This review discusses the mechanisms of neurologic damage during and after global cerebral ischemia caused by cardiac arrest. The different pathways of membrane destruction by radicals, free fatty acids, excitatory amino acids (neurotransmitters), calcium, glucose metabolism, and oxygen availability and demand in relation to metabolic rate are briefly discussed. The main focus of this review paper, however, lies in therapeutic (resuscitative) hypothermia after cardiac arrest. Two pioneering studies of the 1950s and four recent publications (in part preliminary results of ongoing studies) in humans are discussed in detail. The conclusions are as follows: (1) hypothermia holds promise as the only specific brain therapy after cardiac arrest so far; (2) hyperthermia is not tolerable after successful resuscitation; and (3) if the ongoing European multicenter trial of hypothermia after cardiac arrest finds a significant benefit to mild hypothermia, withholding hypothermia may be ethically hard to defend. Curr Opin Crit Care 2001, 7:184-188 © 2001 Lippincott Williams & Wilkins, Inc.

Sudden cardiac death is an everyday problem, and resuscitation is initiated in more than 190 people per day in the United States [1••] and 50 to 66 per 100,000 per year in Europe [2]. Survival and neurologic recovery are well known to be strongly linked to time intervals between cardiac arrest and the initiation of basic life support, including early defibrillation [3,4]. Nonetheless, these crucial time intervals are, with very few exceptions [5], usually not met.

As has been known since the 1950s, the brain tolerates anoxia for up to 2 to 4 minutes [6]. After this time, irreversible neuronal damage begins. Hippocampal neurons were found to be especially vulnerable to ischemia in animals [7] and in humans [8]. The anoxic damage is not so clear in its pathogenetic mechanisms. As a result, the microcellular biochemical reactions are subject to intense research [1••]. The main focus lies in membrane damage through free radicals [9], calcium influx [10], glucose availability and use [9,11,12], free fatty acids [13], excitatory amino acids and neurotransmitters [9,13–15], and signal mediators such as the mitogen-activated protein kinases [16]. It is hypothesized that damage may also occur during reperfusion [1••] and that the onset of capillary reperfusion occurs later than expected, that is, not automatically with the restart of circulation (no reflow phenomenon) [17,18]. This led to the assumption that the cerebral damage after successful resuscitation from cardiac arrest may still proceed after the return of a spontaneous heartbeat. Any specific therapy aimed at this progress of decay looked promising.

Effects of hypothermia on the brain

Hypothermia has been in use for cerebral protection since the 1950s. The simple principle of chemistry that a reduction of 10°C slows a chemical process by approximately 50% was already proven by Rosomoff and Holaday [19] to be valid in cerebral metabolism: cerebral metabolism is slowed by 6.7% with each decrement of 1°C. One hour of hypothermia, applied immediately, with rewarming over 3 hours did not significantly affect patterns of cerebral blood flow and oxygen uptake [20]. Furthermore, cardiac arrest after accidental hypothermia, as in ice water immersion victims, was found to be compatible with much a longer duration of anoxia without neurologic sequelae [21,22]. Protective, meaning prospective, prearrest cooling was started in cardiovascular surgery for the extension of tolerance of anoxia during cardiac arrest [23]. Different levels of hypothermia were defined: mild (33–36°C), moderate

Therapeutic hypothermia after cardiac arrest
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(28–32°C), deep (< 28°C), profound (< 15°C), and ultraprofound (< 5°C) hypothermia. Ultraprofound resuscitative hypothermia is currently under investigation for rapid cooling with very cold fluids in trauma victims [24]. Profound resuscitative hypothermia is currently pursued under the concept of suspended animation [25,26]. Deep protective hypothermia is being used in cardiac surgery with elective cardiac arrest for the duration of the operation [23] or for brain protection during selectively reduced cerebral perfusion [27]. Mild and moderate resuscitative hypothermia was tested for neuroprotection after cardiac arrest in dogs [20,24,28••,29–39], gerbils [40], cats [41], and rats [13,16,17,42–44]. Leonov et al. [30], Sterz et al. [34], Weinrauch et al. [37], and Safar et al. [35] found a significantly improved neurologic deficit score and overall performance category and histologic damage score. In contrast, hyperthermia after cardiac arrest was proven to worsen outcome [41,45–47]. Mild hypothermia was also found to be beneficial for the neurologic outcome of trauma and head injury victims [14,48]. Adverse effects are directly related to the degree of hypothermia: coagulation disorders [49], increase of blood viscosity [50–52], aggravation of infection [53], increasing irritability of the cardiac conduction system [21], and myocardial dysfunction [31].

If hypothermia is to be of beneficial effect, it needs to be initiated as soon as possible [33]. However, even with a delay of 1 hour after global cerebral ischemia, hypothermia was reported to be advantageous as compared with control groups regarding loss of CA1 hippocampal cells [54].

In animal trials mimicking the real-world scenario, in which a patient can be cooled after being brought to a hospital, that is, approximately 1 hour after the collapse, the duration of cooling was 12 to 24 hours [40,42], which is tolerable in humans [14,55,56•,57•,58••,59]. The therapeutic effect of hypothermia may possibly be augmented by the addition of combined neuroprotective drugs. Ebmeyer et al. [39] recently published their experiment of hypothermia (temperature in pulmonary artery [Tpa] 34°C from 15 min to 12 h, rewarming 12–18 h) alone versus hypothermia plus thiopental versus hypothermia plus thiopental plus phenytoin plus methylprednisolone, as compared with a normothermic control group. They found a significantly improved neurologic deficit score and overall performance category and histologic damage score in the hypothermic treatment groups.

Hypothermia after cardiac arrest in humans

In 1958 and 1959, Williams and Spencer [28••] and Benson et al. [60] published their reports on human subjects, first on a test series of four patients [28••] (one child during a bronchogram, one child with fatal asthma, one adult with a traumatic pericardial tamponade, one adult with fatal traumatic pneumothorax), who were therapeutically cooled to 32 to 34°C over 24 to 72 hours after open heart resuscitation. All patients survived the resuscitation, three without any and one with moderate neurologic residual effects. Benson et al. [60] published their experiment in 19 patients with apparent neurologic damage after cardiac arrest; 12 were cooled to 30 to 32°C over 3 hours to 8 days and 7 were normothermic control subjects. The survival rate in the cooling group was 50%, compared with 14% in the control group. None of the survivors had any residual neurologic impairment. The authors concluded that, based on their results in humans and dogs [29], the clinical use of hypothermia after cardiac arrest is justified and warranted.

In 1997, Bernard et al. [56•] published a report on a nonrandomized, prospective hypothermia trial after cardiac arrest in 22 patients compared with historical control subjects. After successful resuscitation from out-of-hospital cardiac arrest, patients were cooled to 33°C with ice packs. Vecuronium was used as neuromuscular blockade during the cooling process to prevent shivering. Once the target temperature was reached, vecuronium was stopped and the patient was sedated and kept at 33°C for 12 hours. Shivering is not mentioned during this period. After the cooling, the patient was actively rewarmed with heating blankets over 6 hours. The results showed that more patients in the hypothermic group survived as compared with the normothermic control group (12 vs 5, \( P < 0.05 \)), and that neurologic outcome among the survivors was also better (Glasgow Outcome Scale 1+2: 11 vs 3, \( P < 0.05 \)).

In 1998, Yanagawa et al. [58••] published a preliminary report on resuscitative hypothermia applied to patients who were brought to the emergency department after successful primary resuscitation. Thirteen patients were included in this feasibility trial, and chart review was used for historical controls. The patients were cooled to 33°C within 5.5 hours (initiation: 78 minutes mean after return of spontaneous circulation) by means of cooling blankets and heat convection through alcohol evaporation and were kept at that target temperature for 48 hours. Midazolam and pancuronium were administered for sedation and neuromuscular blockade for the whole hypothermic period. After 48 hours, patients were (apparently passively) rewarmed at a rate of 1°C per day. The clinical data differed slightly between the control and the hypothermic groups: cardiac arrest was of primary cardiac origin in 9 of 15 versus 5 of 13 patients. The collapse was significantly more often witnessed in the control group (10/15 vs 3/13), and ventricular fibrillation on the first recorded electrocardiogram was slightly more prevalent in the hypothermic group. Also, most importantly, the time interval between the collapse and the emergency medical service call was substantially longer in the hypothermic
group (24.6 ± 62.9 min vs 4.8 ± 7.7 min). The outcome results indicated a slight trend towards improved outcome in the hypothermic group but did not reach statistical significance, possibly because of small sample size. In the control group, 67% of patients died compared with 46% in the hypothermia group. 27% versus 31% suffered severe neurologic damage, and 6% versus 23% could be discharged in good neurologic condition. The results did show a significantly augmented tolerance toward the “no-flow” time interval between collapse and initiation of basic life support; that is, longer “no-flow” periods became survivable. There was no accumulation of neurologically severely damaged patients who otherwise would have died. The study design without prospective, randomized controls, the inclusion criteria with unwitnessed arrest (confounding exact time-interval measurement), and the nonhomogeneous underlying causes of cardiac arrest make the results of this report hard to put into a general perspective for routine application. The feasibility trial does show, however, that resuscitative hypothermia appears to be feasible and safe.

Recently, a nonrandomized, uncontrolled preliminary study was performed in which cardiopulmonary bypass with mild hypothermia and an intravenous balloon pump were applied to 23 of 50 patients in or after cardiac arrest [59]. Cooling was initiated after 2.1 ± 1.9 hours, achieved at 34.2 ± 0.8°C after 6.3 ± 3.4 hours, and maintained over 48 hours, during which time shivering was avoided through the administration of midazolam and pancuronium. Rewarming was extended over at least 2 days (0.5°C per 12 h, then maintained at 35°C for 24 h). The neurologic result was good (Cerebral Performance Category 1–2) in 52% of the included patients. This preliminary report, however, presents no background and no comparative data concerning the patients transported to other hospitals or not included in the study. And because there was no control group, these results are not very lucid. The authors point out the historical survival rate of 1.1% of all cardiac arrests. Compared with this figure, the outcome of the presented study appears beneficial (26%), even if the excluded patients (n = 27/50) are taken into account for calculation.

A European multicenter trial with prospective, randomized, controlled mild hypothermia (33°C) over 24 hours for patients who are stabilized after cardiac arrest was recently described in a preliminary feasibility report by Zeiner et al. [57•]. Again, midazolam, fentanyl, and pancuronium are used during hypothermia. Rewarming is passive by stopping the administration of pancuronium and covering up the patient. In this trial, 10 centers in different European cities collaborate for a total patient number of 500. For reasons of comparability of the hypothermic and the control groups, the inclusion criteria are rather strict concerning the underlying cause of cardiac arrest (only cardiac origin with ventricular fibrillation on first recorded electrocardiogram), time measurements (only witnessed arrests), and intervals (ambulance response time greater than 5 minutes to rule out the extremely good and less than 15 minutes to rule out the hopeless patients). Potential confounding parameters of cerebral perfusion (exclusion if hypotensive over more than 30 minutes or hypoxic to less than 85% oxygen saturation after resuscitation success), and preexisting intracranial or intracerebral disease as well as malignancy and pregnancy are also exclusion criteria. Zeiner describes 27 patients who were brought to the emergency department after successful resuscitation with a core temperature of 35.3°C. Because the arrival of all patients was announced in advance via telephone by the ambulance service, cooling was prepared and could be started 5 minutes after the arrival of the patient. The patients reached the target temperature of 33°C within 4.5 hours. Temperature measurement in the esophagus, the urinary bladder, and the pulmonary artery catheter did not differ, as described before [61]. No patient developed acute renal failure, neutropenia, thrombocytopenia, coagulopathy, or sepsis. Neurologic outcome was favorable (Cerebral Performance Category 1–2) in 52% and unfavorable (Cerebral Performance Category 3–4) in 7%, and death occurred in 41%.

Conclusions
Although the definitive evidence of a beneficial effect of resuscitative hypothermia for the mitigation of neurologic ischemic and anoxic damage is still lacking, with only small patient numbers reported and lack of prospective, randomized control groups in all reports, the concept holds the potential of being the first direct therapy for the brain after cardiac arrest apart from hemodynamic stabilization.

Mild hypothermia of 33 to 34°C seems to be a sufficient compromise between beneficial effects through mitigation of ischemic membrane damage and reperfusion injury and the risk of adverse effects through arrhythmic, inflammatory, hemodynamic, and coagulation disorders.

Hyperthermia is not tolerable any longer in the course of intensive care treatment after cardiac arrest; temperature control to normothermia with antipyretic drugs is the least that should be done.

If the European Hypothermia after Cardiac Arrest Multicenter Trial or any other large-scale, randomized, controlled clinical trial in humans turns out to provide sufficient evidence for the beneficial effect of hypothermia, a discussion should take place about whether withholding the application of hypothermia is ethically justified.
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