release of proinflammatory cytokines and free radicals.[26] It may also significantly reduce the extent of ischemic brain injury by increasing levels of brain-derived neurotrophic factor and other neurotrophins after ischemia.[27]

Hypothermia also acts to prevent apoptosis thanks to its beneficial effects on the interaction between pro-apoptotic and anti-apoptotic proteins. Among other actions, hypothermia may increase the levels of anti-apoptotic proteins such as Bcl-2, block the tumor necrosis factor pathway of apoptosis, inhibit the stress-activated signaling pathways, and also exert a direct inhibitory effect on the caspase pathway.[28-31]

It has also been established that hypothermia decreases cerebral oxygen consumption, glucose utilization and brain metabolism. These effects are accompanied by a proportional decrease in cerebral blood

flow.[32-33] It is possibly due to these effects that hypothermia may decrease post-ischemic cellular levels of lactate and other wastes from anaerobic metabolism, thus decreasing cellular acidosis.[34]

Several other mechanisms have been proposed to explain the cytoprotective effect of hypothermia after an ischemic insult. It has been speculated that TH may:

- decrease the concentrations of thromboxane A_2, thus ameliorating its vasoconstrictor and prothrombotic effects.[35]
- reduce free radicals that are produced during the ischemia-reperfusion procedure and limit the resulting cell damage.[36]
- decrease the production of inflammatory cytokines, leukotrienes, and inflammatory cells such as macrophages.[33,37]
- decrease the cytotoxic edema formed after ischemia, reduce the disruption of the blood–brain barrier and decrease the damage to the endothelial vasculature.[38]
- suppress epileptogenic electrical activity, being effective in both non-convulsive *status epilepticus* and in cases of generalized tonic-clonic seizures.[39]

The mechanisms of action of TH are summarized in Table 1.

Finally, in the heart, hypothermia may decrease the area of injury, promote epicardial blood flow, decrease myocardial metabolic demand, preserve high-energy phosphate stores, and enhance mitochondrial membrane stability.[40-42] There is experimental evidence suggesting that the greatest benefit is achieved when the heart is cooled before reperfusion.[43]

Hypothermia in VF and non-VF cardiac arrest

The first studies to provide strong evidence for the routine use of TH in post-resuscitation care, i.e. the HACA trial and the study of Berard in Australia, were conducted in comatose survivors of OHCA with VF as the first documented rhythm.[12-13] Following the publication of these trials, the International Liaison Committee on Resuscitation (ILCOR) suggested the routine use of TH in this group of patients.[44]

The inclusion of hypothermia into the international guidelines discouraged further studies with patient randomization into control groups without hypothermia. Thus, additional evidence supporting the use of hypothermia in survivors of ventricular fibrillation or ventricular tachycardia (VF/VT) OHCA comes mostly from small, non-randomized cohorts of patients. The most important relevant evidence was published recently in a report from a prospective cohort of 1145 survivors from OHCA in Paris. In this

Table 1. The mechanisms of action of therapeutic hypothermia. Modified from González-Ibarra FP, Varon J and López-Meza EG. Therapeutic hypothermia: critical review of the molecular mechanisms of action. Front Neur. 2011; 2: 4.

Reduces extracellular levels of excitatory neurotransmitters
Decreases brain glycine levels after ischemia
Increases levels of BDNF and other neurotrophins after ischemic injury
Avoids proliferation, migration, transformation, and activation of astroglial cells
Decreases P53 protein levels in the brain and apoptotic neuronal death
Affects the levels of proteins Bcl-2 and cytochrome C
Blocks the TNF pathway of apoptosis
Affects stress-activated signaling pathways avoiding cell apoptosis
Prevents apoptosis by inhibiting the caspase pathway
Blocks the proteins responsible for mediating caspase-independent apoptosis
Induces the formation of cold shock proteins
Lowers lactate levels from anaerobic metabolism decreasing cellular acidosis
Improves brain glucose metabolism and preserves glucose reserves in the brain
Reduces free radical levels after neuronal damage
Blocks delta-PCK and preserves function of epsilon-PCK after ischemia
Reinforces Akt pathway and carries out structural alterations in PTEN
Decreases production of inflammatory cytokines and leukotrienes
Decreases inflammatory cells' functions as macrophages
Suppresses epileptogenic electrical activity
Reduces disruption of blood–brain barrier
Decreases damage of the endothelial vasculature
Decreases the concentrations of thromboxane A2

BDNF – brain-derived neurotrophic factor; TNF – tumor necrosis factor; PCK – protein kinase C; Akt – protein kinase B; PTEN – phosphatase and tensin homolog.

study, if the cause of cardiac arrest was VF/VT, treatment with TH had an independent association with increased odds of a good neurological outcome (adjusted odds ratio, 1.90; 95% CI, 1.18-3.06).[45]

Extrapolation of these data to cardiac arrests with non-shockable initial rhythms seems reasonable, but is supported only by lower-level data derived from non-randomized trials and trials using historical controls.[46-49] No beneficial effect of TH on neurological outcomes in survivors of cardiac arrest was shown in the previously mentioned large observational study by Dumas et al.[45] In a recent meta-analysis of non-randomized trials conducted up to March 2010, Kim et al found that, in adult patients resuscitated from non-shockable cardiac arrest, TH was associated with reduced in-hospital mortality.[50] However, they pointed out that most of the studies had substantial potential sources of bias and therefore the overall quality of the evidence was very low. By contrast, in a more recent trial, Nielsen et al failed to show any clear benefit in neurological outcome with TH in comatose survivors after cardiac arrest.[51]

The possible reasons for this diversity of results have not been clearly defined. Patients presenting with a non-shockable rhythm may have had a VF/VT arrest initially, which has gradually degenerated into a non-shockable rhythm because the patients remained unattended for a significant period of time. In these patients the resuscitation process is expected to be longer, compared to patients who are still in shockable rhythms, and this could lead to a higher rate of post-resuscitation circulatory shock. There is also a chance that the amount of hypothermia given in the studies could have been insufficient.

Post-arrest treatment of survivors of cardiac arrest with a non-shockable initial rhythm is becoming an increasingly important issue, because the proportion of cardiac arrest patients with non-shockable rhythms is increasing in recent registries. According to the recent guidelines, hypothermia in non-shockable patients is of possible benefit, and therefore TH should by no means be withheld in this group of patients.[52,53] It is to be hoped that ongoing randomized controlled trials will give convincing answers to these important clinical questions.

When to start cooling

It has been hypothesized that early achievement of mild TH immediately after successful resuscitation and ROSC might offer the maximum benefit in terms of both neurological outcome and survival. However, the optimal timing of induction of TH remains uncertain.

Effective temperature lowering can be initiated in the pre-hospital setting. Kim et al have shown that pre-hospital administration of cold intravenous fluid in resuscitated OHCA patients was not associated with adverse effects and resulted in a significant temperature decrease by hospital arrival.[54] There was also some clinical evidence for the beneficial effects of early TH induction. In their case series, Wolff et al demonstrated that the time to coldest temperature was an independent predictor of good neurological outcome in patients undergoing endovascular cooling after cardiac arrest.[55]

The finding of a beneficial effect of early cooling was not unanimous among studies. In a recent randomized controlled trial, Bernard et al were unable to find any improvement in patient outcomes at hospital discharge of paramedic-initiated pre-hospital cooling compared with cooling commenced in the hospital.[56] Further evidence in line with these data was provided by Nielsen et al in a report from a multicenter, international registry-based case series of 986 comatose post-cardiac arrest patients. Again, the time to initiation of cooling was not associated with an improved neurological outcome post discharge.[51]

Methods of cooling

Several methods have been used for the induction of hypothermia. Rapid infusion of large-volume (30 ml/kg), ice-cold (4°C) intravenous fluids (normal saline or Ringer's lactate) is a successful and easy way to cool cardiac arrest patients.[54,57-60] Administration of cold intravenous fluid to resuscitated OHCA patients is feasible in the pre-hospital setting before arrival at the emergency department.[54,56,61] The use of simple icepacks placed in the groin, armpits, and around the head and neck has been shown to be adequate in inducing hypothermia.[62,63] Conventional cooling blankets or pads,[62,64,65] and external devices using circulating water or air blankets have also been used for non-invasive surface cooling.

Cold intravenous fluid and/or cooling pads can be used in conjunction with surface or internal cooling devices to facilitate the induction of hypothermia.[63,66] Ice-cold fluids alone cannot maintain hypothermia,[67] but the addition of icepacks can keep the temperature in the target range (32-34°C).[57] In order to avoid episodes of overcooling, which are rather common with the use of cooling blanket/mattress or ice bags,[68] more sophisticated devices have been developed for

external cooling, with capabilities for continuous temperature feedback and tight control of body temperature within the desired limits.[67,68]

Trans-nasal evaporative cooling and helmet cooling devices are also used for inducing local brain hypothermia in the pre-hospital setting.[49,70] There is now evidence that pharmacological induction of hypothermia is feasible and may possibly represent a new method for rapid on-site induction of hypothermia in patients resuscitated from cardiac arrest.[71]

Endovascular cooling devices have been developed to initiate and maintain hypothermia. They consisted of a closed system with a central venous catheter (femoral or subclavian) and an external heat exchange system, which contains saline circulating through balloons within the catheter. The patient is cooled or warmed as venous blood passes over each balloon, exchanging heat without infusing saline into the patient. The system is adjusted to achieve and to maintain a target temperature (32.5-33.5°C), with the patient's core temperature being automatically measured by a sensor probe applied at the nasal septum or esophagus.[58,64,66] These devices have been found to be more reliable than external methods of cooling in maintaining patients' target temperature.[64] No improvement has been shown, however, for patient outcomes with the use of these devices in comparison to noninvasive methods of cooling.

The available methods of cooling are summarized in Table 2.

Rewarming can be achieved with either the same method for external or internal temperature control used to cool the patient, or passive rewarming. The optimal rate of rewarming is not known, but the consensus is currently to let the temperature rise about 0.25-0.5°C per hour.[53,72]

Table 2. Methods of cooling patients undergoing therapeutic hypothermia.

1. *Invasive*
   - Intravascular heat exchange system
   - Cardiopulmonary bypass
2. *Noninvasive*
   - Rapid infusion of 30 ml/kg cold fluids
   - Ice- and/or cold-packs
   - Water circulating blankets:
     - torso wraparound
     - leg wraps
   - Air circulating blankets
   - Water circulating gel-coated pads
   - Intranasal cooling
   - Cool caps

Therapeutic hypothermia and primary coronary intervention (PCI)

Recently, primary PCI has been established as a means of alleviating ischemia in survivors of cardiac arrest with ST-elevation myocardial infarction and/or other strong evidence of persistence of myocardial ischemia after ROSC.[73,74] It is, however, a matter of concern whether TH could be applied at the same time as coronary angiography and intervention.

In survivors of cardiac arrest with ST-segment elevation myocardial infarction, Knafelj et al demonstrated that patients who were treated with primary PCI and hypothermia, which was induced externally with ice packs, had a better cerebral performance category on discharge than historical controls treated with PCI but without hypothermia.[75]

Recent evidence underlines the need to use these interventions as part of an integrated, well planned protocol of post-resuscitation care. In a prospective, observational study Sunde et al demonstrated a benefit in discharge rate from hospital, neurological outcome and 1-year survival, after standardization of post-resuscitation care using a protocol that included revascularization with PCI and TH.[76] Similar effects were yielded in the subgroup of patients recovering from VF cardiac arrest in Göteborg, Sweden.[77]

In contrast with the aforementioned findings, in a recent analysis of data from the prospective German Resuscitation Registry only PCI was associated with a better neurological patient outcome in patients surviving OHCA, while mild TH was not among the independent predictors of a good neurological outcome.[78] The inconclusive results perhaps indicate differences in patient characteristics and allocation to treatment in local registries. It is therefore difficult to draw definite conclusions regarding the combined use of these therapeutic modalities without the results of randomized trials.

There is also concern regarding a possible increase in bleeding complications, because cardiac arrest and hypothermia may both compromise the coagulation system, while anticoagulant and antithrombotic medication are necessary adjunctive measures to coronary interventions. While the overall risk for bleeding requiring transfusion is low (4%) in patients undergoing TH, it increases to 6.2% in patients who also undergo PCI and is significantly higher than the corresponding risk of 2.8% in patients undergoing only TH.[51]

It seems, however, that the combination of primary PCI and hypothermia (interventional or external) is feasible and relatively safe and merits consideration

Table 3. Complications of therapeutic hypothermia.

Shivering
Increased systemic vascular resistance
Arrhythmias (usually bradycardia)
Excess diuresis
Electrolyte disturbance (hypophosphatemia, hypokalemia, hypomagnesemia and hypocalcemia)
Decreased insulin sensitivity, insulin secretion, hyperglycemia
Impairment of coagulation, particularly in patients undergoing percutaneous coronary intervention
Impairment of immune system, increased rate of infections
Increased levels of amylase
Decreased clearance of sedative drugs and neuromuscular blockers

as a therapeutic option in survivors of cardiac arrest after a myocardial infarction.

Complications of hypothermia

A large prospective, observational registry reviewed the adverse events that occurred in all patients treated with TH following OHCA.[79] Complications were common, but only sustained hyperglycemia and seizures treated with anti-convulsants were associated with increased mortality. Other frequent complications included pneumonia (48%), arrhythmias (7-14%), and metabolic and electrolyte disorders (5-37%). Sepsis (4%) and bleeding (6%) were less common and occurred more frequently with the use of any intravascular device—such as cooling devices, intra-aortic balloon pumps or angiography—but neither were associated with an increase in mortality. As there was no control group it was difficult to ascertain whether the observed complications were due to the hypothermia or due to the OHCA itself.

In a controlled trial and cohort studies mild hypothermia was shown to increase systemic vascular resistance and be the cause of arrhythmias (usually bradycardia).[66] It also impairs coagulation and increases bleeding,[12,76,80] although the effect of hypothermia on coagulation is not easy to distinguish from the effect of antithrombotic and antiplatelet drugs that may be administered to patients undergoing TH. There is also evidence that hypothermia can impair the immune system and increase infection rates,[81-83] but other studies have shown no difference in pneumonia[84] or sepsis.[12]

Shivering caused by hypothermia will increase metabolic rate and heat production. Hence, optimal sedation must be given to reduce or prevent shivering. The clearance of sedative drugs and neuromuscular blockers is reduced by up to 30% at a core temperature of 34°C, an effect that can be explained, at least in part, by slowing of the function of cytochrome P450 during hypothermia.[85]

The complications encountered most frequently during therapeutic hypothermia are summarized in Table 3.

Contraindications for hypothermia according to guidelines include severe systemic infection, established multiple organ failure, and preexisting medical coagulopathy (fibrinolytic therapy is not a contraindication for TH).[53]

Implementation

Although mild TH in comatose survivors of cardiac arrest has been strongly recommended by the guidelines since 2003,[44] implementation rates continue to be low worldwide and it seems that TH has not yet been accepted by the majority of physicians. Satisfactory rates of implementation are, however, reported from the UK and the Netherlands.[86,87]

Several factors have been recognized that limit a thorough implementation of TH. Adoption by additional centers is mainly impeded by lack of awareness of supporting data, concerns about its efficacy in the local patient population, and difficulties and costs anticipated for the implementation of TH. Hypothermia is, however, underused even in institutions where it has already been adopted. This is mainly associated with a lack of awareness of TH among personnel, uncertainties concerning the logistics of how to achieve hypothermia, suboptimal inter-professional collaboration, and a lack of familiarity resulting from infrequent use. Implementation is also affected by scientific background, with a more satisfactory implementation in anesthesiology and intensive care units.[88-91]

In a recent report from Canada, treating more than 10 cardiac arrests per year and being a physician for less than 10 years were strong independent predictors for the adoption of TH.[92] According to the authors, the finding that more experienced physicians are less likely to adopt TH may reflect the more recent exposure of younger physician to academic centers and the associated emphasis on novel therapies.

A single-center local experience in Greece

There is no official report concerning the extent to which TH is used, while only a few reports have been published regarding the use of hypothermia in Greece.[93]

In our institution, during a 2-year period of implementation of TH, 30 patients with out-of-hospital

VF cardiac arrest were successfully resuscitated and hospitalized after the return of spontaneous circulation. Sixteen patients were cooled using ice-cold intravenous fluids and icepacks, while 9 patients were treated with hypothermia with an endovascular cooling device. During the same period, in 5 patients with ROSC TH was not performed. It was considered unnecessary in 1 due to the very short duration of resuscitation efforts, futile in another because of significant co-morbidities that were revealed by a review of the patient's history after ROSC, while in 3 it was not possible to maintain the intended target patient temperature using icepacks. Data were also collected on 12 consecutive patients from the era immediately before the implementation of hypothermia.

Cooling is started immediately after ROSC by infusion of 30 ml/kg ice-cold saline. When an intravenous cooling device was not available, patient temperature was maintained for the next 24 h using cold packs, which were placed in the groin, axillae, and along the neck. Although the use of simple icepacks is inexpensive, it is time-consuming for nursing staff, is usually associated with significant temperature fluctuations, and does not enable controlled rewarming.

To overcome the difficulties involved in maintaining hypothermia with ice packs, a commercially available endovascular cooling device was employed. This device senses the patient's temperature using an esophageal thermometer and then adjusts the patient's core temperature using an endovascular catheter that is inserted through the femoral vein. Temperature is controlled by an external heat exchange system, as described previously. Regardless of the method used for cooling, temperature was measured through an esophageal thermometer and was lowered to 32-34°C for 24 hours. Subsequently, patients underwent passive warming if maintenance of hypothermia was performed with external cooling, or were slowly rewarmed at a rate of 0.2-0.5°C per hour if internal cooling was used. Every effort was made to keep patients normothermic (preventing fever) for at least another 24 h after rewarming had been achieved. Extra boluses of cisatracurium were administered with a standard regimen for patient sedation (midazolam alone or with fentanyl) when there was a need to control shivering.

Patient outcomes and complications are shown in Table 4.

It seems that overall survival, particularly survival without neurological damage, is increased with the use of TH. The results are not yet statistically significant, but most probably this has to do with the small number of patients in this report. These results are in accordance with previous reports[12,13] showing the favorable effect of mild hypothermia on the mental status of patients surviving OHCA. More patients need to be followed, however, before definite conclusions can be drawn regarding the overall benefit in terms of mortality and neurologically intact survival. Moreover, the limited number of patients and the use of historical controls prevent us, at this point, from estimating the magnitude of the contribution of hypothermia to improved patient outcomes in comparison to other patient- or treatment-related factors.

There were no excess complications in patients

Table 4. Outcomes and complications of patients resuscitated from cardiac arrest treated with therapeutic hypothermia in comparison with historical controls.

	Control period N=12	Total hypothermia N=25	External cooling N=16	Intravascular cooling N=9	p*
Patient outcomes:					
Survival n (%)	3 (25)	13 (52)	9 (56)	4 (44)	0.17
CPC 1-2	1 (8)	10 (40)	7 (44)	3 (33)	0.06
Complications:					
Recurrent seizures	1 (8)	2 (8)	1 (6)	1 (11)	1.0
Minor bleeding	2 (17)	11 (44)	5 (31)	6 (67)	0.15
Major bleeding†	0	1 (4)	0	1 (11)	1.0
Infections	6 (50)	16 (64)	10 (63)	6 (67)	0.48
Pneumonia	4 (33)	10 (40)	6 (38)	4 (44)	0.98
Atrial fibrillation	2 (17)	4 (16)	3 (19)	1 (11)	1.0
Bradycardia	1 (8)	3 (12)	2 (13)	1 (11)	1.0

*p values refer to the difference between patients treated in the control period and total patients treated with hypothermia as judged by Fischer exact test.
†Bleeding requiring transfusion.
CPC – cerebral performance category.

undergoing TH. This, however, may also have to do with the small number of patients, because an increased rate of bleeding complications and infections may be expected in patients treated with TH in the long run. There was only 1 incidence of bleeding requiring transfusion, while all other bleedings were minor bleedings from puncture sites. Paroxysmal atrial fibrillation was probably the most notable sustained arrhythmia, and was easily controlled with electrolyte replacement, alone or in combination with amiodarone administration. There were no remarkable ventricular arrhythmias other than premature ventricular extrasystoles and salvos of non-sustained VT. Bradycardia was not accompanied by hemodynamic compromise and rather represented adaptation to the decreased metabolic rate during hypothermia.

Recurrent seizures requiring anticonvulsant treatment were observed in 3 patients during the first hours after ROSC. Of these, 1 patient who exhibited an ischemic infarct in the temporal lobe continued to exhibit convulsions several days later, despite intense anticonvulsive treatment.

Conclusion

Mild TH in OHCA survivors is a well-documented therapy that provides a significant improvement in neurological functional recovery at hospital discharge and lower mortality. Currently there is a clear-cut indication for survivors of VF OHCA, but it is also a reasonable treatment for patients with non-VF and in-hospital arrest. It can be induced easily, even in the pre-hospital setting, and there are now several methods for external cooling as well as internal cooling devices. There are a number of complications associated with hypothermia, such as arrhythmias, bleeding disorders and infection, but none seems to be associated with adverse patient outcomes. Despite the strong evidence for its efficacy, universal implementation is hampered by significant difficulties. It seems that patients can benefit from TH when it is adopted as part of an integrated protocol of post-resuscitation care.

References

1. Priori SG, Aliot E, Blømstrom-Lundqvist C, et al. Task Force on Sudden Cardiac Death, European Society of Cardiology. Europace. 2002; 4: 3-18.
2. Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation. 2005; 67: 75-80.
3. Cobb LA, Fahrenbruch CE, Olsufka M, Copass MK. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. JAMA. 2002; 288: 3008-3013.
4. Papadima A, Pappas AB, Lagoudianakis EE, et al. Cardiopulmonary resuscitation by chest compression alone: a reality check. Hellenic J Cardiol. 2010; 51: 55-61.
5. Cobb LA. Variability in resuscitation rates for out-of-hospital cardiac arrest. Arch Intern Med. 1993; 153: 1165-1166.
6. Gatzoulis KA, Archontakis S, Dilaveris P, et al. Ventricular arrhythmias: from the electrophysiology laboratory to clinical practice. Part I: malignant ventricular arrhythmias. Hellenic J Cardiol. 2011; 52: 525-535.
7. Polderman KH. Application of therapeutic hypothermia in the ICU: opportunities and pitfalls of a promising treatment modality. Part 1: Indications and evidence. Intensive Care Med. 2004; 30: 556-575.
8. Su JY, Amory DW, Sands MP, Mohri H. Effects of circulatory arrest and rewarming on regional blood flow during surface-induced hypothermia. Am Heart J. 1980; 100: 332-340.
9. Gilbert M, Busund R, Skagseth A, Nilsen PA, Solbø JP. Resuscitation from accidental hypothermia of 13.7 degrees C with circulatory arrest. Lancet. 2000; 355: 375-376.
10. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation. 2001; 51: 275-281.
11. Felberg RA, Krieger DW, Chuang R, et al. Hypothermia after cardiac arrest: feasibility and safety of an external cooling protocol. Circulation. 2001; 104: 1799-1804.
12. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med. 2002; 346: 549-556.
13. 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: 557-563.
14. Wright WL, Geocadin RG. Postresuscitative intensive care: neuroprotective strategies after cardiac arrest. Semin Neurol. 2006; 26: 396-402.
15. Negovsky VA. Postresuscitation disease. Crit Care Med. 1988; 16: 942-946.
16. Kammersgaard LP, Jørgensen HS, Rungby JA, et al. Admission body temperature predicts long-term mortality after acute stroke: the Copenhagen Stroke Study. Stroke. 2002; 33: 1759-1762.
17. Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: a significant clinical concern. Stroke. 1998; 29: 529-534.
18. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet. 2008; 371: 1955-1969.
19. Foster AC, Fagg GE. Neurobiology. Taking apart NMDA receptors. Nature. 1987; 329: 395-396.
20. Van Harreveld A. A mechanism for fluid shifts specific for the central nervous system. Bibl Psychiatr. 1970; 143: 62-70.
21. Rothman SM, Olney JW. Glutamate and the pathophysiology of hypoxic–ischemic brain damage. Ann Neurol. 1986; 19: 105-111.
22. Benveniste H, Drejer J, Schousboe A, Diemer NH. Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. J Neurochem. 1984; 43: 1369-1374.
23. Globus MY, Busto R, Dietrich WD, Martinez E, Valdes I, Ginsberg MD. Effect of ischemia on the in vivo release of striatal dopamine, glutamate, and gamma-aminobutyric acid studied by intracerebral microdialysis. J Neurochem. 1988; 51: 1455-1464.
24. Okuda C, Saito, A, Miyazaki M, Kuriyama K. Alterations of the turnover of dopamine and 5-hydroxytryptamine in rat brain associated with hypothermia. Pharmacol Biochem Behav. 1986; 24: 79-83.

25. Illievich UM, Zornow MH, Choi KT, Scheller MS, Strnat MA. Effects of hypothermic metabolic suppression on hippocampal glutamate concentrations after transient global cerebral ischemia. Anesth Analg. 1994; 78: 905-911.
26. Matucz E, Móricz K, Gigler G, et al. Reduction of cerebral infarct size by non-competitive AMPA antagonists in rats subjected to permanent and transient focal ischemia. Brain Res. 2004; 1019: 210-216.
27. Huang XC, Xu W, Jiang JY. Effect of resuscitation after selective cerebral ultraprofound hypothermia on expressions of nerve growth factor and glial cell line-derived neurotrophic factor in the brain of monkey. Neurosci Bull. 2008; 24: 150-154.
28. Mattson MP, Culmsee C, Yu ZF. Apoptotic and antiapoptotic mechanisms in stroke. Cell Tissue Res. 2000; 301: 173-187.
29. Bargonetti J, Manfredi JJ. Multiple roles of the tumor suppressor p53. Curr Opin Oncol. 2002; 14: 86-91.
30. Zhao H, Yenari MA, Sapolsky RM, Steinberg GK. Mild postischemic hypothermia prolongs the time window for gene therapy by inhibiting cytochrome C release. Stroke. 2004; 35: 572-577.
31. López-Hernández FJ, Ortiz MA, Piedrafita FJ. The extrinsic and intrinsic apoptotic pathways are differentially affected by temperature upstream of mitochondrial damage. Apoptosis. 2006; 11: 1339-1347.
32. Hägerdal M, Harp J, Nilsson L, Siesjö BK. The effect of induced hypothermia upon oxygen consumption in the rat brain. J Neurochem. 1975; 24: 311-316.
33. Kimura T, Sako K, Tanaka K, Kusakabe M, Tanaka T, Nakada T. Effect of mild hypothermia on energy state recovery following transient forebrain ischemia in the gerbil. Exp Brain Res. 2002; 145: 83-90.
34. Jiang JY, Liang YM, Luo QZ, Zhu C. Effect of mild hypothermia on brain dialysate lactate after fluid percussion brain injury in rodents. Neurosurgery. 2004; 54: 713-7; discussion 717-718.
35. Dogné JM, Hanson J, de Leval X, Masereel B, Kolh P, Pirotte B. New developments on thromboxane modulators. Mini Rev Med Chem. 2004; 4: 649-657.
36. Peters O, Back T, Lindauer U, et al. Increased formation of reactive oxygen species after permanent and reversible middle cerebral artery occlusion in the rat. J Cereb Blood Flow Metab. 1998; 18: 196-205.
37. Merrill JE, Benveniste EN. Cytokines in inflammatory brain lesions: helpful and harmful. Trends Neurosci. 1996; 19: 331-338.
38. Stocchetti N, Colombo A, Ortolano F, et al. Time course of intracranial hypertension after traumatic brain injury. J Neurotrauma. 2007; 24: 1339-1346.
39. Vespa PM, Nuwer MR, Nenov V, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. J Neurosurg. 1999; 91: 750-760.
40. Ning XH, Chi EY, Buroker NE, et al. Moderate hypothermia (30 degrees C) maintains myocardial integrity and modifies response of cell survival proteins after reperfusion. Am J Physiol Heart Circ Physiol. 2007; 293: H2119-2128.
41. Alam HB, Bowyer MW, Koustova E, et al. Learning and memory is preserved after induced asanguineous hyperkalemic hypothermic arrest in a swine model of traumatic exsanguination. Surgery. 2002; 132: 278-288.
42. Scott BD, Hogue T, Fixley MS, Adamson PB. Induced hypothermia following out-of-hospital cardiac arrest; initial experience in a community hospital. Clin Cardiol. 2006; 29: 525-529.
43. Götberg M, Olivecrona GK, Engblom H, et al. Rapid short-duration hypothermia with cold saline and endovascular cooling before reperfusion reduces microvascular obstruction and myocardial infarct size. BMC Cardiovasc Disord. 2008; 8: 7.
44. Nolan JP, Morley PT, Hoek TL, Hickey RW. 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: 231-235.
45. Dumas F, Grimaldi D, Zuber B, et al. Is hypothermia after cardiac arrest effective in both shockable and nonshockable patients?: insights from a large registry. Circulation. 2011; 123: 877-886.
46. Oddo M, Schaller MD, Feihl F, Ribordy V, Liaudet L. From evidence to clinical practice: effective implementation of therapeutic hypothermia to improve patient outcome after cardiac arrest. Crit Care Med. 2006; 34: 1865-1873.
47. Storm C, Steffen I, Schefold JC, et al. Mild therapeutic hypothermia shortens intensive care unit stay of survivors after out-of-hospital cardiac arrest compared to historical controls. Crit Care. 2008; 12: R78.
48. Don CW, Longstreth WT, Maynard C, et al. Active surface cooling protocol to induce mild therapeutic hypothermia after out-of-hospital cardiac arrest: a retrospective before-and-after comparison in a single hospital. Crit Care Med. 2009; 37: 3062-3069.
49. Hachimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. Resuscitation. 2001; 51: 275-281.
50. Kim YM, Yim HW, Jeong SH, Klem ML, Gallaway CW. Does therapeutic hypothermia benefit adult cardiac arrest patients presenting with non-shockable initial rhythms? A systematic review and meta-analysis of randomized and non-randomized studies. Resuscitation. 2012; 83: 188-196.
51. Nielsen N, Hovdenes J, Nilsson F, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand. 2009; 53: 926-934.
52. Deakin CD, Morrison LJ, Morley PT, et al. Part 8: Advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation. 2010; 81 Suppl 1: e93-e114.
53. Deakin CD, Nolan JP, Soar J, et al. European Resuscitation Council Guidelines for Resuscitation 2010. Adult advanced life support. Resuscitation. 2010; 81: 1305-1352.
54. Kim F, Olsufka M, Longstreth WT, et al. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 degrees C normal saline. Circulation. 2007; 115: 3064-3070.
55. Wolff B, Machill K, Schumacher D, Schulzki I, Werner D. Early achievement of mild therapeutic hypothermia and the neurologic outcome after cardiac arrest. Int J Cardiol. 2009; 133: 223-228.
56. Bernard SA, Smith K, Cameron P, et al. Induction of therapeutic hypothermia by paramedics after resuscitation from out-of-hospital ventricular fibrillation cardiac arrest: a randomized controlled trial. Circulation. 2010; 122: 737-742.
57. Larsson IM, Wallin E, Rubertsson S. Cold saline infusion and ice packs alone are effective in inducing and maintaining therapeutic hypothermia after cardiac arrest. Resuscitation. 2010; 81: 15-19.
58. Spiel AO, Kliegel A, Janata A, et al. Hemostasis in cardiac arrest patients treated with mild hypothermia initiated by cold fluids. Resuscitation. 2009; 80: 762-765.
59. Jacobshagen C, Pax A, Unsöld BW, et al. Effects of large volume, ice-cold intravenous fluid infusion on respiratory function in cardiac arrest survivors. Resuscitation. 2009; 80: 1223-1228.
60. Kämäräinen A, Virkkunen I, Tenhunen J, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia during prehospital CPR using ice-cold intravenous fluid. Resuscitation. 2008; 79: 205-211.

61. Hammer L, Vitrat F, Savary D, et al. Immediate prehospital hypothermia protocol in comatose survivors of out-of-hospital cardiac arrest. Am J Emerg Med. 2009; 27: 570-573.
62. Uray T, Malzer R. Out-of-hospital surface cooling to induce mild hypothermia in human cardiac arrest: a feasibility trial. Resuscitation. 2008; 77: 331-338.
63. Haugk M, Sterz F, Grassberger M, et al. Feasibility and efficacy of a new non-invasive surface cooling device in post-resuscitation intensive care medicine. Resuscitation. 2007; 75: 76-81.
64. Hoedemaekers CW, Ezzahti M, Gerritsen A, van der Hoeven JG. Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study. Crit Care. 2007; 11: R91.
65. Hay AW, Swann DG, Bell K, Walsh TS, Cook B. Therapeutic hypothermia in comatose patients after out-of-hospital cardiac arrest. Anaesthesia. 2008; 63: 15-19.
66. 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: 1792-1797.
67. Kliegel A, Janata A, Wandaller C, et al. Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. Resuscitation. 2007; 73: 46-53.
68. Merchant RM, Abella BS, Peberdy MA, et al. Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. Crit Care Med. 2006; 34: S490-494.
69. Heard KJ, Peberdy MA, Sayre MR, et al. A randomized controlled trial comparing the Arctic Sun to standard cooling for induction of hypothermia after cardiac arrest. Resuscitation. 2010; 81: 9-14.
70. Castrén M, Nordberg P, Svensson L, et al. Intra-arrest transnasal evaporative cooling: a randomized, prehospital, multicenter study (PRINCE: Pre-ROSC IntraNasal Cooling Effectiveness). Circulation. 2010; 122: 729-736.
71. Popp E, Schneider A, Vogel P, Teschendorf P, Böttiger BW. Time course of the hypothermic response to continuously administered neurotensin. Neuropeptides. 2007; 41: 349-354.
72. Arrich J. Clinical application of mild therapeutic hypothermia after cardiac arrest. Crit Care Med. 2007; 35: 1041-1047.
73. Arntz HR, Bossaert LL, Danchin N, Nikolaou NI. European Resuscitation Council Guidelines for Resuscitation 2010, Section 5. Initial management of acute coronary syndromes. Resuscitation. 2010; 81: 1353-1363.
74. Garot P, Lefevre T, Eltchaninoff H, et al. Six-month outcome of emergency percutaneous coronary intervention in resuscitated patients after cardiac arrest complicating ST-elevation myocardial infarction. Circulation. 2007; 115: 1354-1362.
75. Knafelj R, Radsel P, Ploj T, Noc M. Primary percutaneous coronary intervention and mild induced hypothermia in comatose survivors of ventricular fibrillation with ST-elevation acute myocardial infarction. Resuscitation. 2007; 74: 227-234.
76. 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.
77. Martinell L, Larsson M, Bång A, et al. Survival in out-of-hospital cardiac arrest before and after use of advanced post-resuscitation care: a survey focusing on incidence, patient characteristics, survival, and estimated cerebral function after postresuscitation care. Am J Emerg Med. 2010; 28: 543-551.
78. Gräsner JT, Meybohm P, Caliebe A, et al. Postresuscitation care with mild therapeutic hypothermia and coronary intervention after out-of-hospital cardiopulmonary resuscitation: a prospective registry analysis. Crit Care. 2011; 15: R61.
79. Nielsen N, Sunde K, Hovdenes J, et al. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med. 2011; 39: 57-64.
80. Spiel AO, Kliegel A, Janata A, et al. Hemostasis in cardiac arrest patients treated with mild hypothermia initiated by cold fluids. Resuscitation. 2009; 80: 762-765.
81. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med. 2009; 37: 1101-1120.
82. Fries M, Stoppe C, Brücken D, Rossaint R, Kuhlen R. Influence of mild therapeutic hypothermia on the inflammatory response after successful resuscitation from cardiac arrest. J Crit Care. 2009; 24: 453-457.
83. Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. Resuscitation. 1998; 39: 61-66.
84. Castrejón S, Cortés M, Salto ML, et al. Improved prognosis after using mild hypothermia to treat cardiorespiratory arrest due to a cardiac cause: comparison with a control group. Rev Esp Cardiol. 2009; 62: 733-741.
85. Tortorici MA, Kochanek PM, Poloyac SM. Effects of hypothermia on drug disposition, metabolism, and response: A focus of hypothermia-mediated alterations on the cytochrome P450 enzyme system. Crit Care Med. 2007; 35: 2196-2204.
86. Binks AC, Murphy RE, Prout RE, et al. Therapeutic hypothermia after cardiac arrest - implementation in UK intensive care units. Anaesthesia. 2010; 65: 260-265.
87. Bouwes A, Kuiper MA, Hijdra A, Horn J. Induced hypothermia and determination of neurological outcome after CPR in ICUs in the Netherlands: results of a survey. Resuscitation. 2010; 81: 393-397.
88. Abella BS, Rhee JW, Huang KN, Vanden Hoek TL, Becker LB. Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey. Resuscitation. 2005; 64: 181-186.
89. Merchant RM, Soar J, Skrifvars MB, et al. Therapeutic hypothermia utilization among physicians after resuscitation from cardiac arrest. Crit Care Med. 2006; 34: 1935-1940.
90. Toma A, Bensimon CM, Dainty KN, Rubenfeld GD, Morrison LJ, Brooks SC. Perceived barriers to therapeutic hypothermia for patients resuscitated from cardiac arrest: a qualitative study of emergency department and critical care workers. Crit Care Med. 2010; 38: 504-509.
91. Skulec R, Dostalova G, Kovarnik T, Linhart A, Seblova J. Therapeutic hypothermia in cardiac arrest survivors: a survey of practice in the Czech Republic. Resuscitation. 2008; 77: 419-420.
92. Bigham BL, Dainty KN, Scales DC, Morrison LJ, Brooks SC. Predictors of adopting therapeutic hypothermia for post-cardiac arrest patients among Canadian emergency and critical care physicians. Resuscitation. 2010; 81: 20-24.
93. Koutouzis M, Nikolaou N, Lazaris E, Kourouklis S, Kyriakides ZS. Interventional hypothermia and primary percutaneous coronary intervention in a patient with anterior wall ST elevation myocardial infarction and aborted sudden death. Hellenic J Cardiol. 2007; 48: 377-379.