Temperature Management

121

Michael Holzer

Hypothermia after cardiac arrest has been studied in animal models since 1950 as a neuroprotective strategy, and many neuroprotective mechanisms have been described. Hypothermia effects are multifactorial and hypothermia influences several cascades that lead to cell death. Hypothermia may protect by decreasing brain metabolism, attenuating reactive oxygen species formation, inhibiting accumulation of excitatory amino acids, altering the immune response during reperfusion, and inhibiting apoptosis.

Hypothermia decreases cerebral metabolic rate by 5–8 %/°C reduction of core temperature. This is reflected by decreased electrical activity, which leads to decreased oxygen demand and CO_2 creation. But the reduction of metabolism with hypothermia is not a sufficient explanation for the protective effect. With the cessation of perfusion and/or ventilation, energy-rich compounds like adenosine triphosphate (ATP) are degraded without the use of oxygen, which leads to failure of ATP-dependent Na-K-ATPase, increase of intracellular Na^+ and Ca^{++}, and intra- and extracellular acidosis. Excitatory amino acids like glutamate are released by cellular hypoxic depolarization. This leads to an increase of Ca^{++} influx. Due to hypoxia, the cell is not able to actively sequester Ca^{++} from the intracellular matrix. Cell death is the consequence of these mechanisms. Hypothermia can lessen the effects of such cascades. The release of glutamate and dopamine after global ischemia is inhibited. Brain-derived neurotrophic factor is induced by hypothermia; this leads to a further reduction of glutamate release. Reperfusion leads to the formation of reactive oxygen species, which induces apoptosis and causes cellular damage by lipid peroxidation and DNA toxicity. Hypothermia can attenuate these oxidative damaging processes and lipid peroxidation.

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After the acute insult, the inflammatory response leads to delayed tissue injury. Hypothermia mediates an immunomodulator function by inhibiting neutrophil infiltration and function. Also lipid peroxidation and leukotriene production are decreased, and levels of cytokines are reduced in cell culture. If hypothermia is started 1 h after restoration of spontaneous circulation (ROSC), blood levels of cytokines are no longer elevated, as peak levels of some inflammatory markers are found only within the first hour after ROSC. Therefore cooling initiated very early after ROSC, if not even during resuscitation, is likely most efficacious. Also, microglial activation is mitigated by hypothermia, which could contribute to neuronal injury by production of nitric oxide and glutamate.

Apoptosis can be activated after ischemia. The amount of apoptosis is regulated by pro- and anti-apoptotic factors. Calcium overload and glutamate release, which are decreased by hypothermia, contribute to induction of apoptosis. Hypothermia acts directly on the caspase cascade by decreasing cytochrome C release. The anti-apoptotic factor Bcl-2 is enhanced, while the pro-apoptotic factor BAX is suppressed by hypothermia. The reduction of brain edema following ischemia is another potentially beneficial effect of hypothermia [1].

121.1 Use of Therapeutic Hypothermia in the Treatment of Drowning

The use of hypothermia gradually evolved in the 1960s–1980s on management of the comatose patient [2] and initial "ABCs" for management of cardiac arrest [3]. In the latter, it was specifically stated that hypothermia should be initiated within 30 min of ROSC in comatose victims of cardiac arrest. Hypothermia specifically in drowning victims built upon that work and also upon isolated reports of remarkable recovery in victims of cold water drowning and was further advanced by the reports on HYPER therapy (diuretics, hyperventilation, profound and sustained hypothermia, barbiturates, and glucocorticoids) for pediatric drowning victims [4]. Hypothermia was a central facet of HYPER therapy. However, therapeutic hypothermia in cerebral resuscitation fell out of favor between 1986 and 1990 [5, 6]. Two small retrospective studies of pediatric drowning victims suggested that profound and sustained hypothermia applied in an aggressive resuscitation regimen to patients with absent vital signs on admission increased survival of patients in a persistent vegetative state, but not intact survival. Therapeutic hypothermia after the insult was also associated with increased risk for infectious complications. These reports are discussed in greater detail below. Laboratory studies in experimental models of brain ischemia and cardiac arrest in the late 1980s provided insight into the need for only mild hypothermia to mitigate neuronal injury, which led to a clinical re-exploration of therapeutic hypothermia as a neuroprotectant. In 2002, two randomized clinical trials of therapeutic external hypothermia after cardiac arrest showed improved neurologic intact survival with the use of therapeutic hypothermia [7, 8].

121.2 Studies in Which Therapeutic Hypothermia was Used Specifically for Drowning Victims

In two non-randomized trials therapeutic hypothermia was compared to normothermia in victims of drowning. The first trial studied 40 children with a regimen of hyperventilation and high-dose phenobarbital while ICP was continuously monitored [5]. Of those, 24 were treated with 30–33 °C for 24–36 h by surface cooling and 16 children were not cooled. There was a nonsignificant higher rate of good neurologic survival in children who were not cooled (RR 0.81, 95 %CI 0.44–1.50), arguing against hypothermia as applied by these investigators. The second trial studied cardiac performance in pediatric drowning victims [9]. Of 29 reported children eight suffered cardiac arrest after drowning. Most of the children were treated with hyperventilation, pentobarbital coma, and mannitol. Six children were treated with therapeutic hypothermia (core temperature 30–32 °C, 24 h). One child in the hypothermia group ($n=6$) survived with good neurologic outcome. Relevant to the aforementioned studies by Bohn et al. [5], Biggart and Bohn [6] reported a follow-up retrospective report in 50 comatose pediatric drowning victims. They observed that hypothermia produced by cold water submersion could lead to intact survival but reported that in the absence of therapeutic hypothermia, outcomes were similar or better than in their prior series—once again arguing against the use of therapeutic hypothermia after cardiac arrest in pediatric drowning victims. However, it should be recognized that temperatures as low as 30 °C and long durations of cooling were used in some patients in the initial series of Bohn et al. [5], and a clinical trial of its use was not performed.

In four case reports [10–13] and five case series [14–18], therapeutic hypothermia was used in victims after drowning. The survival rates in the case series varied between 11 and 39 %.

121.3 Studies of Therapeutic Hypothermia in Asphyxia

All but one study (children [19]) analyzed newborns with perinatal asphyxia (Fig. 121.1). There were two systematic reviews [20, 21], four large randomized clinical trials (RCT) [22–25], and one small RCT [26] showing improved outcome without disabilities with hypothermia therapy (selective head cooling and/or full body cooling temperature <35 °C, most studies used 33–34 °C). The relative risk (RR) varied between 1.35 and 2.43. The first systematic review included 8 RCTs ($n=638$) and showed that therapeutic hypothermia is beneficial to term newborns with hypoxic-ischemic encephalopathy (RR 1.44 (95 % CI 1.17–1.77), death, or major neurodevelopmental disability reduction) [20]. The second systematic review of newborns included 6 RCTs ($n=979$). Therapeutic hypothermia was associated with a highly reproducible reduction in the risk of the combined outcome of mortality or moderate-to-severe neurodevelopmental disability (RR 1.39 (95 % CI 1.22–1.59)) [21].

In 4 RCTs [27–30] and in 1 non-randomized comparative trial [19], no difference was found between hypothermia (selective head cooling and/or full body

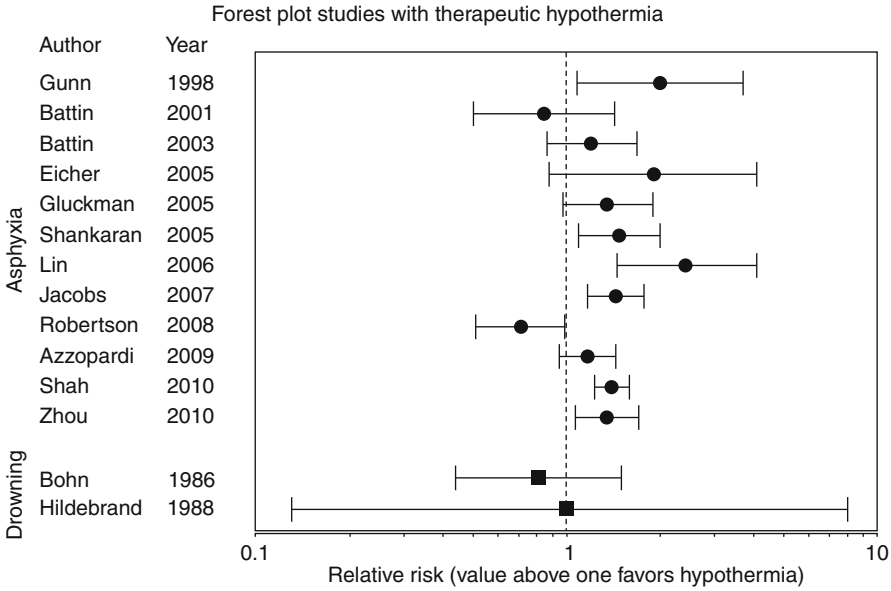

Fig. 121.1 Forrest plot of studies that used therapeutic hypothermia in the treatment of asphyxia and drowning. Relative risk of good neurologic survival is presented. A value above one favors therapeutic hypothermia

cooling temperature <35 °C, most studies used 33–34 °C) and normothermia groups. The RR varied between 0.54 and 1.92.

In 1 RCT [31], which was performed in a low-resource setting in Uganda, there was decreased survival due to hypothermia therapy (33–34 °C for 72 h) (RR 0.71 (95 % CI 0.51–0.99)).

In four case series no comparison was given to normothermia therapy. Survival with good outcome varied between 0.56 and 1.00 (Fig. 121.1).

121.4 Studies of Therapeutic Hypothermia in Cardiac Arrest

Two randomized trials demonstrated improved neurological outcome at hospital discharge or at 6 months after hospital discharge in comatose patients after out-of-hospital ventricular fibrillation cardiac arrest [7, 8]. Cooling was either with ice or with cold air to a target temperature of 32–34 °C which was maintained for 12–24 h. One small ($n = 30$) randomized trial of comatose patients after cardiac arrest with non-shockable rhythms showed a higher rate of neurologic intact survival in patients treated with a cooling cap [32].

A systematic review demonstrated improved neurologic survival from therapeutic hypothermia with a relative risk of 1.55 (95 % CI 1.22–1.96) compared with standard post-resuscitation care [33]. In addition, 14 studies of comatose survivors of cardiac arrest using historical controls found therapeutic hypothermia to improve

neurological outcome [34]. This is in contrast to a more recent meta-analysis [35], which reported a low-quality evidence in existing studies due to not aggressively treating hyperthermia in patients randomized to the control group.

121.5 How to Cool a Patient Who Remains Comatose After Drowning

Patients considered for hypothermia treatment should be sedated, treated with analgesia and neuromuscular blockade to prevent shivering. Continuous EEG monitoring should be considered to detect seizures. There are numerous methods available for induction and maintenance of hypothermia as well as for rewarming. Cooling may be initiated by application of ice packs around the torso, head, neck, and limbs. Infusion of cold saline (4 °C) in patients who can tolerate an intravenous volume load (e.g., 30 ml/kg over 30 min), gastric lavage with cold saline, application of commercial cooling pads, and commercial intravenous cooling catheters can enhance cooling rate and maintain core temperature with a range of 32–34 °C. It is essential that the core temperature be monitored during and after treatment (Fig. 121.2). Possible complications of therapeutic hypothermia should be anticipated and treated

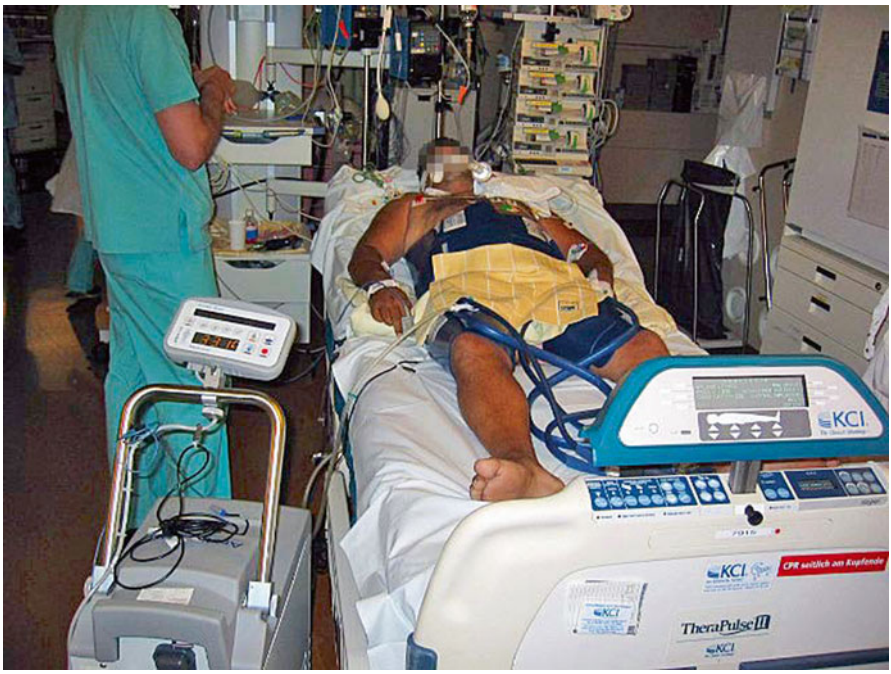

Fig. 121.2 Patient with therapeutic hypothermia treatment. This comatose patient is intubated and ventilated and receives therapeutic hypothermia via surface cooling (Arctic Sun®, Medivance). Temperature measurement and feedback to the cooling device is via a Foley catheter temperature probe

appropriately. These disturbances include hypokalemia, hypomagnesemia, hyperphosphatemia, hyperglycaemia, leukopenia, trombocytopenia, coagulation disorders and pancreatitis. Rewarming must be slow to avoid hyperthermia or thermal injury at a rate no faster than 0.5 °C/h. Aggressive goal-directed intensive care measures should be applied to monitor and manage the patient. A more detailed description of how to treat comatose patients with therapeutic hypothermia has been published [1].

121.6 Summary

As there are no high-level evidence studies that directly evaluated the effect of therapeutic hypothermia on neurologic function and outcome in victims of drowning, treatment recommendations are done by extrapolating from other studies of patients in asphyxia and cardiac arrest. First, prevent hyperthermia in comatose victims of drowning. If hyperthermia occurs, treat it promptly. Second, consider maintaining a target core temperature of 32–34 °C for 12–72 h. Cooling should be started as soon as possible, and rewarming should be slow, at a rate no faster than 0.5 °C/h.

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