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

Curr Opin Crit Care 10:213–217. © 2004 Lippincott Williams & Wilkins

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 pathophysiology 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-

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Current Opinion in Critical Care 2004, 10:213–217

Abbreviation

SEP somatosensory evoked potential

1070-5295

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 programed 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 hypoperfusion 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 postischemic hypoperfusion 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 postischemic 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 postischemic 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 hyperoncotic 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 postreflow 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 blood 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 remains 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.

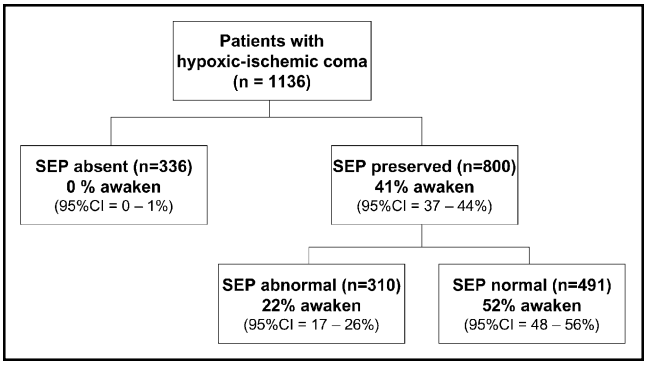
Also, therapeutic hypothermia after cardiac arrest improves neurologic outcome and should be recommended for all comatose patients admitted to the emergency room or the intensive care unit after a ventricular fibrillation cardiac arrest. Several issues with regard to therapeutic hypothermia are still 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 non-awakening 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]. An

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



Adopted from Robinson LR et al. Crit Care Med 2003.

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

1 World Health Organization: The World Health Report 2002: Reducing Risks and Promoting Healthy Life. Geneva: World Health Organization; 2002.

2 •• Holzer M, Sterz F: Therapeutic hypothermia after cardiopulmonary resuscitation. Expert Rev Cardiovasc Ther 2003, 1:317–325.
This is a clear and concise summary of the pathophysiologic mechanisms and management of therapeutic hypothermia in cardiac arrest survivors.

3 Madl C, Kramer L, Domanovits H, et al.: Improved outcome prediction in unconscious cardiac arrest survivors with sensory evoked potentials compared with clinical assessment. Crit Care Med 2000, 28:721–726.

4 •• The Hypothermia After Cardiac Arrest study group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002, 346:549–556.
This landmark study demonstrates the beneficial effect of therapeutic hypothermia on neurologic outcome in cardiac arrest survivors

5 •• Safar P, Behringer W, Böttiger BW, et al.: Cerebral resuscitation potentials for cardiac arrest. Crit Care Med 2002, 30(suppl):140–144.
This review ties together recent findings on pharmacologic and hypothermic cerebral resuscitation, and reports on suspended reanimation for delayed resuscitation.

6 •• Safar P, Behringer W: Brain resuscitation after cardiac arrest. In: Textbook of Neurointensive Care. Edited by Layon AJ, Gabrielli A, Friedman WA. Philadelphia: WB Saunders; 2003:457–498.
This book chapter is an outstanding and comprehensive review of the pathophysiology and complex mechanisms of postischemic–anoxic encephalopathy. The authors also summarize experimental results on cerebral resuscitation efforts.

7 • Basu S, Liu X, Nozari A, et al.: Evidence for time-dependent maximum increase of free radical damage and eicosanoid formation in the brain as related to duration of cardiac arrest and cardio-pulmonary resuscitation. Free Radic Res 2003, 37:251–256.
This experimental paper reports on the oxidative stress response after cardiopulmonary resuscitation.

8 • Liu XL, Wiklund L, Nozari, et al.: Differences in cerebral reperfusion and oxidative injury after cardiac arrest. Acta Anaesthesiol Scand 2003, 47:958–967.
This study demonstrates the positive effect of a free radical scavenger on cerebral oxidative stress after cardiopulmonary resuscitation.

9 • Padosch SA, Popp E, Vogel P, et al.: Altered protein expression levels of Fas/CD95 and Fas ligand–differentially vulnerable brain areas in rats after global cerebral ischemia. Neurosci Lett 2003, 338:247–251.
The study outlines the importance of apoptosis in global cerebral ischemia.

10 Krep H, Fischer M, Hoeft A: The role of endothelin-1 in regional cerebral perfusion during prolonged ventricular fibrillation. Resuscitation 2003, 57:317–318.

11 Holzer F, Sterz F, Behringer W, et al.: Endothelin-1 elevates regional cerebral perfusion during prolonged ventricular fibrillation cardiac arrest in pigs. Resuscitation 2002, 55:317–327.

12 • Krep H, Bottiger BW, Bock C, et al.: Time course of circulatory and metabolic recovery of cat brain after cardiac arrest assessed by perfusion- and diffusion-weighted imaging and MR-spectroscopy. Resuscitation 2003, 58:337–348.
This important study investigates the precise time course of cerebral reperfusion after cardiac arrest.

13 Schaafsma A, de Jong BM, Bams JL, et al.: Cerebral perfusion and metabolism in resuscitated patients with severe post-hypoxic encephalopathy. J Neurol Sci 2003, 210:23–30.

14 Bokesch PM, Marchand J, Seirafi PA, et al.: Immediate–early gene expression in ovine brain after cardiopulmonary bypass and hypothermic circulatory arrest. Anesthesiology 1996, 85:1439–1446.

15 • Kumar R, Krause GS, Yoshida H, et al.: Dysfunction of the unfolded protein response during global brain ischemia and reperfusion. J Cereb Blood Flow Metab 2003, 23:462–471.
This paper documents an experimental study of the influence of altered cerebral gene expression on reperfusion neuronal dysfunction.

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 neurotropic viral vector systems for transferring protective genes to neurons. This review also outlines the gene overexpression of antiapoptotic proteins in cerebral ischemia.

17 Bernard SA, Gray TW, Buist MD, et al.: Treatment of comatose survivors of •• out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002, 346:557–563.
Together with [4••], this outstanding study introduces therapeutic hypothermia as beneficial therapy in ventricular fibrillation cardiac arrest.

18 Sterz F, Holzer M, Roine R, et al.: Hypothermia after cardiac arrest: a treat- •• ment that works. Curr Opin Crit Care 2003, 9:205–210.
This excellent review ties together the different chemical and physical cerebral effects of therapeutic hypothermia and outlines the improved neurologic outcome after therapeutic cooling.

19 Tiainen M, Roine RO, Pettilä V, et al.: Serum neuron-specific enolase and • S-100B protein in cardiac arrest patients treated with hypothermia. Stroke 2003, 34:2881–2885.
This study reports the predictive ability of molecular markers of hypoxic brain injury.

20 Behringer W, Safar P, Wu X, et al.: Survival without brain damage after clinical • death of 60-120 mins in dogs using suspended animation by profound hypothermia. Crit Care Med 2003, 31:1523–1531.
This article discusses the influence of profound hypothermia on functional and histologic brain damage in experimental, long-lasting cardiac arrest.

21 Bernard S, Buist M, Monteiro O, et al.: Induced hypothermia using large vol- • ume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: preliminary report. Resuscitation 2003, 56:9–13.
This is a preliminary report on a novel technique of inducing rapid hypothermia in comatose patients after cardiac arrest.

22 Madl C, Hasibeder W, Lechleitner P, et al.: Prognostic evaluation of cerebral • hypoxia after cardiopulmonary resuscitation–report of the Austrian Interdisciplinary Consensus Conference. Wien Klin Wochenschr 2002, 114:422–427.
This paper presents the results of a consensus conference on the approach to assessing and prognosticating neurologic outcome in cardiac arrest survivors.

23 Zandbergen EGJ, de Haan RJ, Stoutenbeek CP, et al.: Systematic review of early prediction of poor outcome in anoxic-ischaemic coma. Lancet 1998, 352:1808–1812.

24 Robinson LR, Micklesen PJ, Tirschwell DL, et al.: Predictive value of somato- •• sensory evoked potentials for awakening from coma. Crit Care Med 2003, 31:960–967.
This is a systematic review of the evidence available to date on the predictive value of SEPs in comatose patients.

25 Logi F, Fischer C, Murri L, et al.: The prognostic value of evoked responses • from primary somatosensory and auditory cortex in comatose patients. Clin Neurophysiol 2003, 114:1615–1627.
This study supports the high prognostic ability of SEPs in comatose patients after cardiopulmonary resuscitation.

26 Zingler VC, Krumm B, Bertsch T, et al.: Early prediction of neurological out- • come after cardiopulmonary resuscitation: a multimodal approach combining neurobiochemical and electrophysiological investigations may provide high prognostic certainty in patients after cardiac arrest. Eur Neurol 2003, 49:79–84.
This report outlines the predictive value of a multimodal approach combining neurobiochemical and electrophysiologic techniques in cardiac arrest survivors.

27 Madl C, Kramer L, Yeganehfar W, et al.: Detection of nontraumatic comatose patients with no benefit of intensive care treatment by recording of sensory evoked potentials. Arch Neurol 1996, 53:512–516.

28 Madl C, Grimm G, Kramer L, et al.: Early prediction of individual outcome after cardiopulmonary resuscitation. Lancet 1993, 341:855–858.

29 Gendo A, Kramer L, Häfner M, et al.: Time-dependency of sensory evoked potentials in comatose cardiac arrest survivors. Intensive Care Med 2001, 27:1305–1311.

30 Bauer E, Funk GC, Gendo A, et al.: Electrophysiological assessment of the • afferent sensory pathway in cardiac arrest survivors. Eur J Clin Invest 2003, 33:283–287.
This electrophysiologic study outlines the pronounced vulnerability of specific brain regions after global hypoxic–ischemic brain injury.

31 Snyder–Ramos SA, Bottiger BW: Molecular markers of brain damage– •• clinical and ethical implications with particular focus on cardiac arrest. Restor Neurol Neurosci 2003, 21:123–139.
This is an excellent, comprehensive overview of the most important molecular markers on neurologic outcome prediction in patients after cardiopulmonary resuscitation.

32 Meynaar IA, Straaten HM, van der Wetering J, et al.: Serum neuron-specific • enolase predicts outcome in post-anoxic coma: a prospective cohort study. Intensive Care Med 2003, 29:189–195.
This article demonstrates that high serum levels of neuron-specific enolase predict an unfavorable neurologic outcome.

33 Mussack T, Biberthaler P, Kanz KG, et al.: Serum S-100B and interleukin-8 as predictive markers for comparative neurological outcome analysis of patients after cardiac arrest and severe traumatic brain injury. Crit Care Med 2002, 30:2669–2674.

34 Geppert A, Zorn G, Delle–Karth G, et al.: Plasma concentrations of van Wil- • lebrand factor and intracellular adhesion molecule-1 for prediction of outcome successful cardiopulmonary resuscitation. Crit Care Med 2003, 31:805–811.
This study discusses the prognostic value of markers of endothelial activation and injury in patients after cardiac arrest.