REVIEW ARTICLE

Post cardiac arrest therapeutic hypothermia in adult patients, state of art and practical considerations

P.F. Beccaria[1], S. Turi[1], M. Cristofolini[2], S. Colombo[1], C. Leggieri[1], F. Vinciguerra[1], A. Zangrillo[1]

[1]Department of Anaesthesia and Intensive Care, Università Vita-Salute San Raffaele, Milano, Italy;
[2]Department of Anaesthesia and Intensive Care, Ospedale Santa Chiara, Trento, Italy

HSR Proceedings in Intensive Care and Cardiovascular Anesthesia 2010; 2: 93-103

ABSTRACT

The importance of therapeutic hypothermia in selected categories of patients has been widely demonstrated. Laboratory, animal, and human studies permitted to understand the molecular mechanisms underlying cooling and its importance in preventing the ischemia/reperfusion injury of the brain. The development of new technologies offered the possibility to reach the desired temperature effectively and rapidly, reducing related side effects. Nevertheless, the application of systematic protocols of cooling has not been adequately reached in many hospitals. In this paper the most recent findings regarding hypothermia, its physiological bases and ways of application are reviewed.

Keywords: *therapeutic hypothermia, cardiac arrest, ischemia-reperfusion injury, neuroprotection, cooling, rewarming.*

Out-of-hospital cardiac arrest claims 225,000 lives each year in the United States and a similar number in Europe, accounting for about half of all deaths due to cardiovascular disease (1). Even when resuscitation efforts are successful, recovery is too often limited by post-anoxic encephalopathy.

The interest regarding hypothermic therapy to protect brain after cardiac arrest started in late '50s of the past century and the first publication dates 1959 (2).

In spite of promising evidences, mostly because of the absence of simple and reliable cooling methods, apart from some farseeing and lonely voices as Peter Safar (3), the curtain falls over therapeutic hypothermia (TH) in the following decades.

After almost forty years of oblivion, interest in cooling was rekindled in the early 1980s by the positive results from animal experiments suggesting that neurological outcome could be improved by using mild to moderate hypothermia (31°C-35°C) rather than deep hypothermia (30°C), with far fewer and less severe side effects (4-6).

Following the promising results obtained from laboratory and animal models, in 2002 two important randomized multicentric studies on humans were realized (7, 8). In the first, the European Hypothermia after cardiac arrest study group enrolled 275 patients, with 137 patients randomly as-

Corresponding author:
Paolo Federico Beccaria
Department of Anaesthesia and Intensive Care,
Università Vita-Salute San Raffaele
Via Olgettina, 60 - 20132 Milan, Italy
email: beccaria.paolo@hsr.it

signed to the hypothermia group and 138 to the normothermia group. (i.e., the group that received standard care after resuscitation). The study included only patients who had been resuscitated after witnessed out-of-hospital cardiac arrest due to ventricular fibrillation (VF) that were randomly assigned to undergo TH (target bladder temperature, 32°C to 34°C) over a period of 24 hours or to receive standard treatment with normothermia. The temperature was maintained at 32°C to 34°C for 24 hours from the start of cooling, followed by passive rewarming, which was expected to occur over a period of 8 hours. This study demonstrated that systemic cooling increases the chance of survival and of a favorable neurological outcome, as compared with standard normothermic life support without significant differences in terms of complications in the two groups.

In the second study 77 patients who remained unconscious after resuscitation from out of hospital cardiac arrest were randomly assigned to treatment with hypothermia (33° C core body temperature for 12 hours) or normothermia. In the TH group 49% survived with a good outcome (home or rehabilitation facility discharge) compared with the 26% (P = 0.046) of the normothermia group.

Considering these results, the 2005 American Heart Association guidelines for cardiopulmonary resuscitation and post resuscitation support concluded that clinicians should not actively rewarm hemodynamically stable patients who spontaneously develop a mild degree of hypothermia (33°C) after resuscitation from cardiac arrest (9). The same guidelines state that mild hypothermia may be beneficial to neurologic outcome and is likely to be well tolerated without significant risk of complications. In a select subset of patients who were initially comatose but hemodynamically stable after a witnessed VF cardiac arrest of presumed cardiac etiology, active induction of hypothermia was beneficial (class IIa). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (class IIb).

Although eight years passed from the original publications and several studies clarified many mechanism of TH and described feasibility and efficacy of different cooling methods (10, 11), this therapeutic approach is far from being extensively and widely used in everyday practice.

In a survey carried out in 2005 in the US (12), of 265 physician (practicing emergency medicine, critical care and cardiology) who were asked if they had ever used TH after cardiac arrest, 87% answered no. Among reasons for non-use they mentioned not enough data to support TH, non-inclusion in ACLS protocol or technical difficulties.

While a recent survey carried out on all UK intensive care units showed that 85% of departments considered TH as a part of post cardiac arrest management with a major implementation in use on the last three years (13), another recent review underlined that an informal online survey of cardiology conference attendees showed that 20% of respondents were even aware of the American Hospital Association guidelines (14).

Many studies tried to identify the reasons why, despite scientific evidence, TH fatigues to reach a routinely utilization. A recent study conducted on a 43 Canadian hospital network identifies some pivotal elements: lack of familiarity and availability of concrete TH protocols, availability of equipment, equipment costs, and higher workload demands for emergency nurses are the most perceived barriers. Awareness of these general, individual and local barriers may improve adherence to evidence-based practice (15).

Moreover, the majority of out-of-hospital

cardiac arrest patients nowdays are conducted to emergency medical services with non-VF (pulseless electrical activity, asystole) as the initial cardiac rhythm, For this reason, clinicians have to decide whether or not to use TH in this patient group, considering the feasibility, possible benefit, and potential adverse side effects of hypothermia in patients with neurological injury who have been resuscitated from non-VF cardiac arrest (16).

Some studies tried to evaluate feasibility and efficacy of TH in other medical emergency situations and with cardiac arrest presentation rhythms different from VF (17-19), although some authors believe that it will be difficult to find significant evidence due to the low incidence and poor outcome of this condition. As Bernard maintains, these trials would require a very large sample size to detect a significant change in an important outcome measure such as survival with good neurological function.

Bernard et al suggest that, considering the few adverse effects related to the use of hypothermia and their relatively easy management, it would appear reasonable for clinicians to cool most patients with suspected neurological injury following prolonged cardiac arrest, whatever the initial cardiac rhythm (20).

Since a recent retrospective study (21) conducted on 491 patient shows no significant improvement in neurologic outcomes in patients whose initial rhythm was different from VF, further prospective studies are needed to clarify whether TH is effective also in asystole and pulseless electrical activity or not.

Another key point for the future is the identification of poor and good outcome predictors after TH post cardiac arrest. Glasgow Coma Scale monitoring and particularly motor response from third day after cardiac arrest remains a powerful tool to predict outcome of patients treated with TH (22). Promising data come from the utilization of bispecrtal index (BIS) and suppression ratio during TH as an early predictor of neurologic outcome (23, 24).

For the future, larger prospective studies are needed to re-assess the validity of traditional clinical, biochemical and instrumental outcome predictors in patients treated with hypothermia and the identification of good outcome predictors is of paramount importance.

MECHANISMS OF ACTION

Animal and laboratory findings during 1980s and 1990s allowed a better knowledge of the molecular mechanisms underlying hypothermia, helping to define adequate strategies of cooling and to prevent possible side effects.

In the 1950s and 1960s, when the first procedures of cooling were realized, it was presumed that the beneficial effects of hypothermia were related to the reduction of brain metabolic requests (25). Although this statement is correct (a decrease in cerebral metabolism by 6% to 10% for each grade of body temperature reduction has been observed) this is not the unique involved mechanism (26).

Brain damages after a cardiac arrest may be considered as a model of ischemia-reperfusion injury. Animal and laboratory findings during ’80s and ’90s showed an increase in apoptosis, a dysfunction in mitochondrial activity, and an alteration in ion pump function controlling the influx of calcium into cells (27). During cooling an inhibition of caspase enzyme activation, a prevention of mitochondrial dysfunction, a decreased overload of excitatory neurotransmitters, and a modification of intracellular ion concentrations were observed, (28, 29). Immune system is also activated in the injured brain. One hour after the ischemic insult

an increase of inflammatory molecules (interleukin-1, tumor necrosis factor alpha) released by microglia, endothelial cells and astrocytes is detectable (26). This phenomenon is associated to chemotaxis and complement system activation facilitating neutrophil, macrophages and monocytes passage trough the endothelium (30).
Numerous animal experiments and some clinical studies showed that hypothermia suppresses ischemia-induced inflammatory reactions and release of pro-inflammatory cytokines and decreases the production of nitric oxide, which is a key agent in the development of post-ischemic brain injury (31). In addition, hypothermia can impair neutrophil and macrophage function, reducing white blood cell count (32).
Another mechanism of damage is related to the increase of free radicals such as superoxide, peroxynitrite, hydrogen peroxide, and hydroxyl radicals that play an important role in determining whether injured cells will recover or die (33). Cooling seems to reduce the production of free radicals and to mitigate the damage, allowing the cells a better recovery after injury. This function and the ability in preserving the integrity of blood-brain barrier also determine a reduction of cerebral edema and the consequent intracranial hypertension (34).
In addition, brain glucose utilization is affected by ischemia-reperfusion, and there is evidence suggesting that hypothermia can improve brain glucose metabolism; in particular the ability of the brain to utilize glucose (35).
A disruption in equilibrium of vaso-active substances such as endothelin, thromboxane A2 (TxA2), and prostaglandin I2, following an ischemic or traumatic event, can lead to vasoconstriction, hypoperfusion, and thrombogenesis in injured areas of the brain (36, 37).
Several studies showed how hypothermia affects the local secretion of these agents in the brain and in other sites reproducing the natural haemostasis of vasoactive agents (38).
In some patients, during the post-ischemic phase, it is also detectable an epileptic activity, probably associated to the ongoing brain damage. Hypothermia is associated to a reduction in the convulsive activity, providing an adequate neuro-protection (39).
Hypothermia increases the expression of the so called immediate early genes, which are a part of the protective cellular stress response to injury, and stimulates the induction of cold shock proteins, which can protect the cell from ischemic and traumatic injury (40). Ischemia-reperfusion also leads to substantial rises in cerebral lactate levels that are shown to be reduced during cooling (41). The importance of the protective effect of hypothermia on the brain can also be deduced by the observation that fever is associated with an increase risk for adverse outcome, worsening mortality in brain injures (42).

Cooling strategy

Thanks to a better knowledge of hypothermia mechanisms a rationale approach and management of cooling strategy was established and three main phases identified (43).
The first is the induction phase, with the target to reach a mild hypothermia (a core temperature between 32°C-34°C), as soon as possible. Some animal experiments suggest that neuro-excitotoxicity can be blocked or reversed only if the treatment is initiated in the very early stages of the neuro-excitatory cascade (44). Other studies have reported somewhat wider time frames, ranging from 30 minutes to up to 6 hours (45). The possibility of reaching hypothermia in the field for out-hospital cardiac arrest is still object of debate. One not adequately powered trial demonstrated a trend toward a better neurological outcome

when cooling was started out-of-hospital with 4°C saline rapid infusion (17), and preliminary data from the PRINCE study showed that cooling before ROSC with a nasal cooling device is feasible, and in selected groups of patients allowed higher neurologically intact survival rate when compared with TH started in hospital (19).
The second phase is the maintenance one, with the aim to maintain core temperature as close as possible to the target (maximum fluctuation 0,2-0,5 ^{0}C).
The third phase is the rewarming period, which consists in a slow and controlled return to normothermia (0,2-0,3 ^{0}C/h). This phase starts 24 hours after hypothermia induction and ends when the patient reaches normothermia. Slow de-cooling avoids violent hemodynamic fluctuations and electrolytes disorders and prevent hypoglycemia due to increased insulin sensitivity. Moreover some studies (46, 47) suggest that rapid rewarming could reverse some protective effects of hypothermia while a significant decrease in jugular venous oxygen saturation during rapid rewarming of patient following cardiac surgery is demonstrated (48, 49), and the incidence and severity of jugular bulb desaturation may be lessened by a slower rewarming.
Each TH phase is characterized by physiological changes. Shivering is a protective strategy activated by human organism in contrast to temperature loss and leads to an undesirable increase in metabolic rate and oxygen consumption (50).
Its prevention and aggressive treatment requires subsequent steps: a rapid cooling below 34°C, magnesium administration, adequate sedation and analgesia, and eventually neuromuscular blockade (51). Some authors describe benefits from skin warming during cooling (52). Shivering prevention and treatment is of paramount importance to avoid TH benefits loss.
During mild to moderate hypothermia (32°C-34°C), cardiac output decreases by 25% to 40%, mainly due to a decrease in heart rate; since metabolic decrease exceeds cardiac output reduction, overall circulatory system result unchanged or improved. At 32°C heart rate usually decrease around 40-45 beats per minute and when heart rate is allowed to decrease, systolic function usually increases. Conversely myocardial contractility decreases when chronotropic agents are administrated or a pacing is placed; if an increase in heart rate is necessary rewarming the patient to a slightly higher temperature may be sufficient. Occurrence of malignant arrhythmias is described only for severe hypothermia (53, 54).
The increase in venous return induced by hypothermia can lead to activation of atrial natriuretic peptide and a decrease in the levels of anti-diuretic hormone leading to a marked increase in diuresis, which may lead to hypovolemia, renal electrolyte loss, and hemoconcentration with increased blood viscosity (55). Hypovolemia is the most frequent cause of haemodinamic instability during the induction phase, its prevention and prompt treatment is of pivotal importance (56).
Hypothermia also induces electrolytic disorders: during the induction phase potassium and magnesium levels decrease due to urinary loss and intracellular shift. While electrolytes correction may prevent arrhythmias, it is necessary to consider that in the rewarming phase electrolytes movement occur in the opposite direction (57).
In cooled patients a reduction in metabolism is also observed. Caloric intake and mechanical ventilation should be decreased in order to balance O_2 and CO_2 and to avoid alterations that can worse the ischemic/reperfusion injury (58).
A decreased insulin secretion and, in many patients, a moderate (and sometimes severe) insulin resistance is observed. This

can lead to hyperglycaemia and/or a significant increase in doses of insulin required to maintain glucose levels within an acceptable range (59).
Despite standard coagulation tests will show no abnormalities unless they are performed at the patient's actual core temperature, due to effects on platelet count and function, kinetics of clotting enzymes and other steps in the coagulation cascade, hypothermia produces a mild bleeding diathesis (60-64).
Hypothermia begins to affect platelet function only when temperature decrease below 35°C, and other coagulation factors are affected when temperature decrease below 33°C (60-64); the risk of clinically significant bleeding induced by hypothermia in patients who are not already actively bleeding is very low.
Drugs clearance is affected by cooling, the half-life is increased and higher plasmatic concentrations are achieved with the same doses (64). This must be kept on mind while administrating sedatives, analgesics, neuromuscular blockade agents or other required medicaments.
Multiple evidences show that hypothermia can suppress epileptic activity (65-67), even if during TH antiepileptic medicaments are administered for patient sedation, continuous EEG monitoring is recommended when seizures or non-seizures epileptic activity is suspected, especially when muscle relaxant are required for shivering control.
Hypothermia impairs immune functions and inhibits various inflammatory responses, increasing the risk of infections (68). Incidence of pneumonia is described to increase in some cases, particularly for prolonged hypothermia and some authors suggest prophylactic treatments. Appropriate attention must be taken in wound care (68).
Other minor alteration, like transient impaired bowel function or amylase count occurs but they normalize once normothemia is reached.
In *table 2* a list of laboratory and instrumental tests we use in our department to monitor and prevent changes, side effects and potential complications due to TH.

Cooling methods

After having identified patient to cool and excluded conditions that contraindicate TH (*Table 1*), clinicians should start cooling as soon as possible and should consider the different options to get the target temperature.
Needs for other procedures such as percutaneous coronary intervention shouldn't delay cooling, as TH during percutanueous transluminal coronary angioplasty is shown to be feasible and safe (69).

Table 1 - *Indications and contraindications to therapeutic hypothermia.*

INDICATIONS: • Return Of Spontaneous Circulation (ROSC) after cardiac arrest (any rhythm of presentation, any location) • Coma (does not open eyes to pain, does not follow verbal command) • Age ≥18
CONTRAINDICATIONS: • Time from ROSC > 6 h • Other possible causes for coma (stroke, intoxication, head trauma, hypoglicaemia, seizures) • Significant pre-existing neurologic impairment • Systolic arterial pressure < 90 mmHg despite fluids and vasopressors • Refractory Ventricular Arrhythmia • Pre-existing coagulopaty or severe bleeding (Disseminated Intravascular Coagulation, severe thrombocytopenia, liver failure) NOTE: anticoagulant and antiplatelet therapy are not a contraindication • Pregnancy • Sepsis • Known pre-existing terminal illness
SUSPEND COOLING PROTOCOL WHEN: • sepsis or pneumonia • refractory haemodynamic instability • severe refractory arrhythmia

Table 2 - *Timetable for laboratory and instrumental tests in use in our institute.*

Time from TH induction (h)	0	2	8	12	16	24	36	48	72
Blood Urea Nitrogen Creatinine	⊗					⊗		⊗	⊗
Albumin, Proteinaemia	⊗					⊗		⊗	⊗
Creatine Phosphokinase	⊗		⊗		⊗	⊗		⊗	⊗
Aspartate Transaminase Alanine Transaminase Lactate dehydrogenase bilirubin	⊗		⊗		⊗	⊗		⊗	⊗
Creatine Kinase Myocardial Band isoenzyme, Troponin	⊗		⊗		⊗	⊗		⊗	⊗
Coagulation tests	⊗					⊗		⊗	⊗
Amylase, lipase	⊗					⊗			⊗
Lactate	⊗					⊗		⊗	⊗
Complete Blood Count	⊗					⊗		⊗	⊗
Arterial Blood Gas + electrolytes + glycaemia	⊗	⊗	⊗	⊗	⊗	⊗		⊗	⊗
Electrocardiography	⊗		⊗		⊗	⊗		⊗	⊗
Echocardiography	⊗								⊗
Chest X-Ray	⊗					⊗			
Electroencephalography (continuous when needed)									⊗
Evoked potential									⊗
Computed Tomography scan (if need to exclude other causes for coma)	⊗								

First of all a temperature probe must be positioned. The site chosen to measure core temperature is of key importance. Pulmonary artery catheter is the gold standard for core temperature detection but risks linked to the procedure must be considered; oesophageal and bladder probes are less precise and slower in detecting temperature changes but widely used due high correlation to core temperature, relative simple positioning and few side effects.

Tympanic probes are also used, particularly indicated for out-of-hospital measurements, they are quick and easy to place, may reflect brain temperature but readings sometimes may be inaccurate.

The best way to achieve rapid cooling, temperature maintenance and a slow and controlled rewarming is to integrate different cooling methods.

Administration of cold fluids in the induction phase is a common, practical, effective, safe and cheap procedure. A rapid bolus of 20-30 ml/kg 4°C isotonic saline solution is effective in decreasing temperature and its use is supported by multiple evidences in pre-hospital setting as in emergency department (70-74).

Modern cooling devices work in a controlled feedback manner, continuously measuring patient's temperature and consequently changing the temperature of the cooling elements (catheters, pads, or blankets).

Intravascular cooling devices permit to achieve a tight temperature control but are

affected by risks and complications of central venous catheterization (75, 76).
Surface cooling devices allow a good temperature control, are well tolerated and relative safe because of the infrequency of overcooling and lack of vascular catheterization complications and are useful for maintenance of normotermia after cooling (70). Both this kind of devices represent, at the moment, the best and preferred choice for the maintenance and rewarming period. Preliminary data from the PRINCE study show that intranasal cooling in feasible and effective and more studies are needed to confirm benefits on outcome when used in out-of-hospital setting (19).
Low cost methods as covering the patient with ice or placing ice packs on groin, neck and axillas are also used. Those techniques are cheap but lack in loop control with the core body temperature and expose the patient to an overcooling risk, don't allow a tight temperature control, don't allow a controlled rewarming and produce an extra workload for nurses.
Other methods like body cavity lavage, whole-body ice water immersion, cooling helmets or extracorporeal devices are less used due to lack in efficacy or higher risks and costs/effectiveness (77).

CONCLUSIONS

Beneficial effects of mild TH in patients with a witnessed FV cardiac arrest are clearly demonstrated. However, a widespread use of TH in daily practice is still far to be reached, as demonstrated by several surveys. Reasons may be related to general, individual and local barriers.
Lack of institutional protocols, lack of agreement with supporting evidence, absence of adequate instrumentation useful to reduce nurse work load and optimize management are the most perceived barriers. Extensive and rapid diffusion of protocols and process issues, further training and more studies in this field are essential key points for new developments and TH application increasing.

No conflict of interest acknowledged by the authors.

REFERENCES

1. Curfman GD. Hypothermia to protect the brain. New England Journal of Medicine 2002; 346: 546.
2. Benson DW, Williams GR, Spencer FC, et al. The use of hypothermia after cardiac arrest. Anesth Analg 1959; 38: 423-428.
3. Safar P. Cerebral resuscitation after cardiac arrest: a review. Circulation 1986; 74: 138-153.
4. Weinrauch V, Safar P, Tisherman S, et al. Beneficial effect of mild hypothermia and detrimental effect of deep hypothermia after cardiac arrest in dogs. Stroke 1992; 23: 1454-1462.
5. Leonov Y, Sterz F, Safar P, Radovsky A. Moderate hypothermia after cardiac arrest of 17 minutes in dogs: effect on cerebral and cardiac outcome. Stroke 1990; 21: 1600-1606.
6. Leonov Y, Sterz F, Safar P, et al. Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. J Cereb Blood Flow Metab 1990; 10: 57-70.
7. The Hypothermia after cardiac arrest study group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. NEJM 2002; 346: 549-556.
8. Bernard AS, Timothy WG, Buist MD, et al. Treatment of comatose survivors of out-hospital cardiac arrest with induced hypothermia. NEJM 2002; 346: 557-563.
9. American Heart Association Guidelines for Cardiopulmonary Resuscitation and Post Resuscitation Support. Circulation 2005; IV: 84-88.
10. Boddicker KA, Zhang Y, Zimmerman MB, et al. Hypothermia improves defibrillation success and resuscitation outcomes from ventricular fibrillation. Circulation 2005; 111: 3195-3201.
11. 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.
12. Abella BS, Rhee JW, Huang KN, et al. Induced hypothermia is underused after resuscitation from cardiac arrest: a current practice survey. Resuscitation 2005; 64: 181-186.
13. Binks AC, Murphy RE, Prout RE, et al. Therapeutic

hypothermia after cardiac arrest - implementation in UK intensive care units. Anaesthesia. 2010; 65: 260-265.
14. Herr DL, Badjatia N. Therapeutic temperature management: why, who, when, where, and how. Critical Care Medicine 2009; 37: 185.
15. Toma A, Bensimon CM, Dainty KN, et al. 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.
16. Cobb LA, Fahrenbruch CE, Olsufka M, et al. Changing incidence of out-of-hospital ventricular fibrillation, 1980-2000. JAMA 2002; 288: 3008-3013.
17. Kim F, Olsufka M, Longstreth W, 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.
18. Hay AW, Swann DG, Bell K, et al. Therapeutic hypothermia in comatose patients after out-of-hospital cardiac arrest. Anaesthesia 2008; 63: 15-19.
19. Susan Jeffrey. Prehospital Intranasal Cooling After Cardiac Arrest Feasible, May Improve Survival. www.medscape.com/viewarticle/712430
20. Bernard S. Hypothermia after cardiac arrest: expanding the therapeutic scope. Crit Care Med 2009; 37: 227-233.
21. Don CW, Longstreth WT Jr, 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.
22. Schefold JC, Storm C, Krüger A, et al. The Glasgow Coma Score is a predictor of good outcome in cardiac arrest patients treated with therapeutic hypothermia. Resuscitation 2009; 80: 658-661.
23. Seder DB, Fraser GL, Robbins T, et al. The bispectral index and suppression ratio are very early predictors of neurological outcome during therapeutic hypothermia after cardiac arrest. Intensive Care Med 2010; 36: 281-288.
24. Stammet P, Werer C, Mertens L, et al. Bispectral index (BIS) helps predicting bad neurological outcome in comatose survivors after cardiac arrest and induced therapeutic hypothermia. Resuscitation 2009; 80: 437-442.
25. Williams GR, Spencer FC. The clinical use of hypothermia after cardiac arrest. Annals of Surgery 1959; 148: 462-468.
26. Small DL, Morley P, Buchan AM. Biology of ischemic cerebral cell death. Prog Cardiovasc Dis 1999; 42: 185-207.
27. Siesjo BK, Bengtsson F, Grampp W, et al. Calcium, excitotoxins, and neuronal death in brain. Ann NY Acad Sci 1989; 568: 234-251.
28. Povlishock JT, Buki A, Koiziumi H, et al. Initiating mechanisms involved in the pathobiology of traumatically induced axonal injury and interventions targeted at blunting their progression. Acta Neurochir Suppl 1999; 73: 15-20.
29. Xu L, Yenari MA, Steinberg GK, et al. Mild hypothermia reduces apoptosis of mouse neurons in vitro early in the cascade. J Cereb Blood Flow Metab 2002; 22: 21-28
30. Schmidt OI, Heyde CE, Ertel W, et al. Closed head injury-an inflammatory disease? Brain Res Brain Res Rev 2005; 48: 388-399.
31. Fischer S, Clauss M, Wiesnet M, et al. Hypoxia induces permeability in brain microvessel endothelial cells via VEGF and NO. Am J Physiol 1999; 276: 812-820.
32. Fischer S, Renz D, Wiesnet M, et al. Hypothermia abolishes hypoxia-induced hyperpermeability in brain microvessel endothelial cells. Brain Res Mol 1999; 74: 135-144.
33. Globus MY, Busto R, Lin B, et al. Detection of free radical activity during transient global ischemia and recirculation: effects of intraischemic brain temperature modulation. J Neurochem 1995; 65: 1250-1256.
34. Novack TA, Dillon MC, Jackson WT. Neurochemical mechanisms in brain injury and treatment: a review. J Clin Exp Neuropsychol 1996; 18: 685-706.
35. Chatauret N, Zwingmann C, Rose C, et al. Effects of hypothermia on brain glucose metabolism in acute liver failure: a H/C-nuclear magnetic resonance study. Gastroenterology 2003; 125: 815-824.
36. Leffer CW. Prostanoids: Intrinsic modulation of cerebral circulation. News Physiol Sci 1997; 12: 72-77.
37. Dogne JM, de Leval X, Hanson J, et al. New developments on thromboxane and prostacyclin modulators part I: thromboxane modulators. Curr Med Chem 2004; 11: 1223-1241.
38. Aibiki M, Maekawa S, Yokono S. Moderate hypothermia improves imbalances of thromboxane A2 and prostaglandin I2 production after traumatic brain injury in humans. Crit Care Med 2000; 28: 3902-3906.
39. Karkar KM, Garcia PA, Bateman LM, et al. Focal cooling suppresses spontaneous epileptiform activity without changing the cortical motor threshold. Epilepsia 2002; 43: 932-935.
40. Schaller B, Graf R. Hypothermia and stroke: the pathophysiological background. Pathophysiology 2003; 10: 7-35.
41. Chatauret N, Rose C, Therrien G, et al. Mild hypothermia prevents cerebral edema and CSF lactate

accumulation in acute liver failure. Metab Brain Dis 2001; 16: 95-102.
42. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008; 371: 1955-1969.
43. Poldeman KH. Mechanisms of action, physiological effects and complications of hypothermia. Critical Care Medicine 2009; 37: 186-202.
44. Kuboyama K, Safar P, Radovsky A, et al. 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: 1348-1358.
45. Baker CJ, Onesti ST, Solomon RA. Reduction by delayed hypothermia of cerebral infarction following middle cerebral artery occlusion in the rat: A time-course study. J Neurosurg 1992; 77: 438-444.
46. Sessler DI. Thermoregulatory defense mechanisms. Crit Care Med 2009; 37: 203-210.
47. Maxwell WL, Watson A, Queen R, et al. Slow, medium, or fast re-warming following post-traumatic hypothermia therapy? An ultrastructural perspective. J Neurotrauma 2005; 22: 873-884.
48. Hildebrand F, van Griensven M, Giannoudis P, et al. Effects of hypothermia and rewarming on the inflammatory response in a murine multiple hit model of trauma. Cytokine 2005; 31: 382-393.
49. Kawahara F, Kadoi Y, Saito S, et al. Slow rewarming improves jugular venous oxygen saturation during rewarming. Acta Anaesthesiol Scand 2003; 47: 419-424.
50. Bissonnette B, Holtby HM, Davis AJ, et al. Cerebral hyperthermia in children after cardiopulmonary bypass. Anesthesiology 2000; 93: 611-618.
51. De Witte J, Sessler DI. Perioperative shivering: Physiology and pharmacology. Anesthesiology 2002; 96: 467-484.
52. Van Zanten AR, Polderman KH. Blowing hot and cold? Skin counter warming to prevent shivering during therapeutic cooling. Critical Care Medicine 2009; 37: 2106-2108.
53. Fischer UM, Cox CS Jr, Laine GA, et al. Mild hypothermia impairs left ventricular diastolic but not systolic function. J Invest Surg 2005; 18: 291-296.
54. Goldberg LI. Effects of hypothermia on contractility of the intact dog heart. Am J Physiol 1958; 194: 92-98.
55. Pozos RS, Danzl D. Human physiological responses to cold stress and hypothermia. In: Medical Aspects of Harsh Environments, Vol Textbooks of Military Medicine. Pandolf KB, Burr RE (Eds). Washington, DC, Borden Institute, Office of the Surgeon General,US Army Medical Department 2001; 351-382.
56. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Critical Care Medicine 2009; 37: 1101-1120.
57. Polderman KH, Peerdeman SM, Girbes ARJ. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. J Neurosurg 2001; 94: 697-705.
58. Bacher A. Effects of body temperature on blood gases. Intensive Care Medicine 2005; 31: 24-27.
59. Michelson AD, MacGregor H, Barnard MR, et al. Hypothermia-induced reversible platelet dysfunction. Thromb Haemost 1994; 71: 633-640.
60. Valeri CR, MacGregor H, Cassidy G, et al. Effects of temperature on bleeding time and clotting time in normal male and female volunteers. Crit Care Med 1995; 23: 698-704.
61. Reed RL, Bracey AW, Hudson JD, et al. Hypothermia and blood coagulation: Dissociation between enzyme activity and clotting factor levels. Circ Shock 1990; 32: 141-152.
62. Valeri CR, Feingold H, Cassidy G, et al. Hypothermia-induced reversible platelet dysfunction. Ann Surg 1987; 2005: 175-181.
63. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. NEJM 2001; 345: 1359-1367.
64. 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 (review). Crit Care Med 2007; 35: 2196-2204.
65. Polderman KH, Ely EW, Badr AE, et al. Induced hypothermia in traumatic brain injury: Considering the conflicting results of meta-analyses and moving forward. Intensive Care Medicine 2004; 30: 1860-1864.
66. Corry JJ, Dhar R, Murphy T, et al. Hypothermia for refractory status epilepticus. Neurocrit Care 2008; 9: 189-197.
67. Lundgren J, Smith ML, Blennow G, et al. Hyperthermia aggravates and hypothermia ameliorates epileptic brain damage. Exp Brain Res 1994; 99: 43-55.
68. Kurz A, Sessler DI, Lenhardt R, et al. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. NEJM 1996; 334: 1209-1215.
69. Batista LM, Lima FO, Januzzi JL Jr, et al. Feasibility and safety of combined percutaneous coronary intervention and therapeutic hypothermia following cardiac arrest. Resuscitation 2010; 81: 398-403.
70. Hoedemaekers CW, Ezzahti M, Gerritsen A, et al. Comparison of cooling methods to induce and maintain normo and hypothermia in intensive care unit patients: a prospective intervention study. Critical Care 2007; 11: 91.

71. Bernard S, Buist M, Monteiro O, et al. 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.
72. Rajek A, Greif R, Sessler DI, et al. Core cooling by central venous infusion of ice-cold (4 degrees C and 20 degrees C) fluid: isolation of core and peripheral thermal compartments. Anesthesiology 2000; 93: 629-637.
73. Virkkunen I, Yli-Hankala A, Silfvast T. Induction of therapeutic hypothermia after cardiac arrest in prehospital patients using ice-cold Ringer's solution: a pilot study. Resuscitation 2004; 62: 299-302.
74. Polderman KH, Rijnsburger ER, Peerdeman SM, et al. Induction of hypothermia in patients with various types of neurologic injury with use of large volumes of ice-cold intravenous fluid. Crit Care Med 2005; 33: 2744-2751.
75. Simosa HF, Petersen DJ, Agarwal SK, et al. Increased risk for deep venous thrombosis with endovascular cooling in patients with traumatic head injury. Am Surg 2007; 73: 461-464.
76. 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: 109-118.
77. Holzer M. Devices for rapid induction of hypothermia. Eur J Anaesthesesiol 2008; 25: 31-38.