CME Cerebral Resuscitation After Cardiocirculatory Arrest

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Cardiopulmonary resuscitation can restore spontaneous circulation in up to 50% of patients suffering from cardiac arrest. However, most of these patients still die during the postresuscitation period. Mortality is largely due to neuronal injury after global cerebral ischemia. There is, therefore, a clear need for therapies, which restore and protect brain function after cardiac arrest. Several years ago, mild therapeutic hypothermia was introduced into clinical practice. It represents the first treatment to improve both survival and neurological outcome of patients after out-of-hospital cardiac arrest, according to randomized clinical trials. In addition to therapeutic hypothermia, various other therapeutic options are currently being investigated experimentally and/or clinically. These include thrombolytic therapy, specific infusion regimens, or antiapoptotic drugs. In this article, we review both the pathophysiological background and the efficacy of different measures that might be useful for cerebral resuscitation.

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Cardiac arrest occurs frequently and is still often fatal. Nationwide registries are presently being installed[1,2]; however, data extrapolated from single studies suggest that resuscitation is attempted in about 500,000 individuals each year in North America and in the same number in the European Union.[3–5] Spontaneous circulation can be restored in 20%–50% of these patients[3,4] (Fig. 1). Unfortunately, although, many of these patients still die during the postresuscitation period. Two percent to 15% of patients who are resuscitated after out-of-hospital cardiac arrest are discharged alive from the hospital. Most deaths during the postresuscitation period can be attributed to neuronal damage, which develops as a consequence of global cerebral ischemia during cardiac arrest.[6] Furthermore, 40%–50% of surviving patients suffer from permanent impairment of cognitive functions, such as memory, attention, and executive functioning.[7,8]

Multistage algorithms have been developed for cardiopulmonary resuscitation (CPR); however, when it comes to cerebral resuscitation, i.e., restoring and protecting brain function after cardiac arrest, our possibilities are still limited. The purpose of this article is to review different approaches to cerebral resuscitation. These include not only mild therapeutic hypothermia, which is the current clinical standard, but also various experimental methods which might find their way to the clinic in the future.

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PATHOPHYSIOLOGY OF CARDIAC ARREST

Cascades of Death

Cardiac arrest is a state of global ischemia and the brain is extremely susceptible to this condition. Only 5–6 s after the onset of circulatory arrest, the patient loses consciousness.[9] Without a supply of blood, cerebral tissue oxygen tension declines continuously reaching 0 after about 2 min.[10] Simultaneously, neuronal energy in terms of adenosine triphosphate is depleted and metabolites, such as adenosine, lactate, and hydrogen ions, accumulate in the cells.[11,12] Dysfunction of the cell membrane ion pumps leads to a severe breakdown in cellular homeostasis. One particular consequence is a massive accumulation of calcium in the cell cytosol when calcium efflux pumps fail, voltage-gated calcium channels open, and ligand-gated channels are activated by released excitatory amino acids, such as glutamate and aspartate.[13,14] This calcium overload is considered a key factor in cellular toxicity.[15]

If the ischemia persists long enough, neuronal necrosis ultimately ensues throughout the brain.[16] However, neuronal energy is recovered rapidly upon reperfusion because of CPR and return of spontaneous circulation.[11,12] Therefore, reperfusion does stop neuronal degeneration to a certain degree; yet it does not necessarily completely restore function. During reperfusion, free radicals form when the oxygen supply is restored, which might even aggravate cellular damage.[17] The main characteristic of the reperfusion period is that refueling adenosine triphosphate gives the cell the opportunity to actively react to the damage. This is associated with the expression of immediate early genes, a complex machinery involving both cell

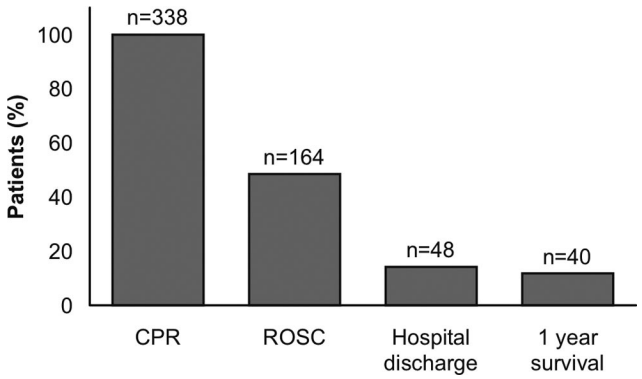

Figure 1. Outcome after cardiopulmonary resuscitation (CPR). The study included 338 patients suffering from out-of-hospital cardiac arrest of cardiac etiology. ROSC = restoration of spontaneous circulation.[3]

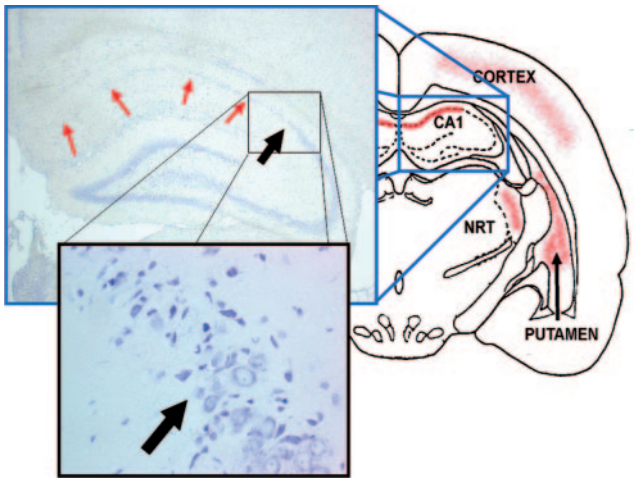

Figure 2. Selectively vulnerable areas of the rat brain. Neuronal degeneration after cardiac arrest is seen particularly in the CA-1 sector of the hippocampus, the nucleus reticularis thalami (NRT), the putamen, and distinct layers of the cortex. Neurons of the hippocampus are visualized by Nissl staining. The black arrow indicates the border between degenerated neurons in the CA-1 sector (red arrows) and the adjacent, less vulnerable CA-2 sector.[128]

survival and cell death cascades.[18–21] The morphological correlate of "subnecrotic" cellular damage is delayed neuronal death, which shows typical signs of apoptosis and occurs mainly in so-called selectively vulnerable brain areas such as the CA-1 sector of the hippocampus, the nucleus reticularis thalami or distinct layers of the cortex[18–20] (Fig. 2).

Cerebral Circulation Disorders

Return of cardiac function does not automatically restore normal cerebral circulation. Depending on the duration of the ischemic period, cerebral vessel dysfunction develops, which likely contributes to neuronal damage. Experimentally, different phenomena can be distinguished. First, reperfusion fails completely in circumscribed areas of the brain (no-reflow phenomenon).[22–24] These areas increase with the duration of ischemia.[22,24] No-reflow is probably caused by capillary congestion because of edema of endothelium and perivascular glia,[25] blood cell sludging,[26,27] leukocyte adhesion,[25,28] and disseminated intravascular coagulation.[26,29–31]

Local no-reflow is paralleled by global cerebral hyperemia during the early period of reperfusion.[32,33] This is probably caused by the accumulation of metabolites such as adenosine, lactate, or hydrogen ions during ischemia,[12] which are potent vasodilators. However, within the first hour after reperfusion, reactive hyperermia is followed by a global reduction in cerebral blood flow (delayed hypoperfusion).[32–34] This phenomenon is probably caused by cerebral vasospasms because of dysfunctional nitric oxide and endothelin metabolism.[35–37]

Systemic Sequelae

In addition to primarily cerebral injury, ischemic damage also occurs, of course, in other vital organs, leading to so-called postresuscitation disease.[38] Typically, myocardial function is markedly reduced after circulation is restored.[39–41] Both systolic contractility and diastolic relaxation are impaired, leading to pronounced hemodynamic instability. The underlying pathophysiology of this myocardial stunning is often complex. Like the brain, the myocardium is particularly susceptible to the state of global ischemia.[42] Additionally, as the cause of cardiac arrest is often of cardiac origin (e.g., 50%–70% of patients have myocardial infarction), this exacerbates the damage to the heart.[40] Even therapeutic interventions during CPR could cause further damage to the heart, namely, electrical defibrillation[43] and administration of epinephrine.[44]

Cardiac arrest induces systemic inflammation, whereby leukocytes and complement are activated and levels of cytokines increased.[45,46] Furthermore, coagulatory cascades are activated immediately but without concomitant stimulation of endogenous fibrinolysis.[29,47]

Pathological changes in the different organ systems can further affect one another. Activation of coagulation contributes to cerebral no-reflow.[26,29–31] Systemic inflammation impairs myocardial function.[48] Hemodynamic instability worsens cerebral perfusion, because autoregulation of the cerebral vessels is often defective after cardiac arrest.[49] Moreover, and irrespective of all the specific interactions, the simple truth is that the brain will only survive if the rest of the body does.

BASIC THERAPEUTIC GOALS

After ischemia the brain is highly susceptible to disturbances in general physiological homeostasis.[49–51] The first goal of all therapeutic measures should be to establish an optimal environment for cerebral recovery. The international guidelines on CPR recommend maintaining normotension, normoglycemia, and normocapnia.[52,53] However, "normal" target values originate from healthy individuals. We do not entirely know whether they are always ideal

for the injured brain too, or whether we must do even better.

Concerning arterial blood pressure, animal experimental data suggest that increasing blood pressure might improve outcome.[54] This might be due to impaired cerebral autoregulation after ischemia.[49] However, no data in this regard are available from clinical studies.

Concerning blood glucose levels, van den Berghe et al.[55] showed that tight glucose control (80–110 mg/dL vs 180–200 mg/dL) improved outcome in the critical care setting. However, recent studies focusing on patients after cardiac arrest suggest that only slightly elevated blood glucose (<150 mg/dL) might not be associated with worsened outcome.[56,57] It is possible that during tight glucose control with insulin, periods of hypoglycemia that could impair outcome might not be recognized.

MILD THERAPEUTIC HYPOTHERMIA

Hypothermia has been used therapeutically in cardiac and neurosurgery for more than 50 yr to protect the brain from ischemia. The first reports of postischemic therapeutic hypothermia were published in the late 1950s.[58–60] Systematic investigations were initiated in the late 1980s and have produced a vast amount of both experimental and clinical data showing beneficial effects of mild therapeutic hypothermia after cardiac arrest.[61–71] Evidence is provided in particular by two major randomized clinical trials that were published in 2002.[61,68] Both studies investigated mild therapeutic hypothermia in comatose adult patients after out-of-hospital cardiac arrest because of ventricular fibrillation.

The European multicenter trial conducted by the Hypothermia After Cardiac Arrest study group included 275 patients, of whom 137 were cooled to 32°C–34°C for 24 h while body temperature in the control group was not decreased.[68] Regarding outcome at 6 mo, mortality was reduced by 26% (41% vs 55%, $P = 0.02$) and the portion of patients with favorable neurological outcome increased by 40% (55% vs 39%, $P = 0.09$) (Fig. 3).

The Australian trial by Bernard et al.[61] covered 77 patients; hypothermia of 33°C for 12 h was applied in 43 patients. At hospital discharge, the likelihood for good neurological outcome was 85% higher in the hypothermic group (49% vs 26%, $P = 0.046$).

In a subsequent individual patient data meta-analysis, Holzer et al.[72] calculated the number-needed-to-treat to allow one additional patient to leave the hospital with no or only minimal neurological damage to be six. As a consequence, the International Liaison Committee on Resuscitation recommended in 2003 that mild therapeutic hypothermia be used in comatose adult patients after out-of-hospital cardiac arrest because of ventricular fibrillation.[73] This recommendation was implemented into the revised international guidelines on CPR in 2005[52,53] (Table 1). In fact, mild therapeutic hypothermia currently represents the only measure which has proven efficacy in cerebral resuscitation. However, it is still underused in many hospitals.[74,75]

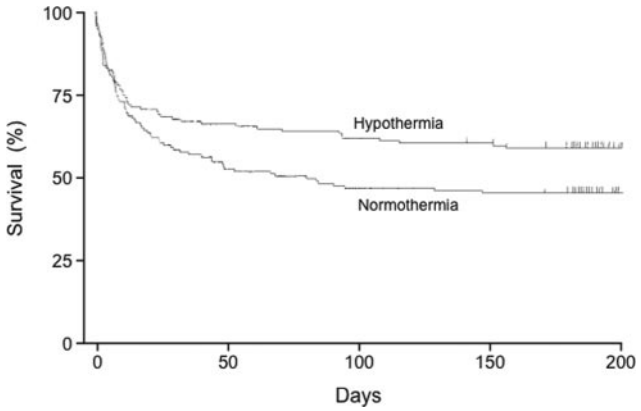

Figure 3. Mild therapeutic hypothermia and outcome after cardiac arrest. The study included 275 patients successfully resuscitated after out-of-hospital cardiac arrest because of ventricular fibrillation. Patients in the hypothermia group were cooled to 32°C–34°C for 24 h.[68]

Table 1. Indications for Mild Therapeutic Hypothermia[53]

Unconscious adult patients with spontaneous circulation after out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C–34°C. Cooling should be started as soon as possible and continued for at least 12–24 h.
Induced hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a nonshockable rhythm or cardiac arrest in hospital.
A child who regains a spontaneous circulation but remains comatose after cardiopulmonary arrest may benefit from being cooled to a core temperature of 32°C–34°C for 12–24 h.

A variety of physiological effects that are exerted by mild therapeutic hypothermia underlie the efficacy of this therapy. Hypothermia reduces metabolism, and thus cerebral oxygen demands.[76] There is a decrease in reactive oxygen species[77] and excitatory amino acids[78,79] during hypothermia as well as direct inhibition of apoptosis.[80] Furthermore, inhibition of coagulation cascades[81] and inflammatory reactions[82] might improve cerebral reperfusion. Finally, hypothermia alters gene expression in a complex manner, e.g., by enhancing the expression of brain-derived neurotrophic factor (BDNF)[83] or the antiapoptotic protein Bcl-2,[84] whereas suppressing the proapoptotic protein Bax[84] or matrix metalloproteinase-9.[85] Mild therapeutic hypothermia, therefore, acts broadly on different sequelae of cardiac arrest at the same time, which makes it the current clinical standard in cerebral resuscitation.

Hypothermia can be induced by different methods, e.g., surface cooling, ice-cold infusions or endovascular cooling catheters. Although there are great differences in efficacy and invasiveness among them, it is

currently not clear whether one particular technique should be preferred to the others. No studies are available that have compared different cooling devices with respect to "hard" clinical end points, i.e., mortality and morbidity.

However, it is commonly accepted and recommended by the guidelines that hypothermia should be initiated with minimal delay after cardiac arrest.[52,53] Surface cooling or ice-cold infusions can be used preclinically. Kim et al.[86] conducted a randomized clinical trial in which patients were assigned to either receiving 4°C normal saline or not in the out-of-hospital setting. After arrival at the hospital, patients were treated according to the local preferences, i.e., patients were cooled or not regardless of the randomization. Survival rates tended to be higher in patients who had received out-of-hospital cooling treatment.

Possible adverse effects of hypothermia include electrolyte and intravascular volume changes, impaired immune defense and impaired coagulation. However, these complications can usually be managed by intensive care strategies. The two large randomized clinical trials did not find a significant increase in severe complications when compared with normothermia.[61,68] The safety of hypothermia treatment has also been confirmed by newer observational studies.[87]

Therapeutic hypothermia continues to be one of the most important topics in clinical resuscitation research today. Questions that still need to be addressed include establishing the indications for therapeutic hypothermia (intrahospital cardiac arrest and treatment in children) and cooling characteristics (target temperature, cooling rate, and duration of hypothermia) and cooling methods (external or internal). Several current clinical trials are focusing on these issues. To name only two, a trial in Germany is investigating therapeutic hypothermia in in-hospital cardiac arrest ($n = 440$),[88] whereas a trial being conducted in France is comparing endovascular and surface cooling in a randomized fashion ($n = 400$).[89]

AMELIORATING MICROCIRCULATION

Thrombolysis

There are two underlying rationales for using thrombolytics during CPR. First, cardiac arrest is caused by acute myocardial infarction or pulmonary embolism in 50%–70% of patients.[90–92] In these two situations, thrombolysis represents a causal and standard therapy. Second, there is evidence that coagulation disorders are involved in the no-reflow phenomenon, and thus in impaired cerebral circulation after cardiac arrest. Cardiac arrest leads to activation of coagulation without adequate fibrinolysis.[29,47] Microscopic examination of cerebral vessels shows that multiple microemboli develop during cardiac arrest and resuscitation.[26] Although this was not known in detail in the 1950s, Crowell et al.[30,93] had already shown at that time that pretreatment with heparin or streptokinase improved survival in dogs after cardiac arrest. Then, 40 yr later, Fischer et al.[31] demonstrated a strong reduction in cerebral no-reflow in cats by postarrest thrombolytic treatment with plasminogen activator and heparin.

Clinical investigations have been less conclusive thus far. Several small studies suggest that thrombolysis during CPR might be beneficial, particularly in patients with pulmonary embolism, but also in those who suffer myocardial infarction.[94–97] Randomized clinical trials investigating a general use of thrombolytics during CPR have produced differing results. Whereas Fatovich et al. found an increase in resuscitability (35 patients randomized), Abu-Laban et al. did not find any benefits from thrombolytics (233 patients randomized).[98,99] The largest amount of data are provided by the European multicenter Thrombolysis in Cardiac Arrest trial.[100] After inclusion of 1050 patients, the study was prematurely halted, because preliminary findings indicated that there was no likely benefit of thrombolytic therapy over placebo. Further analyses are expected soon. Nevertheless, all studies have consistently shown that thrombolysis during CPR is largely safe and not associated with increased bleeding complications.[98,99]

Thrombolytic therapy during CPR was included in international CPR guidelines in 2005 but only when pulmonary embolism[52,53] or myocardial infarction[53] is suspected.

Hypertonic, Hyperoncotic Infusions

A different approach to promoting microcirculation is the use of special infusion regimens which improve the rheological characteristics of the blood. After initial experiments with dextran 40 or isotonic saline,[101,102] current research is focusing on hypertonic-hyperoncotic NaCl/hydroxyethyl starch (HES) solutions. Several animal studies have shown that hypertonic-hyperoncotic solutions given during CPR, or immediately after restoration of spontaneous circulation, decrease cerebral no-reflow.[31,103,104] Some studies also investigated markers of neuronal damage. Krieter et al.[105] found a decrease in release of astroglial protein S-100 after cardiac arrest in pigs after therapy with hypertonic-hyperoncotic infusion. Noppens et al.[104] found improvements in both neurological deficit scores and brain histology in rats. Besides having positive effects on cerebral microcirculation, hypertonic saline also seems to ameliorate cardiac function during and after CPR.[105–107]

Up to now, one clinical trial has been published on the effect of hypertonic-hyperoncotic solutions in CPR.[108] Bender et al. randomized 66 patients who suffered out-of-hospital cardiac arrest into two groups. The patients received 2 $mL \cdot kg^{-1} \cdot 10\ min^{-1}$ of either hypertonic saline with HES (7.2% NaCl with 6% HES 200,000/0.5) or HES alone during continuous CPR. Resuscitation success tended to be higher in patients receiving hypertonic saline with HES (66.7%

vs 51.5%, $P = 0.21$) and hospital admission rates were also increased (57.6% vs 39.4%, $P = 0.14$). There were no severe side effects of hypertonic saline. However, larger clinical trials are needed to further elucidate the short- and long-term effects of hypertonic-hyperoncotic solutions after cardiac arrest.

Although hypertonic-hyperoncotic infusions hold potential for clinical use, hypothermia and thrombolysis already represent, at least in part, clinical routine for resuscitation. Thus, it would seem logical to combine these different approaches. However, each combination must first be carefully evaluated and experimental studies are still sparse. Lin et al.[109] showed that dextran 40 and streptokinase synergistically improved cerebral recovery in dogs with cardiac arrest as measured by electroencephalogram activity. Safar et al.[110] combined dextran 40 with hypothermia and arterial hypertension in dogs with cardiac arrest. This combination produced the best functional and histological outcome these investigators had ever experienced in that particular model in 15 yr of research, including experiments in which the animals had received dextran, hypothermia, or hypertension alone. Although there is still a long road ahead, these experiments suggest that the future might lie in combined therapies.

INFLUENCING APOPTOSIS

Inhibitors of Apoptosis

It has been suggested that delayed neuronal death after cardiac arrest is caused by apoptosis.[18,19] Apoptosis is characterized by activation of proteolytic cascades, which ultimately result in degradation of cellular components. The proteolytic enzyme, caspase 3, is one of the key executioners of apoptosis. Therefore, it seemed reasonable that neuronal damage after cardiac arrest could be ameliorated by inhibiting caspase 3.

This question was first addressed by Chen et al.[19] In a rat model of global cerebral ischemia produced by four-vessel occlusion, they investigated the effects of the caspase 3 inhibitor Z-DEVD-FMK. After 7 days of reperfusion, they found an increased number of surviving cells in the selectively vulnerable CA-1 sector of the hippocampus along with a decrease in apoptotic cells in CA-1. However, other groups failed to reproduce neuroprotective effects of this or other caspase inhibitors in experimental global cerebral ischemia or cardiac arrest.[111–113]

It is now thought that the pathophysiology of neuronal degeneration is too complex to be reduced to only one molecule. There are probably various other "key" effectors independent of the caspases. One particular target is the calpain proteolytic system.[114,115] It has been shown that inhibiting both calpains and caspases produces a synergistic effect in preventing neuronal damage after global cerebral ischemia.[115] However, inhibition of apoptotic cascades is still a highly experimental endeavor. Additional studies are required to further elucidate the therapeutic effects of specific interventions.

Growth Factors

Apoptotic cell death is highly regulated. Physiologically, a variety of apoptosis-inducing factors are counterbalanced by different antiapoptotic, i.e., survival, factors. In pathological settings such as cerebral ischemia, apoptosis is induced by a massive release of death signals such as that from mitochondrial *cytochrome c*.[116] Theoretically, if it were possible to amplify survival factors in the same way, cell death should be prevented. Such an approach might be initiated by administering growth factors, which have antiapoptotic properties. Interestingly, endogenous nerve growth factor (NGF) and BDNF are upregulated in neurons after cerebral ischemia[20]; the expression of BDNF is even enhanced by therapeutic hypothermia.[83] Administration of exogenous growth factors after cerebral ischemia has produced inconclusive results.

One of the first such studies was conducted by Shigeno et al.[117] They gave NGF or vehicle intracerebroventricularly before and after induction of global cerebral ischemia in gerbils (four-vessel occlusion). After 1 wk of reperfusion, a significant reduction in neuronal cell death was observed in CA-1 in both NGF pre- and posttreatment groups. However, subsequent work suggested that this treatment effect was transient and diminished after 4 wk, leading to the same degree of neuronal degeneration in NGF- and vehicle-treated animals.[118]

Kiprianova et al.[119] investigated postischemic intracerebroventricular infusion of BDNF in rats with global cerebral ischemia (four-vessel occlusion). This treatment regimen completely prevented neuronal death in CA-1 after 7 days of reperfusion. In contrast, Popp et al.[120] failed to show any beneficial effects of BDNF after cardiac arrest in rats.

Similarly conflicting results have been reported for other growth factors such as insulin-like growth factor I,[121,122] granulocyte colony-stimulating factor[123,124] or erythropoietin.[125–127] Although some groups demonstrated positive effects of these growth factors,[122,123,125] others failed to show any benefit for outcome.[121,124,126] In conclusion, it is still not known whether any growth factor is capable of improving outcome after cardiac arrest.

It is certainly too simple to assume that it does not matter whether we reduce cellular death cascades (selectively, for example, with caspase inhibitors or in a much broader way with hypothermia) or activate cellular protection (e.g., with growth factors). Cells in a state of reduced energy and substrate levels might fail to respond to stimulation by growth factors. "Stepping on the gas" under such circumstances might perhaps even accelerate degeneration.

SUMMARY

Neuronal injury is one of the key factors in determining outcome after cardiac arrest. Cerebral resuscitation starts with rapid restoration of spontaneous circulation by immediate CPR and defibrillation and continues in the postresuscitation period. Basic measures consist of good critical care practice, such as maintaining normotension, normoglycemia, and normocapnia. In addition, several more specific postresuscitation treatment options have been explored in recent years. All therapies for cerebral resuscitation must face the challenge presented by the complex pathophysiological network, which is activated by global ischemia. An effective therapy should act on multiple pathways simultaneously. This is what therapeutic hypothermia does. Two large randomized clinical trials have proven that mild therapeutic hypothermia is effective in improving both survival and neurological outcome of patients after out-of-hospital cardiac arrest. Mild therapeutic hypothermia of 32°C–34°C for 12–24 h is, therefore, clearly recommended by the 2005 international guidelines on CPR. Other cerebral resuscitation approaches are currently being investigated experimentally and/or clinically. Thrombolytic therapy, specific infusion regimens, or antiapoptotic drugs might perhaps complement mild therapeutic hypothermia in the future.

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