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Scandinavian Clinical practice guidelines for therapeutic hypothermia and post-resuscitation care after cardiac arrest

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Background and aim: Sudden cardiac arrest survivors suffer from ischaemic brain injury that may lead to poor neurological outcome and death. The reperfusion injury that occurs is associated with damaging biochemical reactions, which are suppressed by mild therapeutic hypothermia (MTH). In several studies MTH has been proven to be safe, with few complications and improved survival, and is recommended by the International Liaison of Committee on Resuscitation. The aim of this paper is to recommend clinical practice guidelines for MTH treatment after cardiac arrest from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI).
Methods: Relevant studies were identified after two consensus meetings of the SSAI Task Force on Therapeutic Hypothermia (SSAITFTH) and via literature search of the Cochrane Central Register of Controlled Trials and Medline. Evidence was assessed and consensus opinion was used when high-grade evidence (Grade of Recommendation, GOR) was unavailable. A management strategy was developed as a consensus from the evidence and the protocols in the participating countries.
Results and conclusion: Although proven beneficial only for patients with initial ventricular fibrillation (GOR A), the SSAITFTH also recommend MTH after restored spontaneous circulation, if active treatment is chosen, in patients with initial pulseless electrical activity and asystole (GOR D). Normal ethical considerations, premorbid status, total anoxia time and general condition should decide whether active treatment is required or not. MTH should be part of a standardized treatment protocol, and initiated as early as possible after indication and treatment have been decided (GOR E). There is insufficient evidence to make definitive recommendations among techniques to induce MTH, and we do not know the optimal target temperature, duration of cooling and rewarming time. New studies are needed to address the question as to how MTH affects, for example, prognostic factors.

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Sudden cardiac arrest survivors suffer from an ischaemic brain injury that may lead to poor neurological outcome and death. The injury during cardiopulmonary resuscitation (CPR) and successfully restored spontaneous circulation (ROSC) is described as a global ischaemia–reperfusion injury. This initiates a cascade of deleterious inflammatory reactions in the body that may continue for several days. Treatment directed at minimizing the inflammatory response and cell death in the reperfusion period may improve outcome following cardiac arrest. Until recently, post-resuscitation treatment was regarded as the 'weak link in the chain of survival'.[1] However, the introduction of mild therapeutic hypothermia (MTH), defined as a reduction of body temperature to 32–34 °C, following cardiac arrest, has emphasized the importance of appropriate post-resuscitation treatment. The main protective effect of MTH is a reduction of the global cerebral injury, such as a reduction of the following: body and cerebral metabolism,[2,3] apoptosis,[4–6] influx of Ca^{2+} into the cell,[7] intra- and extracellular

acidosis,[8,9] accumulation of the exitotoxic neurotransmitter glutamate,[10–12] release of glycine,[13] inflammation,[14,15] nitric oxide production[7] and free radical production.[11,16] These are all factors associated with poor outcome. It will also reduce the disruption in the blood–brain barrier as well as vascular permeability and thereby decreased cerebral oedema formation.[17–19]

MTH has been recommended by the International Liaison Committee on Resuscitation (ILCOR) since 2003.[20] The aim of this paper is to review the recent publications on MTH after cardiac arrest, and recommend Clinical Practice Guidelines for MTH treatment from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (SSAI). The proposed management strategy represents a consensus from evidence and protocols in the participating five Nordic countries.

Methods

Relevant studies were identified after two consensus meetings of the SSAI Task Force on Therapeutic Hypothermia (SSAITFTH) and via a literature search from the Cochrane Central Register of Controlled Trials and Medline. The following search words were used: therapeutic hypothermia, induced hypothermia, post-resuscitation, cardiac arrest, ventricular fibrillation, cardiopulmonary resuscitation, CPR, outcome, hypoxia–ischaemia and brain. Evidence was assessed and consensus opinion was used when high-grade evidence was unavailable. A management strategy was developed as a consensus from the evidence and the protocols in the participating countries.

The grading system used is presented in Table 1,[21] with grading of recommendation (GOR) from A to E, and grading of evidence (GOE) from I to V. Only clinical studies are graded. In this SSAI Guideline Recommendation, we have attempted to address several important aspects regarding post-resuscitation care and treatment with MTH such as how, when, for how long, to whom, methods, timing of other interventions including monitoring, prognostication as well as complications and side effects.

Table 1

Grading system used.

1. Grading of recommendations
   - A. Supported by at least two level I investigations
   - B. Supported by one level I investigations
   - C. Supported by level II investigations only
   - D. Supported by at least one level III investigation
   - E. Supported by level IV or V evidence
2. Grading of evidence
   - I. Large, randomized trials with clear-cut results; low risk of false-positive (α) error or false-negative (β) error
   - II. Small, randomized trials with uncertain results; moderate-to-high risk of false-positive (α) and/or false-negative (β) error
   - III. Non-randomized, contemporaneous controls
   - IV. Non-randomized, historical controls, and expert opinion
   - V. Case series, uncontrolled studies and expert opinion

Results

The support of MTH after cardiac arrest is based on three randomized-controlled studies[22–24] considered to be GOE I–II. There have also been several previous studies with historical controls[25–27] considered as GOE IV, and experimental studies.[28–31] Recently, several observational studies, with historical controls[32–35] (GOE IV), uncontrolled studies[36,37] (GOE V) and a European registry[39] (GOE V), all show that MTH is feasible, safe, has few side effects and seems to contribute toward improved survival.

Which patients to cool?

ILCOR recommended in 2003 that all comatose cardiac-arrested patients with initial ventricular fibrillation (VF) should be cooled for 12–24 h.[20] Further, they stated: 'For any other rhythm, or cardiac arrest in hospital, such cooling may also be beneficial'.[20] Recently, observational studies[32,34] (GOE IV) and two registry reports[39,40] (GOE V) have reported the feasibility of treating patients with non-VF cardiac arrest. Although the prognosis for this group of cardiac-arrested patients is worse,[39] recent survival data on non-VF patients are promising[38] (GOE V). In addition, despite being a different aetiology, the promising results of 72 h of MTH use on newborns after asphyxial cardiac arrest in two randomized studies[41,42] (GOE I) favour the use of MTH in the presence of global cerebral ischaemia.

Recommendation: Although proven beneficial only for comatose patients with initial VF (GOR A), we recommend MTH after ROSC, if active treatment is decided, in comatose patients with initial pulseless electrical activity and asystole (GOR D). Normal ethical considerations, premorbid status, total anoxia time and general condition should decide whether active treatment is required or not.

Methods for MTH

Several different methods can be used to achieve MTH. It is not the aim of this paper to present all the available different cooling methods, but rather to recommend the interested reader to a recent review by Holzer.[43] In Table 2, however, we provide a brief overview of the advantages and disadvantages of different cooling methods, ranging from simple external methods to advanced invasive techniques. A combination of different methods may be necessary, at least during induction of MTH. No specific methods can be recommended, because there are only a few studies comparing feasibility and efficacy[44,45] (GOE V), and no studies have evaluated implications on survival between different cooling methods. Some differences in cooling rate and stability have been described[44,45] (GOE III, IV). Recently, a pilot study identified significant differences in the rating of key nursing aspects of different cooling methods[46] (GOE V).

MTH treatment can be divided into three parts: rapid induction, stable and controlled maintenance and controlled rewarming. Induction can easily be induced with ice-cold i.v. fluids (30–40 ml/kg)[35,47–50] (GOE II–V) or removal of clothes and with the use of ice packs, placed in the groins, armpits and around the neck and head[33,51] (GOE IV and II). Although traditional external cooling has proven its feasibility[33,51,52] (GOE IV, V, II), its use may lead to overcooling[53] (GOE V). Ice-cold i.v. fluids alone are not sufficient for keeping the patients in a stable hypothermic state over time[54] (GOE V). Shivering can be avoided by primarily deepening the sedation and, if necessary, single dosages/infusion of muscle relaxants. Rewarming can be performed with external or invasive cooling devices or with other more conventional heating systems.

To avoid overcooling, appropriate temperature monitoring is absolutely necessary, but studies focusing on the optimal temperature monitoring sites during cooling after cardiac arrest are lacking. Tympanic, nasopharyngeal and rectal probes are useable, but the bladder, oesophagus or blood (pulmonary artery or Picco catheter) are most frequently used for temperature control during MTH maintenance.[55]

Recommendation: We recommend that a rapid, efficient and safe cooling strategy be used (GOR D). There are no specific methods for MTH that can be recommended. Each institution should use a method (or a combination of methods) that suits their infrastructure, logistics, financial resources and treatment plan.

Table 2

Methods for induction and maintenance of mild therapeutical hypothermia.

Methods	Advantages	Disadvantages
Simple external cooling		
Ice-bags, cold wet blankets, (ice-cold water, alcohol, etc.)	Simple, non-invasive easy initial cooling prehospital use	Long time to reach target temperature workload local wounds body fat isolates
Advanced external cooling		
Cooling blankets, pads, dress or similar devices (mainly water-filled or other cooling elements) more advanced systems such as cooling tents (with cold air), cooling beds/mattresses (with cold water)	Relatively stable excellent for maintenance easy to apply and use can be easily combined with ice-cold fluids very fast cooling with some devices prehospital use (some of the devices)	Varying effect, depending on contact area, circulating substance and system used some devices not for prehospital use costs (system dependent) cooling tent and beds/mattresses requires space
Infusion of cold fluids		
0.9% saline peripheral intravenously, 40 ml/kg, 1–3 l	Fast, easy and cheap induction of cooling prehospital use (requires cooling capacity in the ambulance)	Not sufficient for maintenance (can be used in combination with other methods) large volume contraindicated if major left heart pump failure
Endovascular cooling		
A saline-filled catheter for thermo-regulation	Stable excellent for maintenance less shivering	Invasive procedure skilled personnel for catheter placement (anaesthesiologists) not for prehospital use

When, and for how long?

The real benefit of rapid cooling, the optimal target temperature, the duration of the cooling and the rewarming phase are currently unknown. Animal studies have demonstrated that hypothermia initiated during or immediately after ROSC is associated with better organ preservation and increased survival.[56,57] Recently, in 49 patients treated with MTH, early achievement of the target temperature was an independent factor for good outcome[58] (GOE V). However, larger trials are warranted to assess the advantage of early vs. late cooling in humans. It is worth noting that although it took 8 h to reach the target temperature in the HACA trial, there was still a beneficial effect on cerebral out-

Table 3

Monitoring for the postresuscitation period.

Recommended
Arterial catheter
O_2 saturation
Continuous ECG
Central venous pressure
Temperature (bladder, oesophagus)
Arterial blood gases (pH, BE, pCO_2, pO_2)
Lactate
Blood glucose, electrolytes and general blood sampling
X-ray thorax
Echocardiography (daily for the first days)
sVO_2 (from the central venous line)
Optional
PA catheter/PICCO or other cardiac output monitoring
EEG (on indication/continuously): early seizure detection and treatment
SSEP: prognostication (after day 3)
NSE/protein s-100: prognostication
(CT/MRI)

come and death compared with normothermic patients[21] (GOE I).

The optimal duration of therapeutic hypothermia is undetermined. All recent clinical studies have maintained the target temperature for 24 h[32–35] (GOE III–V), as in the HACA study[22] (GOE I). A European hypothermia registry study[39] (GOE V) reported that the majority of the patients were MTH treated for 24 h. However, 12-h protocols have also been used.[23,33] Newborns with asphyctial cardiac arrest have been successfully treated for 72 h[41,42] (GOE I), and it may be that even adults with a severe reperfusion injury due to hypoxic-induced cardiac arrest should be treated with MTH of a longer duration. Further studies are warranted to address this important question.

The rate of rewarming is not known, but the traditional recommendation is 0.3–0.5 °C[20] (GOE I–V). Rebound hyperthermia should be avoided.[59,60]

Recommendation: We recommend that MTH be initiated as early as possible after the decision has been made (GOR E), and be maintained for 24 h (GOR A–E).

Timing of other interventions

Comatose patients in the post-resuscitation period are critically ill and require extensive intensive care treatment depending on the cause of the arrest, the severity of the post-resuscitation disease and myocardial dysfunction[61,62] or the presence of general complications. Each hospital should have a well-defined standardized plan, including MTH, for intervention and treatment according to the local conditions, infrastructure and logistics (GOE IV).

Table 4

A standardized treatment plan during the postresuscitation period.

Treatment	Goal	Mean
Reperfusion	Early reperfusion	PCI, thrombolytic agents
Temperature	As soon as possible 32–34°C for 24 h (12–72 h?)	Cold fluids, blankets, ice packs, external and internal devices
Blood pressure	MAP $\geq$ 65–70 mmHg	Volume, vasopressors, inotropic agents, IABP. Drug treatment according to local procedures (dopamine, norepinephrine, epinephrine, dobutamine and levosimedane)
Pulse	40–100/min	Volume, sedation, glycerylnitrate, and β-blockers
CVP	8–12 mmHg (individual differences)	Volume, vasodilatation
Arterial blood gases	SO_2: 95–98	Respirator adjustment (FiO_2, PEEP, avoid hyperoxia
	paO_2: 10–15 kPa	
	pCO_2: 5.0–6 kPa	Avoid hyperventilation
	pH > 7.1,	Natriumbicarbonate,
	BE > − 10	Trometamol
Haemoglobin	Normal values	Transfusion if necessary
Electrolytes	Normal values	Substitution or specific treatment if required (obs hyperkalaemia during rewarming)
Diuresis	> 0.5–1.0 ml/kg/h	Volume, furosemide, vasopressors
Blood glucose	5–8 mmol/l	Actrapid (observed hypoglycaemia)
Fluids	Positive fluid balance	Cristalloids, colloids
Nutrition	Early nutrition	Enteral 10 ml/h and G5% 1–1.5 l/24 h
Sedation	MAAS 0, no pain, comfort, no shivering	Fentanyl and propofol or midazolam (or other according to local protocol) (drug doses: titrate to wanted effect)
Muscle relaxation	Avoid shivering	If needed, rocuronium or cisatracurium
Seizures	Early diagnosis, treatment or prevention	Increase sedation, or specific anticonvulsive medication.
Rewarming	0.3–0.5°C/h until 37°C	Depending on equipment used for MTH
Prognostication	Not earlier than 72 h post arrest	EEG, SEP, clinical signs (with caution), NSE, Protein s-100

Such a plan enables doctors and nurses to focus on when and how to treat, and monitor, the patients under different circumstances.[33] Table 4 summarizes these interventions, and the most important ones are as follows:

1. *Diagnosing the cause of the cardiac arrest*. Early coronary angiography with subsequent PCI should be recommended for primary resuscitated cardiac-arrested patients suspected to have myocardial infarction or severe coronary heart disease[34–36] (GOE IV, V). MTH can be initiated and maintained during coronary angiography and PCI[34,63] (GOE IV) Pre- or in-hospital thrombolysis is recommended for patients with ST elevation if there are no facilities for immediate PCI. Other causes of arrest, both of cardiac and non-cardiac aetiology, should also be diagnosed and receive specific treatment, if possible. A CT scan of the brain must be considered early if a cerebral haemorrhage or a similar condition is suspected.

2. *Early stabilization and normalization of haemodynamics*. The optimal blood pressure after ROSC is not known, but both the damaged brain and the heart must be adequately perfused without placing undue strain on the heart. A positive fluid balance, use of vasopressors, inotropic drugs and/or the intra-aortic ballon pump are required depending on the clinical situation and cause of the arrest[34,62] (GOE IV–V). Cardiogenic shock should not be considered as a contraindication for MTH treatment[34,36,62,64] (GOE IV–V).

3. *Mechanical ventilation*. For controlled ventilation, mechanical ventilation should be initiated as early as possible, aiming for normo-oxygenation and -ventilation. Both hyperoxia[65] and hypoxia should be avoided. Hyperventilation may reduce cerebral perfusion,[66] and hypoventilation may have serious negative effects on cardiopulmonary interactions, causing a further increase in tissue acidosis (GOE II).

4. *Treat hyperglycaemia*. Non-intervention studies have shown increased mortality among cardiac arrest patients with high levels of blood glucose[60,67,68] (GOE IV–V). Aggressive insulin treatment in patients with critical illness has reduced long-time mortality[69] (GOE I). Thus, hyperglycaemia should be avoided and treated with insulin infusions (GOR B). We do not know the optimal target, but a strict protocol does not seem necessary and may lead to increased numbers of dangerous hypoglycaemia.[70] A target level of 5–8 mmol/l seems appropriate (GOE II, IV). Hypoglycaemia may also occur during rewarming because insulin sensitivity and secretion will increase with temperature.

5. *Monitoring*. These patients, therefore, require routine intensive care monitoring, which can be divided into two categories (Table 3): recommended (general intensive care monitoring) and optional (both more advanced haemodynamic monitoring and cerebral monitoring). For diagnostics, control of the myocardial dysfunction and optimizing therapy, at least echocardiography, should be performed daily for the first days after a cardiac arrest[34] (GOE IV).

6. *Awakening and extubation*. When the patient reaches normothermia, the sedation may be discontinued. The haemodynamic, respiratory and neurological status must be monitored carefully before the patient is extubated. Because of reduced elimination caused by MTH, the different drugs used for sedation will have prolonged effects, which may prolong awakening and time for extubation.[71,72]

Recommendation: Standardized treatment with a focus on early treatment of the cause and normalizing haemodynamics and metabolism is required (GOR C-E). Although difficult to prove through randomized studies, we recommend that all patients be monitored routinely with general intensive care monitoring following a local standardized treatment protocol (GOR E). The additional use of more advanced haemodynamic monitoring and/or cerebral monitoring must be decided based on local use and protocols. Frequent blood gas analyses for control of oxygenation, ventilation, blood sugar and electrolytes are necessary, especially during cooling and rewarming (Table 4).

Prognostication

Time from arrest until completed rewarming under normal circumstances is at least 36 h on average. Further, clinical prognostication on the first 2–3 days after a cardiac arrest is difficult[73–75] (GOE IV). Experienced physicians reviewed clinical data in resuscitated patients 24 h after cardiac arrest and were able to predict the clinical outcome correctly in only 52% of the patients[75] (GOE IV). However, signs such as persisting coma after discontinuation of sedatives (prolonged effects during therapeutic hypothermia), no signs of breathing, absence of papillary light reflexes or corneal reflexes and no motor response to pain on days 2–3 post arrest are clinical signs of a bad outcome[73,74] (GOE IV). In addition, somatonsensory-evoked potentials on

day 3 are the best predictors of a bad outcome[76,77] (GOE II). These studies, however, are from the era before MTH treatment, and we do not know how MTH will affect these prognostication aspects. As metabolism and drug elimination is reduced, it is reasonable to assume that prognostication may also be delayed. Recent reports show good survival even in patients with initially bad prognostic signs[78,79] (GOE V).

Another important aspect is EEG, either continuously or when indicated, to detect, prevent and treat early occurrence of seizures. In a Swedish study, continuous EEG was used as a predictor of outcome[80] (GOE V). Moreover, biochemical tests such as s-100 and NSE have also been used successfully[81] (GOE II), and in a recent study NSE corelated with time to reach the target temperature[58] (GOE V). The prognostic value of CT and MRI is not known today, but both are recommended if a cerebral cause or complication is suspected. More studies are warranted on prognostication in patients treated with MTH.

Recommendation: Although not much data are available, we recommend that the outcome prognostication following MTH should not be initiated before 72 h post arrest to avoid early treatment withdrawal in patients who may still recover (GOR C). We recommend the use of EEG, SEP and biochemical markers if available (GOR D).

Adverse effects and complications of MTH

Although MTH exerts various effects on several organ systems, clinical studies show that MTH does not increase the risk or the number of complications compared with similar patients not treated with MTH[22,34,35,39,82] (GOE I–V). Induction of hypothermia may affect haemodynamic stability. However, echocardiographic and invasive studies during infusion of cold fluids to induce hypothermia several hours after ROSC show that haemodynamic stability is preserved[49,50] (GOE V), and a trend towards improved cardiac output and increased arterial pressure after infusion of ice-cold saline has been reported[47] (GOE V). Comatose cardiac arrest victims often suffer from a post-resuscitation sepsis-like syndrome with reduced systemic vascular resistance[50,82] (GOE V), and cooling may therefore be beneficial[32,34] (GOE IV). A reduced heart rate may also be beneficial, because β-blocker use in the early post-resuscitation period has been associated with an improved outcome[68] (GOE V). MTH may have an effect on the platelet count and clotting time, increasing the risk of haemorrhagic complications, and may impair immune function and increase the risk of infections. However, this has not been confirmed in clinical studies[22,23,34,35,39] (GOE I–V). MTH may induce hyperglycaemia by decreasing insulin sensitivity and secretion, but this is usually easy to control with insulin treatment. Prolonged drug effects due to decreased clearance should be kept in mind[71,72] (GOE IV).

Pneumonia, due to aspiration and/or mechanical ventilation, may be the most important complication during the post-resuscitation period, occurring in approximately 50% of patients.[21,33] The rate is similar in patients treated and not treated with MTH[22,33,34] (GOE 1, IV).

Renal failure has not been reported to be present more often in patients treated with MTH than in ICU patients in general[35] (GOE IV). MTH may cause tubular dysfunction and increase diuresis, and may lead to hypophosphataemia, hyponatraemia (may increase cerebral oedema due to hypoosmolality), hypomagnesaemia, hypocalcaemia or hypokalaemia[71] (GOE IV). MTH-related deaths have not been reported.

Conclusion: MTH after cardiac arrest appears to be safe, well tolerated and not associated with more complications than in patients not treated with MTH (GOR A).

Recommendation: Careful control of blood glucose, electrolyte levels and fluid balance is advised during induction, maintenance and the rewarming phase of MTH (GOR E).

Summary of the recommendations

Although proven beneficial only for patients with initial VF (GOR A), the SSAITFTH also recommends MTH after ROSC, if active treatment is decided, in patients with initial pulseless electrical activity and asystole (GOR D). Normal ethical considerations, premorbid status, total anoxia time and general condition should decide whether active treatment is required or not. MTH should be part of a standardized treatment protocol, and initiated as early as possible after indication and treatment has been decided (GOR E). There is insufficient evidence to make definitive recommendations among the techniques to induce MTH, and we do not know the optimal target temperature,

duration of cooling and rewarming time. New studies are needed to address the question as to how MTH affects, for example, prognostic factors.

References

1. Peberdy MA, Ornato JP. Post-resuscitation care: is it the missing link in the chain of survival? *Resuscitation* 2005; **64** (2): 135–7.
2. Milde LN. Clinical use of mild hypothermia for brain protection: a dream revisited. *J Neurosurg Anesthesiol* 1992; **4**: 211–5.
3. Small DL, Moorley P, Buchan AM. Biology of ischemic cerebral cell death. *Prog Cardiovasc Dis* 1999; **42**: 185–207.
4. Xu L, Yenari MA, Steinberg GK, Giffard RG. Mild hypothermia reduces apoptosis of mouse neurons in vitro early in the cascade. *J Cerebral Blood Flow Metab* 2002; **22**: 21–8.
5. Adachi M, Sohma O, Tsuneishi S, Takada S, Nakamura H. Combination effect of systemic hypothermia and caspase inhibitor administration against hypoxic-ischemic brain damage in neonatal rats. *Pediatric Res* 2001; **50**: 590–5.
6. Ning XH, Chen SH, Xu CS, Li L, Yao LY, Qian K, Kreuger JJ, Hyyti OM, Portman MA. Hypothermic protection of the ischemic heart vial alterations in apoptotic pathways as assessed by gene array analysis. *J Appl Physiol* 2002; **92**: 2200–7.
7. Siesjö BK, Bengtsson F, Grampp W, Theander S. Calcium, excitotoxins, and neuronal death in brain. *Ann NY Acad Sci* 1989; **568**: 234–51.
8. Ding D, Moskowitz SI, Li R, Lee SB, Esteban M, Tomaselli K, Chan J, Bergold PJ. Acidosis induces necrosis and apoptosis of cultered hippocampal neurons. *Exp Neurol* 2000; **162**: 1–12.
9. Chopp M, Knight R, Tidwell CD, Helpern JA, Brown E, Welch KM. The metabolic effects of mild hypothermia on global cerebral ischemia and recirculation in the cat: comparison to normothermia and hypothermia. *J Cereb Blood Flow Metab* 1989; **9**: 141–8.
10. Winfree CJ, Baker CJ, Connolly Jr ES, Fiore AJ, Solomon RA. Mild hypothermia reduces prenumbral glutamate levels in the rat permanent focal cerebral ischemia model. *Neurosurgery* 1996; **38**: 1216–22.
11. Globus MY-T, Alonso O, Dietrich WD, Busto R, Ginsberg MD. Glutamate release and free radical production following brain injury: effects of post-traumatic hypothermia. *J Neurochem* 1995; **65**: 1704–11.
12. Takata K, Takeda Y, Sato T, Nakatsuka H, Yokoyama M, Morita K. Effects of hypothermia for a short period on histologic outcome and extracellular glutamate concentration during and after cardiac arrest in rats. *Crit Care Med* 2005; **33**: 1340–5.
13. Baker AJ, Zornow MH, Grafe MR, Scheller MS, Skilling SR, Smullin DH, Larsson AA. Hypothermia prevents ischemia-induced increases in hippocampal glycine concentrations in rabbits. *Stroke* 1991; **22**: 666–73.
14. Kimura A, Sakurada S, Ohkuni H, Todome Y, Kurata K. Moderate hypothermia delays proinflammatory cytokine production of human peripheral blood mononuclear cells. *Crit Care Med* 2002; **30**: 1499–502.
15. Aibiki M, Maekawa S, Ogura S, Kinoshita Y Kawai N, Ykono S. Effect of moderate hypothermia on systemic and internal jugular plasma IL-6 levels after traumatic brain injury in humans. *J Neurotrauma* 1999; **16**: 225–32.
16. Globus MY-T, Busto R, Lin B, Schnippering H, Ginsberg MD. Detection of free radical activity during transient global ischemia and recirculation: effects of intraischemic brain temperature modulation. *J Neurochem* 1995; **65**: 1250–6.
17. Huang ZG, Xue D, Preston E, Karbalai H, Buchan AM. Biphasic opening of the blood–brain barrier following transient focal ischemia: effects of hypothermia. *Can J Neurol Sci* 1999; **26**: 298–304.
18. Chi OZ, Liu X, Weiss HR. Effects of mild hypothermia on blood–brain barrier disruption during isoflurane or pentobarbital anesthesia. *Anesthesiology* 2001; **95**: 933–8.
19. Jurkovich GJ, Pitt RM, Curreri PW, Granger DN. Hypothermia prevents increased capillary permeability following ischemia–reperfusion injury. *J Surg Res* 1988; **44**: 514–21.
20. Nolan JP, Morley PT, Hoel 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. Committee on Resuscitation. *Resuscitation* 2003; **57**: 231–5.
21. Bell DD, Brindley PG, Forrest D, Al Muslim O, Zygun D. Management following resuscitation from cardiac arrest: recommendations from the 2003 Rocky Mountain Critical Care Conference. *Can J Anesth* 2005; **52**: 309–22.
22. The Hypothermia After Cardiac Arrest (HACA) Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2002; **346**: 549–56.
23. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346**: 557–63.
24. Hashimi-Idrissi S, Corne L, Ebinger G, Michotte Y, Huyghens L. Mild hypothermia induced by a helmet device: a clinical feasibility study. *Resuscitation* 2001; **51**: 275–81.
25. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann Emerg Med* 1997; **30**: 146–53.
26. Yanagawa Y, Ishihara S, Norio H, Takino M, Kawakami M, Takasu A, Okamoto K, Kaneko N, Terai C, Okada Y. Preliminary outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. *Resuscitation* 1998; **39**: 61–6.
27. Zeiner A, Holtzer M Sterz F, Behringer W, Schorkhuber W, Mullner M, Frass M, Siostrzonek P, Ratheiser K, Kaff A, Laggner AN. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest. A clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) Study Group. *Stroke* 2000; **31**: 86–94.
28. Sterz F, Safar P, Tisherman S, Radovsky A, Kuboyama K, Oku K. Mild hypothermic cardiopulmonary resuscitation improves outcome after prolonged cardiac arrest in dogs. *Crit Care Med* 1991; **19**: 379–89.
29. Xiao F, Safar P, Radovsky A. Mild protective and resuscitative hypothermia for asphyxial cardiac arrest in rats. *Am J Emerg Med* 1998; **16**: 17–25.
30. Hicks SD, DeFranco DB, Callaway CW. Hypothermia during reperfusion after asphyxial cardiac arrest improves functional recovery and selectively alters stress-induced protein expression. *J Cereb Blood Flow Metab* 2000; **20**: 520–30.
31. D'Cruz BJ, Fertig KC, Filiano AJ, Hicks SD, DeFranco DB, Callaway CW. Hypothermic reperfusion after cardiac arrest augments brain-derived neurotrophic factor activation. *J Cereb Blood Flow Metab* 2002; **22**: 848–51.
32. Oddo M, Schaller M-D, 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**: 1865–73.
33. Busch M, Soreide E, Lossius HM, Lexow K, Dickstein K. Rapid implementation of therapeutic hypothermia in comatose out-of-hospital cardiac arrest survivors. *Acta Anaesthesiol Scand* 2006; **50**: 1277–83.
34. Sunde K, Pytte M, Jacobsen D, Mangschau A, Jensen LP, Smedsrud C, Draegni T, Steen PA. Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation* 2007; **73**: 29–39.
35. 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**: 227–34.
36. Hovdenes J, Laake JH, Aaberge L, Haugaa H, Bugge JF. Therapeutic hypothermia after out-of-hospital cardiac arrest: experiences with patients treated with percutaneous coronary intervention and cardiogenic shock. *Acta Anaesthesiol Scand* 2007; **51**: 137–42.
37. 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**: 525–9.
38. Oddo M, Ribordy V, Feihl F, Rossetti AO, Schaller MD, Chioléro R, Liaudet L. Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. *Crit Care Med* 2008; **36** (8): 2296–301.
39. Arrich J. The European Resuscitation Council Hypothermia After Cardiac Arrest Registry Study Group. Clinical application of mild therapeutic hypothermia after cardiac arrest. *Crit Care Med* 2007; **35**: 1041–7.
40. Nielsen N. The Hypothermia Network Steering Group. Outcome after cardiac arrest with focus on therapeutic hypothermia–a report from the hypothermia network. *Resuscitation* 2008; **77** (Suppl. 1): S27.
41. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, Polin RA, Robertson CM, Thoresen M, Whitelaw A, Gunn AJ. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 2005; **365**: 663–70.
42. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, Fanaroff AA, Poole WK, Wright LL, Higgins RD, Finer NN, Carlo WA, Duara S, Oh W, Cotten CM, Stevenson DK, Stoll BJ, Lemons JA, Guillet R, Jobe AH. National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischemic encephalopathy. *N Engl J Med* 2005; **353**: 1574–84.
43. Holzer M. Devices for rapid induction of hypothermia. *Eur J Anaesthesiol Suppl* 2008; **42**: 31–8.
44. 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** (4): R91.
45. Flint AC, Hemphill JC, Bonovich DC. Therapeutic hypothermia after cardiac arrest: performance characteristics and safety of surface cooling with or without endovascular cooling. *Neurocrit Care* 2007; **7** (2): 109–18.
46. Våga A, Busch M, Karlsen TE, Nilsen OB, Søreide E. A pilot study of key nursing aspects with different cooling methods and devices in the ICU. *Resuscitation* 2008; **76** (1): 25–30.
47. Kim F, Olsufka M, Carlbom D, Deem S, Longstreth Jr WT, Hanrahan M, Maynard C, Copass MK, Cobb LA. Pilot study of rapid infusion of 2 L of 4 degrees C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation* 2005; **112**: 715–9.
48. Kliegel A, Janata A, Wandaller C, Uray T, Spiel A, Losert H, Kliegel M, Holzer M, Haugk M, Sterz F, Laggner AN. Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. *Resuscitation* 2007; **73**: 46–53.
49. Kim F, Olsufka M, Longstreth Jr WT, Maynard C, Carlbom D, Deem S, Kudenchuk P, Copass MK, Cobb LA. Pilot randomized clinical trial of prehospital induction of mild hypothermia in out-of-hospital cardiac arrest patients with a rapid infusion of 4 °C normal saline. *Circulation* 2007; **115**: 3064–70.
50. Bernard S, Buist M, Monteiro O, Smith K. Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003; **56**: 9–13.
51. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2002; **346**: 557–63.
52. Rubertsson S, Larsson IM, Wallin E. Cold saline infusion and ice packs is an effective method to induce and maintain therapeutic hypothermia after cardiac arrest. 29th Congress of SSAI Gothenburg 2007. *Acta Anaesthesiol Scand* 2007; **51** (Suppl. 118): 1–24.
53. Merchant RM, Abella BS, Peberdy MA, Soar J, Ong ME, Schmidt GA, Becker LB, Vanden Hoek TL. Therapeutic hypothermia after cardiac arrest: unintentional overcooling is common using ice packs and conventional cooling blankets. *Crit Care Med* 2006; **34** (12, Suppl.): S490–4.
54. Kliegel A, Janata A, Wandaller C, Uray T, Spiel A, Losert H, Kliegel M, Holzer M, Haugk M, Sterz F, Laggner AN. Cold infusions alone are effective for induction of therapeutic hypothermia but do not keep patients cool after cardiac arrest. *Resuscitation* 2007; **73**: 46–53.
55. Lefrant JY, Muller L, de La Coussaye JE, Benbabaali M, Lebris C, Zeitoun N, Mari C, Saïssi G, Ripart J, Eledjam JJ. The recommended temperature measurement in intensive care patients: comparison of urinary bladder, oesophageal, rectal, axillary, and inguinal methods versus pulmonary artery core method. *Intensive Care Med* 2003; **29**: 414–8.
56. Kuboyama K, Safar P, Radovsky A, Tisherman SA, Stezoski SW, Alexander H. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Crit Care Med* 1993; **21**: 1348–58.
57. Nozari A, Safar P, Stezoski SW, Wu X, Kostelnik S, Radovsky A, Tisherman S, Kochanek PM. Critical time window for intra-arrest cooling with cold saline flush in a dog model of cardiopulmonary resuscitation. *Circulation* 2006; **113** (23): 2690–6.
58. 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* 2008 [Mar 17, Epub ahead of print].
59. Zeiner A, Holzer M, Sterz F, Schorkhuber W, Eisenburger P, Havel C, Kliegel A, Laggner AN. Hyperthermia after cardiac arrest is associated with an unfavorable neurologic outcome. *Arch Intern Med* 2001; **161**: 2007–12.
60. Langhelle A, Tyvold SS, Lexow K, Hapnes S, Sunde K, Steen PA. In-hospital factors associated with improved

outcome after out-of-hospital cardiac arrest. A comparison between four regions in Norway. *Resuscitation* 2003; **56**: 247–63.
61. Kern KB, Hilwig RW, Rhee KH, Berg RA. Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. *J Am Coll Cardiol* 1996; **28**: 32–40.
62. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Bourgeois B, Cariou A, Rozenberg A, Carli P, Weber S, Dhainaut JF. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. *J Am Coll Cardiol* 2002; **40**: 2110–6.
63. Wolfrum S, Pierau C, Radke PW, Schunkert H, Kurowski V. Mild therapeutic hypothermia in patients after out-of-hospital cardiac arrest due to acute ST-segment elevation myocardial infarction undergoing immediate percutaneous coronary intervention. *Crit Care Med* 2008; **36** (6): 1780–6.
64. 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**: 419–20.
65. Balan IS, Fiskum G, Hazelton J, Cotto-Cumba C, Rosenthal RE. Oximetry-guided reoxygenation improves neurological outcome after experimental cardiac arrest. *Stroke* 2006; **37**: 3008–13.
66. Buunk G, van der Hoeven JG, Meinders AE. Cerebrovascular reactivity in comatose patients resuscitated from a cardiac arrest. *Stroke* 1997; **28**: 1569–73.
67. Van Den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, Vlasselaers D, Ferdinande P, Lauwers P, Bouillon R. Intensive insulin therapy in critically ill patients. *N Engl J Med* 2001; **345**: 1359–67.
68. Skrifvars MB, Pettila V, Rosenberg PH, Castrén M. A multiple logistic regression analysis of in-hospital factors related to survival at six months in patients resuscitated from out-of-hospital ventricular fibrillation. *Resuscitation* 2003; **59**: 319–28.
69. Mullner M, Sterz F, Binder M, Schreiber W, Deimel A, Laggner AN. Blood glucose concentration after cardiopulmonary resuscitation influences functional neurological recovery in human cardiac arrest survivors. *J Cereb Blood Flow Metab* 1997; **17**: 430–6.
70. Oksanen T, Skrifvars M, Varpula T, Kuitunen A, Pettilä V, Nurmi J, Castrén M. Strict versus moderate glucose control after resuscitation from ventricular fibrillation. *Intensive Care Med* 2007; **33**: 2093–100.
71. 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 Med* 2004; **30**: 757–69.
72. Sessler DI. Complications and treatments of mild hypothermia. *Anesthesiology* 2001; **95**: 531–43.
73. Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis of comatose survivors of cardiac arrest. *Lancet* 1994; **343**: 1055–9.
74. Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004; **291**: 870–9.
75. Madl C, Kramer L, Domanovits H, Woolard RH, Gervais H, Gendo A, Eisenhuber E, Grimm G, Sterz F. Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. *Crit Care Med* 2000; **28**: 721–6.
76. Wijdicks EF, Hijdra A, Young GB, Bassetti CL, Wiebe S. Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: prediction of outcome in comatose survivors after cardiopulmonary resuscitation (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2006; **67**: 203–10.
77. Zandbergen EG, de Haan RJ, Stoutenbeek CP, Koelman JH, Hijdra A. Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. *Lancet* 1998; **352**: 1808–12.
78. Hovland A, Nielsen EW, Kluver J, Salvesen R. EEG should be performed during induced hypothermia. *Resuscitation* 2006; **68**: 143–6.
79. Sunde K, Dunlop O, Rostrup M, Sandberg M, Sjoholm H, Jacobsen D. Determination of prognosis after cardiac arrest may be more difficult after introduction of therapeutic hypothermia. *Resuscitation* 2006; **69**: 29–32.
80. Rundgren M, Rosén I, Friberg H. Amplitude-integrated EEG (aEEG) predicts outcome after cardiac arrest and induced hypothermia. *Intensive Care Med* 2006; **32**: 836–42.
81. Tiainen M, Roine RO, Pettilä V, Takkunen O. Serum neuron-specific enolase and S-100B protein in cardiac arrest patients treated with hypothermia. *Stroke* 2003; **34**: 2881–6.
82. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut JF, Cavaillon JM. Successful cardiopulmonary resuscitation after cardiac arrest as a ''sepsis-like'' syndrome. *Circulation* 2002; **106**: 562–8.

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