Brain function after resuscitation from cardiac arrest
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Purpose of review
In industrial countries the incidence of cardiac arrest is still increasing. Almost 80% of cardiac arrest survivors remains in coma for varying lengths of time and full cerebral recovery is still a rare event. After successful cardiopulmonary resuscitation, cerebral recirculation disturbances and complex metabolic postreflow derangements lead to death of vulnerable neurons with further deterioration of cerebral outcome. This article discusses recent research efforts on the pathophysiology of brain injury caused by cardiac arrest and reviews the beneficial effect of therapeutic hypothermia on neurologic outcome along with the recent approach to prognosticate long-term outcome by electrophysiologic techniques and molecular markers of brain injury.

Recent findings
Recent experimental studies have brought new insights to the pathophysiology of secondary postischemic anoxic encephalopathy demonstrating a time-dependent cerebral oxidative injury, increased neuronal expression, and activation of apoptosis-inducing death receptors and altered gene expression with long-term changes in the molecular phenotype of neurons. Recently, nuclear MR imaging and MR spectroscopic studies assessing cerebral circulatory recovery demonstrated the precise time course of cerebral reperfusion after cardiac arrest. Therapeutic hypothermia has been shown to improve brain function after resuscitation from cardiac arrest and has been introduced recently as beneficial therapy in ventricular fibrillation cardiac arrest.

Summary
Electrophysiologic techniques and molecular markers of brain injury allow the accurate assessment and prognostication of long-term outcome in cardiac arrest survivors. In particular, somatosensory evoked potentials have been identified as the method with the highest prognostic reliability. A recent systematic review of 18 studies analyzed the predictive ability of somatosensory evoked potentials performed early after onset of coma and found that absence of cortical somatosensory evoked potentials identify patients not returning from anoxic coma with a specificity of 100%.

Keywords
cardiac arrest, cerebral oxidative injury, molecular markers, somatosensory evoked potentials, therapeutic hypothermia

Introduction
The incidence of out-of-hospital cardiac arrest is estimated between 36 and 128 per 100,000 subjects per year [1]. In these victims, cardiopulmonary resuscitation efforts are made in as many as 86%, and return of spontaneous circulation can be achieved in 17 to 49% [2••]. In patients who are initially resuscitated, hypoxic–ischemic brain damage is the leading cause of morbidity and mortality. Almost 80% of patients who initially survive a cardiac arrest remain in coma for varying lengths of time, approximately 40% enter a persistent vegetative state, and 80% are dead at 1 year [3]. Full cerebral recovery is still a rare event. Even in select patients with a witnessed cardiac arrest after ventricular fibrillation and an estimated interval no longer than 15 minutes between cardiac arrest and advanced cardiac life support, mortality at 6 months is between 40 and 55% [4••].

After successful cardiopulmonary resuscitation and restoration of spontaneous circulation, complex secondary cerebral postreflow derangements lead to impaired cerebral reperfusion and to the death of vulnerable neurons, with further deterioration of cerebral outcome [5••]. Recent research has been focused on the pathophysiologic as well as the therapeutic aspects of this secondary postischemic–anoxic encephalopathy. This review provides a brief overview of the pathophysiologic of brain injury caused by cardiac arrest and resuscitation, and discusses clinical manifestations of postresuscitation brain dysfunction along with the approach to assess and prognosticate long-term outcome in cardiac arrest survivors.

Pathophysiology of brain injury caused by cardiac arrest
A stop of cerebral circulation depletes the neuronal oxygen stores within 20 seconds and lead to unconsciousness of the individual. Within 5 minutes of complete cerebral anoxia, brain glucose and ATP stores are lost. The con-
secutive dysfunction of neuronal membrane pumps and membrane depolarization leads to influx of calcium, lactate acidosis, glutamate release, occurrence of free fatty acids, and excitatory amino acids [6••]. Oxidative stress induced by free radicals and cerebral eicosanoid formation indicating inflammatory response leading to neuronal damage has been reported [6••]. A recent experimental cardiac arrest model demonstrates a time-dependent maximum increase of 8-iso-PGF2-α, indicating oxidative injury immediately after restoration of spontaneous circulation [7•]. This increase was greatest in animals subjected to the longest period of no or low blood flow and demonstrates a time-dependent cerebral oxidative injury in cardiac arrest [7•]. These results were supported by the positive effect of a free radical scavenger, which resulted in less cerebral oxidative stress, possibly by promoting normal distribution of cerebral blood flow [8•]. Reoxygenation-induced chemical reactions, which are partly based on free radical-triggered injury cascades, are followed by delayed excitotoxicity in selectively vulnerable neurons [6••]. This could lead to delayed calcium loading and consecutively to lipid peroxidation of membranes and primary necrosis, or triggering of programmed cell death (apoptosis). Recently, for the first time, a possible role of the apoptosis-inducing death receptor Fas/CD95 and Fas ligand has been demonstrated in global cerebral ischemia [9•]. Three hours after experimental cardiac arrest, an increased expression of the Fas ligand in the thalamus was observed. Such an neuronal expression may lead to a significant activation of the apoptosis-inducing death receptor Fas/CD95 [9•].

Preservation of intact neuronal function is also severely compromised by cerebral recirculation disturbances [5••]. Immediately after cerebral anoxia, a transient phase of reactive global hyperemia resulting from vasoparalysis persisted for 15 to 30 minutes. Thereafter, a prolonged global and multifocal cerebral hyperperfusion was present for 2 to 12 hours. Activation of endothelin-1 is involved in this cerebral hemodynamic disturbance [10]. A selective endothelin receptor antagonist reverses posts ischemic hyperperfusion after global cerebral ischemia and leads to an improved neurologic recovery in rats [10]. In contrast, a recent experimental trial in pigs demonstrated that endothelin-1, a nonadrenergic vasoconstrictor, elevates regional cerebral perfusion during cardiopulmonary resuscitation and enhances cerebral blood flow better than adrenaline [11•]. However, the effect of endothelin-1 on the posts ischemic circulation is still unknown. A recent study assessing cerebral circulatory recovery after cardiac arrest by perfusion and diffusion-weighted nuclear MR imaging and MR spectroscopy demonstrates the precise time course of cerebral reperfusion [12•]. After 20 minutes of cardiac arrest, the posts ischemic flow pattern demonstrates an initial hyperperfusion after 30 minutes of recirculation followed by delayed hypoperfusion after 4 hours. These variations of regional cerebral blood flow were reliably monitored both in the cortex and in the basal ganglia [12•]. The authors could also demonstrate that initial cerebral recirculation could be improved by hypertonic and hypothermic therapy, whereas this therapy failed to mitigate delayed hypoperfusion [12•]. MR spectroscopic measurements of lactate revealed a prolonged preservation of anoxic cerebral anaerobic metabolism. A positron emission tomographic study in eight patients with severe posthypoxic encephalopathy indicated, even 24 hours after resuscitation, a marked decrease of cerebral metabolic activity [13]. The gray matter glucose consumption was 54% of normal values, whereas white matter uptake of glucose was 70% of normal [14].

Distinct regions of the brain (hippocampus, neocortex, and cerebellum) exhibit a special vulnerability to ischemia. This seems to be, among other causes, the result of altered immediate/early gene expression and long-term changes in the molecular phenotype of these neurons [14]. A recent report demonstrates dysfunction of the unfolded protein response [15•]. Endoplasmic reticulum stress, seen after brain ischemia and reperfusion, triggers the unfolded protein response and leads to a compensatory response of sensor proteins. These proteins were decreased after cardiac arrest in the rat brain by 80% in the cortex and by 50% in the brainstem and hippocampus [15•]. Dysfunction of the unfolded protein response results in increased cell death and may play an important key factor in reperfusion neuronal dysfunction [15•]. Recently, in experimental models of cardiac arrest, gene therapy using neurotropic viral vector systems leads to a transfer of protective genes to neurons [16••]. This gene overexpression, in particular the antiapoptotic protein BCL-2, enhances neuronal survival by protecting neurons from apoptotic death. BCL-2 overexpression was also found in therapeutic hypothermia [16••], which has been clinically shown to be beneficial in cardiac arrest survivors [4••,17••].

**Therapeutic hypothermia in cardiac arrest**

Two landmark studies published 2002 in the New England Journal of Medicine clearly demonstrate the beneficial effect of mild therapeutic hypothermia on neurologic outcome in cardiac arrest survivors [4••,17••]. In one study favorable neurologic outcome was achieved by therapeutic hypothermia (target temperature, 32 to 34°C) in 55% and in the normothermia group in 39% (corresponding results in the other study were 49% in the hypothermia group and 26% in the normothermia group) [4••,17••].

Therapeutic hypothermia has different chemical and physical cerebral effects by preventing or mitigating secondary cerebral postflow derangements [18••]. The multifactorial processes of therapeutic hypothermia leading to neuronal protection includes inhibition of biosyn-
thesis, release and uptake of different neurotransmitters, reduction of damage to the blood–brain barrier, preservation of ATP stores, mitigation of free oxygen radicals, beneficial effects on low-flow regions during reperfusion by reducing oxygen needs without impairing microvasculature flow, inhibition of the accumulation of lipid peroxidation, attenuation of brain edema and of intracellular acidosis, and improvement of postischemic cerebral microcirculation [2••,5••,6••,18••]. A recent, prospective, randomized trial demonstrates decreased levels of neuron-specific enolase, a marker of hypoxic brain injury, in patients after successful cardiac arrest compared with a normothermia group of patients [19•]. A decrease in neuron-specific enolase values between 24 and 48 hours after cardiac arrest was observed in 88% of patients treated with hypothermia and was associated with favorable cerebral outcome [19•]. Interestingly, the S-100B protein, also known to be a prognostic parameter of cerebral outcome after cardiac arrest, did not differ between the hypothermia group and the normothermia group [19•].

The optimal duration and temperature of therapeutic hypothermia as well as different cooling techniques still remain the subject of investigation [2••]. An experimental series of studies in dogs recently revealed that profound cerebral hypothermia with a target tympanic temperature of 10°C achieved survival without functional or histologic brain damage even after cardiac arrest with no flow of 60 and 90 minutes [20•]. So far, most clinical trials used surface cooling, with the disadvantage of relatively slow decreases of core temperature. In a recent preliminary trial in 22 cardiac arrest survivors, hypothermia could be rapidly induced without adverse effects using intravenous infusion over 30 minutes with 30 mL/kg ice-cold (4°C) lactated Ringer solution [21]. This rapid infusion resulted in a significant decrease in median core temperature of 1.6°C.

Also, therapeutic hypothermia after cardiac arrest improves neurologic outcome and should be recommended for all comatose patients admitted to the emergency room or the intensive care unit after a ventricular fibrillation cardiac arrest. Several issues with regard to therapeutic hypothermia are still unknown and should be the aim of further resuscitation research.

**Neurologic outcome prediction in cardiac arrest survivors**

A variety of clinical parameters, neurologic examination models, biochemical tests, and neuroimaging and electrophysiologic techniques has been proposed for prognostic evaluation of brain function in comatose cardiac arrest survivors. So far, more than 100 different parameters have been studied with respect to the detection of cerebral hypoxia. Based on the results of scientific publications and after critical evaluation, the members of the Austrian interdisciplinary consensus conference identified 26 parameters that allow a prognostic evaluation [22•]. Among these parameters, however, the strength of evidence and the level of recommendation vary widely.

A systematic review, published in the *Lancet* identified recording of somatosensory evoked potentials (SEPs) as the method with the highest prognostic reliability [23]. Only recently have SEPs become the most frequently applied method in clinical as well experimental studies evaluating outcome after cardiopulmonary resuscitation. Specifically, bilateral absence of median nerve-stimulated SEPs is, in the literature, uniformly associated with unfavorable outcome, because widespread cortical necrosis is required to obliterate cortical SEP peaks. Recently, a systematic review of 18 studies analyzed the predictive ability of SEPs acquired early after onset of coma in 1136 adult patients with hypoxic–ischemic encephalopathy [24••]. The results revealed an absence of cortical SEP peaks associated with the likelihood of nonawakening from coma with a high level of certainty. All 336 patients with bilaterally absent cortical N20 SEP peaks did not awake from coma (Fig. 1). The calculated 95% CI is 0 to 1%, which means that adults in coma from hypoxic–ischemic encephalopathy with absent cortical SEP responses have a chance of awakening of less than 1% [24••]. These results were confirmed by two other recent clinical trials that also found that absence of cortical SEP peaks identify patients not returning from anoxic coma, with a specificity of 100% [25•,26•]. However, the presence of cortical N20 SEP responses is not a guarantee for awakening from coma [24••,27]. In these circumstances, recording of long-latency SEPs, in particular the N70 peak, provides additional information on the cortical integrity with high predictive accuracy [3,28]. Cerebral recirculation disturbances and posthypoxic metabolic injury may influence the prognostic ability of SEP recording during the initial hours after cardiac arrest [29]. A substantial improvement of SEP peak latencies has been observed within 24 hours after restoration of spontaneous circulation in most studied patients [29].

**Figure 1. Somatosensory evoked potentials (SEP) in adult comatose patients with hypoxic-ischemic encephalopathy—A systematic review of 18 studies**

electrophysiologic assessment in 305 cardiac arrest survivors demonstrates that the extent of hypoxic–ischemic brain damage increases along the afferent sensory pathway [30•]. This leads to a stepwise decrease of detectable SEP peaks and amplitudes, indicating a pronounced vulnerability of thalamic and cortical brain regions to hypoxia.

During the last few years, serum levels of molecular markers for brain injury have been studied with respect to the detection of the extent of cerebral damage and neurologic outcome in cardiac arrest survivors. In particular, increased serum levels of the neuron-specific enolase, a cytoplasmic enzyme of glycolysis, and the astroglial protein S100, a calcium-binding protein regulating neuronal differentiation and apoptosis, are known to be associated with hypoxic–ischemic brain injury and unfavorable neurologic outcome [31••]. These results were confirmed by three recent clinical studies. In 110 cardiopulmonary resuscitated patients, serum neuron-specific enolase at 24 and 48 hours after cardiac arrest was significantly higher in patients who did not regain consciousness [32•]. No patient with a neuron-specific enolase level more than 25 μg/L at any time regained consciousness. In another study, a decrease in the neuron-specific enolase levels was found in 88% of patients with therapeutic hypothermia and was associated with a better neurologic outcome at 6 months [19•]. Interestingly, these effects were not shown for the S100 protein [19•]. An increase of molecular markers for brain injury may be associated with increased levels of systemic inflammation, because increased S100 protein levels at 12 hours after cardiac arrest could be found to the same extent and time as interleukin-8 levels [33]. The close correlation between hypoxic–ischemic brain injury and endothelial activation and injury has been shown recently [34•]. Patients with unfavorable neurologic outcome had significantly higher von Willebrand factor antigen and soluble intracellular adhesion molecule-1 levels, both known to be excellent markers of endothelial injury. Von Willebrand factor antigen concentrations more than 166% and soluble intracellular adhesion molecule-1 levels more than 500 ng/DL had a 100% specificity for adverse outcome in cardiac arrest survivors [34•]. In addition, serum levels of molecular markers of brain injury are a useful tool for cerebral outcome prediction in cardiac arrest survivors. Determination of precise cutoff levels at different time intervals is needed and should be the aim of further resuscitation research.

References and recommended reading

Papers of particular interest, published within the annual period of review, are highlighted as:

• Of special interest
•• Of outstanding interest


16 Yenari MA, Zhao H, Giffard RG, et al.: Gene therapy and hypothermia for stroke treatment. Ann N Y Acad Sci 2003, 993:54–68. This is an excellent review of gene therapy using neurotrophic viral vector systems for transferring protective genes to neurons. This review also outlines the gene overexpression of antiapoptotic proteins in cerebral ischemia.
This study reports the predictive ability of molecular markers of hypoxic brain injury.


This excellent review ties together the different chemical and physical cerebral effects of therapeutic hypothermia and outlines the improved neurologic outcome after therapeutic cooling.


This study reports the predictive ability of molecular markers of hypoxic brain injury.


This paper presents the results of a consensus conference on the approach to assessing and prognosticating neurologic outcome in cardiac arrest survivors.


This is a preliminary report on a novel technique of inducing rapid hypothermia in comatose patients after cardiac arrest.


This is a preliminary report on the novel technique of inducing hypothermia in comatose patients after cardiac arrest.


This article discusses the influence of profound hypothermia on functional and histologic brain damage in experimental, long-lasting cardiac arrest.


This study supports the high prognostic ability of SEPs in comatose patients after cardiopulmonary resuscitation.


This is a systematic review of the evidence available to date on the predictive value of SEPs in comatose patients.


This report outlines the predictive value of a multimodal approach combining neurobiochemical and electrophysiological techniques in cardiac arrest survivors.


This electrophysiological study outlines the pronounced vulnerability of specific brain regions after global hypoxic–ischemic brain injury.


This is an excellent, comprehensive overview of the most important molecular markers on neurologic outcome prediction in patients after cardiopulmonary resuscitation.


This article demonstrates that high serum levels of neuron-specific enolase predict an unfavorable neurologic outcome.


This study discusses the prognostic value of markers of endothelial activation and injury in patients after cardiac arrest.