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Neurological prognostication after cardiac arrest—Recommendations from the Swedish Resuscitation Council

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ABSTRACT

Cardiopulmonary resuscitation is started in 5000 victims of out-of-hospital cardiac arrest in Sweden each year and the survival rate is approximately 10%. The subsequent development of a global ischaemic brain injury is the major determinant of the neurological prognosis for those patients who reach the hospital alive. Induced hypothermia is a recommended treatment after cardiac arrest and has been implemented in most Swedish hospitals.

Recent studies indicate that induced hypothermia may affect neurological prognostication and previous international recommendations are therefore no longer valid when hypothermia is applied. An expert group from the Swedish Resuscitation Council has reviewed the literature and made recommendations taking into account the effects of induced hypothermia and concomitant sedation.

A delayed neurological evaluation at 72 h after rewarming is recommended for hypothermia treated patients. This evaluation should be based on several independent methods and the possibility of lingering pharmacological effects should be considered.

1. Introduction

In Sweden, 10,000 people suffer sudden and unexpected, out-of-hospital cardiac arrest every year. In approximately 5000 of these, cardiopulmonary resuscitation (CPR) is initiated.[1,2] Due to improved pre-hospital care, an increasing number of patients regain spontaneous circulation and are hospitalized for continued treatment.[2] In hospitals, attitudes towards unconscious cardiac arrest patients have undergone a dramatic change. Underlying coronary artery disease is now frequently treated in its acute phase. Moreover, most patients receive adequate intensive care, which often involves hypothermia treatment.[3] Thanks to these improvements, the proportion of patients who survive has increased, although there may be significant differences between hospitals.[4,5] Despite improvements, registration data indicate that the long-term survival rate after out-of-hospital cardiac arrest in Sweden amounts to no more than 10 percent.[1,2]

Once cardiac function has been stabilized, the neurological prognosis depends mainly on the length of time without circulation to the brain. It is estimated that ischaemic brain injury is responsible for 70 percent or more of mortality in patients treated following cardiac arrest.[6–8] Induced hypothermia has been shown to protect the brain in experimental cardiac arrest models.[9] It has become a recommended treatment[10,11] since clinical studies have shown that cooling to 32–34 °C during a 12- to 24-h period decreased mortality and improved neurological function.[12,13] In Sweden, hypothermia treatment is used at most hospitals but it is recognized that the optimal target temperature and duration of treatment are not yet known.[14] Hypothermia treatment is typically continued for 24 h and as a consequence, the patient is sedated and mechanically ventilated, sometimes for several days after normal body temperature has been restored. Patients who regain consciousness spontaneously shortly after the cardiac arrest, as well as those who wake up while sedation is being phased out after completed hypothermia treatment, have a favourable neurological prognosis. These patients are usually able to resume an independent life,

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although minor cognitive difficulties are common.[15] In patients who do not regain consciousness, the prognosis deteriorates with the duration of unconsciousness or coma.[16] A structured neurological prognostication is crucial as a foundation for informing relatives, prioritizing intensive care resources and avoiding futile care in cases where a vegetative state or death can be anticipated.

Neurological prognostication should be founded on available, evidence-based methods. Written local routines should be available at all hospitals treating cardiac arrest patients. US guidelines for prognostication after cardiac arrest, published in 2006 by the American Academy of Neurology (AAN), have had a great impact worldwide.[17] Current international[10] and AAN guidelines have the disadvantage of being primarily based on earlier studies on patients not treated with hypothermia. Thus, these guidelines have limited applicability for the majority of cardiac arrest patients in Sweden. The Swedish Resuscitation Council has commissioned the task force on post resuscitation care to develop national recommendations for neurological prognostication. Members of the task force (TC, HF, SR) have, together with an expert panel (MB, LJL, IR, CR), carried out non-systematized literature reviews within their respective areas of expertise. The final results have been formulated during consensus meetings. It has not been the intention of the group to cover all aspects of available prognostication methods. Our aim has rather been to present a simple, safe and, as far as possible, evidence-based model that can be applied to patients who have or have not received hypothermia treatment after cardiac arrest. This document has been circulated for consideration and comment to the respective Swedish specialist associations for neurology, anaesthesia and intensive care, neurophysiology, and cardiology. The recommendations have previously been published in Swedish in Läkartidningen, the Journal of the Swedish Medical Association[18] and are aimed at all hospital personnel involved in cardiac arrest care and treatment.

2. When should neurological prognostication be carried out?

After just a few minutes of circulatory arrest, all brain functions cease. If circulation is restored, the nervous system will make a gradual recovery. Brainstem reflexes return first, then the motor response to pain and, finally, cortical activity and consciousness.[19] Prolonged circulatory arrest results in more delayed and incomplete recovery. In consequence, non-recovered brainstem reflexes and stereotypic or absent pain reactions in patients with continued unconsciousness gradually become more certain signs of widespread brain injury and an unfavourable neurological prognosis.

In previous guidelines,[11,17] 72 h after cardiac arrest has been established as a suitable time for prognostication. This is because, by that time, several clinical findings can support an unfavourable prognosis with a very high certainty, and patients with a favourable prognosis have typically regained consciousness. Since induced hypothermia changes the conditions for the clinical neurological examination, there is good reason to postpone the final assessment of hypothermia treated patients to at least 72 h after normothermia, which corresponds to approximately 4.5 days after the arrest.

3. What is the prognostic significance of factual circumstances?

Several circumstances related to the cardiac arrest have a clear statistical association with the prognosis. In a nationwide Swedish dataset involving more than 30,000 patients,[20] the following factors were found to be associated with a favourable prognosis (here listed in order of importance): (1) ventricular fibrillation as the first registered rhythm, (2) short wait for an ambulance, (3) cardiac arrest outside the patient's home, (4) witnessed cardiac arrest, (5) cardiopulmonary resuscitation performed by a layperson while waiting for the ambulance, and (6) young age. In the absence of all of these circumstances, the survival rate after one month was only 0.4 percent. The main problem in relation to prognostication, however, is that most of these circumstances are uncertain predictors at the individual level. For example, the exact moment when blood ceased to flow to the brain may be difficult to ascertain, particularly if cardiac arrest occurred after a period of unconsciousness and poor respiration. Moreover, the effectiveness of cardiopulmonary resuscitation is difficult to determine. Information obtained from the ambulance service regarding time may seem exact, but is often based on estimations. The first registered rhythm may be difficult to interpret. In addition, in recent years, an increased survival rate has been observed in connection with asystole[21] and pulseless electrical activity.[22] Therefore, it is always necessary to wait for the factual neurological outcome in each individual case, which should be carefully tested and evaluated using the methods indicated below.

3.1. Findings at the clinical neurological examination

Observation of visible seizures, reactions to painful stimuli and testing of brainstem reflexes are the most important elements of a clinical neurological examination. Absence of pain reactions or an extensor pattern at 72 h after cardiac arrest have previously been considered reliable signs of an unfavourable prognosis.[17] However, several studies have shown that this is not true for all patients who have undergone hypothermia treatment,[23–25] and that one contributory cause may be the lingering effects of analgesia and sedation.[26] Even among patients treated with hypothermia, bilateral absence of pupillary reflexes 72 h after cardiac arrest is a reliable sign of an unfavourable prognosis,[23,24,26,27] but in exceptional cases, bilateral absence of corneal reflexes has been compatible with recovery.[26] Other brainstem reflexes such as the vestibulo-ocular ("doll's eye") reflex, the cough and gag reflexes, and spontaneous breathing pattern are important elements of the assessment, though not equally well documented. Absence of all brainstem functions suggests the possibility of total brain infarction, i.e. clinical brain death, which occurs in a small portion of cardiac arrest patients.[6] Other findings that may suggest total brain infarction are generalized oedema and brainstem herniation on CT or MRI images as well as absence of electrocerebral activity in the electroencephalogram (EEG). Swedish legislation on determination of death in humans stipulates that 33 °C is the lowest body temperature at which death may be declared by establishing total brain infarction using two clinical neurological examinations, so-called direct criteria. If the body temperature is lower, the clinical examinations must be confirmed using conventional cerebral angiography. This also applies when the cause of brain death is unclear or when there is a risk that the patient's brain functions may be metabolically or pharmacologically affected.[28] The latter situation is at hand during ongoing hypothermia treatment, and there is a risk of a lingering pharmacological effect also after normal body temperature has been achieved.

3.2. Neurophysiological methods (EEG/SSEP)

Examination using *somatosensory evoked potentials* (SSEP) involves electrical stimulation of the median nerve at the wrist. Responses are registered over the brachial plexus (N10 potential), and over the contralateral sensory cerebral cortex (N20 potential). In contrast to EEG, SSEP responses are considered robust even when the patient is sedated.[26,29]

Studies carried out prior to the introduction of hypothermia treatment have shown that bilateral absence of N20 at 24 h after

cardiac arrest or later has entailed death or vegetative status with a specificity of nearly 100 percent. In more recent studies of patients treated with hypothermia, specificity has continued to be very high with bilateral absence of N20 responses, provided that the examination is carried out after restoration of normal body temperature.[30,31] Only a few cases of favourable outcome have been reported in patients with absence of the N20 potential.[32,33] The disadvantages of SSEP include low availability outside larger hospitals and limited sensitivity in predicting an unfavourable prognosis, as approximately half of patients with preserved N20 nevertheless have a poor neurological outcome.[29]

Conventional EEG is usually recorded during a 30-min time period using approximately 20 scalp electrodes. Continuous EEG monitoring has been employed to an increasing extent in neurointensive care, often with a reduced number of electrodes and a supplementary trend analysis to facilitate interpretation. The latter method may be used during the hypothermia phase to assess the development of background activity and the presence of epileptiform activity.[34] Alternatively, one or more conventional EEGs may be performed.

Testing reactivity amounts to determining whether different kinds of stimulation, such as verbal address, eye opening or pain, change the patient's background EEG-activity. An absence of reactivity during and after the hypothermia phase is strongly associated with an unfavourable prognosis.[25] An initially flat pattern (<10 μV) during hypothermia treatment is common and thus lacking in prognostic value. In contrast, development of continuous background activity during hypothermia treatment or after the patient has been rewarmed is strongly associated with awakening and a favourable prognosis.[34] A spontaneous burst-suppression (BS) pattern following cardiac arrest entails an unfavourable prognosis in most cases,[34] although satisfactory outcomes have been reported in individual patients.[35,36]

Among the disadvantages of EEG are its sensitivity to medications and lack of a generally accepted classification system for epileptiform activity.

4. Clinical and electrographic seizures

Seizures usually take the form of myoclonic muscle twitches in the face, the trunk or the extremities.[37,38] However, generalized tonic-clonic and focal epileptic seizures also occur. Sedatives routinely administered during hypothermia treatment have a suppressive effect on myoclonus and other manifestations of epilepsy. Pronounced and generalized myoclonus appearing during the first 24 h after cardiac arrest is usually,[23,27] but not always,[25,35,39] a sign of severe brain damage and an unfavourable prognosis. This condition is referred to as myoclonic status and is usually associated with BS or a status epilepticus pattern on the EEG.

Hypothermia per se may have an anticonvulsive effect.[40] During the rewarming phase and weaning of sedation, seizures are sometimes observed. These seizures do not have the same negative prognostic implications as early myoclonic status. A few days after cardiac arrest, an action-induced myoclonus, also called Lance-Adams syndrome,[41] may sometimes be observed. This condition is quite compatible with good recovery even if the myoclonus may be difficult to treat.

Ongoing electrographic seizure activity, electrographic status epilepticus (ESE), is sometimes detected in patients without clinically obvious seizure manifestations. When ESE develops from a BS pattern already during hypothermia, and when the EEG background is unreactive, an unfavourable prognosis is implied. In contrast, development of ESE from a continuous and reactive background indicates a potential for recovery and may justify extended intensive care.[25,34,42] Although antiepileptic treatment is often combined with sedation to suppress seizure activity in ESE after cardiac arrest, there are no comparative studies to date that provide guidance as to choice of therapy or intensity of treatment. It is, as a rule, relatively easy to suppress both clinical and electrographic seizure activity using sedation,[43] whereas the effect of conventional antiepileptic medications such as phenytoin or valproate is less convincing.

5. Diagnostic imaging (CT/MRI)

Injuries arising as a consequence of cardiac arrest affect both the cortex and white matter of the brain. However, they appear more prominent in certain central areas such as the basal ganglia and thalami. In CT imaging, ischaemic injuries appear as blurred boundaries, i.e. decreased differentiation, between grey and white matter. This can be observed within 24 h of the cardiac arrest.[44–49] Brain swelling may be present and may lead to brain-stem herniation in some cases. Using MRI, diffusion-weighted sequences are sensitive to acute ischaemic injuries, seen as cytotoxic oedema and appearing most clearly within 3–5 days following cardiac arrest. MRI findings have been related to neurological function in several smaller studies.[50–55] However, neither CT nor MRI has sufficient specificity to be used for prognostication by themselves. On the other hand, both CT and MRI images of the brain may add prognostic information when used in combination with other tools and regardless of hypothermia treatment. If trauma or intracranial haemorrhage is suspected, CT of the brain should be carried out in an early phase. In the event of trauma, CT imaging should also include the cervical spine.

6. Biochemical markers

The most thoroughly studied biomarkers of cardiac arrest are S-100B and neuron-specific enolase (NSE),[56–58] the latter being included in the AAN recommendations.[17] The release profile of these biomarkers in plasma differs. At least two samples should be analysed to reduce the risk of error and to evaluate the trend. The reliability of using biomarkers in prognostication following hypothermia treatment has been called into question.[30,57,59–61] However, the correlation between NSE levels and brain injury is often good.[36,62] Equipment for measuring NSE, a potential standard marker, has been incorporated into the modern laboratory setup. The use of biomarkers is frequently subject to various sources of error, which obviously limits their usefulness. For instance, haemolysis results in erroneously elevated values for NSE and the plasma level of S-100B depends on renal function. Thus, elevated values are not always caused by severe brain injury, whereas low values in a comatose patient should alert clinicians to the presence of a potentially treatable condition.[62] In conclusion, due to lack of standardization and a significant variability in published studies, biomarkers are yet of limited value for decision-making following cardiac arrest.

7. Recommended routine for prognostication

Intensive care measures following cardiac arrest follow the same priorities as other intensive care, i.e. they are prioritized based on the function and prognosis of all vital organs. In this patient group, however, the neurological outcome is decisive in most cases. Daily clinical examination is the most important instrument for assessing the extent of brain injury. Level of consciousness is assessed using a validated coma scale such as the GCS taking the possible effects of sedatives, analgesics and antiepileptics into consideration. Pupillary, corneal, cough, gag and vestibulo-ocular reflexes are tested in a simple neurological examination. The

Table 1
Glascow coma scale – motor response to pain.

1.	No motor response
2.	Extension to pain
3.	Flexion to pain
4.	Withdrawal from pain
5.	Localizing pain
6.	Obeys commands

presence of seizures is noted. Further investigations are guided by whether the patient develops a significant reaction to pain (GCS-M $\geq$ 5)[63] as a sign of recovery or continues to be deeply unconscious with a stereotypic pain reaction (GCS-M $\leq$ 3) (Table 1).

In patients displaying an adequate reaction to painful stimuli, sedative drugs should be phased out unless there are special reasons for maintaining them. In patients where reactions continue to improve, further investigations are usually unnecessary, and the prognosis for recovery is favourable.[64] A late developing status epilepticus (>24–48 h after cardiac arrest) can be detected by EEG in a small group of comatose patients as the only sign of brain injury.[62] These patients may recover well even after prolonged treatment (1–2 weeks).

Patients who show no signs of recovery during the first few days and who show a stereotypic or no pain reaction should be scheduled for a prognostic evaluation. In cases where hypothermia treatment has been applied, it is recommended that such an evaluation be carried out no sooner than 72 h after restoration of normal body temperature. If hypothermia was not used, the evaluation can be carried out at 72 h after cardiac arrest. At the decisive neurological examination, it is important that analgesic and sedative treatment has been withheld for a sufficiently long period that medication effects can be excluded. When in doubt, naloxone is recommended to reverse the effect of opiates and flumazenil to counter the effect of benzodiazepines. Since flumazenil may lower the seizure threshold, epileptic activity should first be excluded using EEG.

The patient's clinical status serves as the primary guidance, but the goal should be to base decisions on comprehensive data. Table 2 presents a survey of tests that, in our view, (1) should be expected to have been carried out, (2) are advisable or (3) may provide valuable information in particular cases. All Swedish hospitals treating cardiac arrest patients should have the capacity to perform a cranial CT scan and EEG. In Sweden, the SSEP method is not well established outside the university hospitals. Increased availability is desirable, as SSEP is the most reliable method for confirming an unfavourable prognosis. Continuous EEG registration, as well as biomarkers, may provide early information about the evolution of brain injury or recovery, even when the patient is being sedated and treated with hypothermia. However, more studies are needed before these methods can be considered established. The combined results of all prognostic tests should be considered (Table 3) and related to the circumstances of the cardiac arrest as well as other clinical information. A decision to withdraw intensive care should not be based upon a single test since false predictions may occur with all methods for neurological prognostication.

Table 2
Methods of prognostication.

(1) The following basic methods should be available at all hospitals in which cardiac arrest patients are treated
- Neurological examination including level of consciousness and brainstem functions
- Conventional EEG
- Cerebral CT scan

(2) Desirable methods for reliable assessment of an unfavourable prognosis
- SSEP

(3) Methods that may add useful information and that have a potential for development
- Continuous, simplified EEG registration
- Cerebral MRI with diffusion-weighted sequences
- Biomarkers

In exceptional cases, some negative prognostic signs may justify performing an evaluation earlier than the typical recommendation at 72 h after rewarming. Myoclonic status appearing within 24 h after primary cardiac arrest is an ominous sign, although exceptions have been described.[35] This condition may justify an SSEP examination early *after* normothermia, as continuation of intensive care for several days may be considered unethical. In patients who develop clinical muscle twitches, neuromuscular blocking is recommended to avoid muscular disturbances during the SSEP examination. The combination of early myoclonic status and bilateral absence of the cortical N20 potentials in a normothermic, non-sedated patient who is GCS-M 1–2, could be considered a reliable sign of a poor neurological prognosis. Note that myoclonic status is relatively common in patients with cardiac arrest secondary to hypoxia in connection with, e.g. an asthmatic attack, drowning, or pulmonary embolism. In those patients, myoclonic status does not have the same predictive weight, and patients may survive with good function.

Another exception that may justify earlier prognostication is when the patient loses all brainstem functions, indicating total cerebral infarction, brain-stem herniation and brain death. This suspicion usually arises upon observation of dilated pupils, unresponsive to light. These patients should be examined using normal routines for determination of brain death (see the section on neurological examination).

Table 3
Positive and negative predictors in an early and a late phase.

Early positive	Early negative
•Reaction to pain GCS-M $\geq$ 5 (2)	•Clinical myoclonic status (1)
•Normal brainstem reflexes (2)	•Loss of cranial nerve reflexes (2)
•Continuous EEG background (2)	•EEG: Burst-suppression pattern or status epilepticus (2)
•Reactive EEG background (2)	•Cerebral CT: Generally decreased contrast between grey and white matter (2)
•Normal cranial CT (3)	•High levels of biomarkers (3)
•Low levels of biomarkers (3)	
Late positive	**Late negative**
•Reaction to pain GCS-M $\geq$ 5 (2)	•Reaction to pain GCS-M 1–2 (2)
•Continuous EEG background (2)	•Bilateral lack of pupillary reflex (1)
•Reactive EEG background (2)	•Bilateral lack of corneal reflex (2)
•Normal cranial CT (3)	•SSEP: Bilateral lack of N20 (1)
•Normal MRI brain diffusion (2)	•EEG: Burst-suppression, electro-cerebral inactivity or status epilepticus without a reactive background (2)
•Low levels of biomarkers (3)	•Widespread bilateral ischaemia in cerebral CT scan (2) or MRI brain diffusion (2)
	•High levels of biomarkers (3)

Early: During the first 24 h or before onset of rewarming (24 h). Late: After the first 24 h or after rewarming has been initiated. 1: Good support in the literature and good reliability. 2: Good support in the literature, but moderate reliability. 3: Some support in the literature and limited reliability.

If the overall outcome of the neurological evaluation indicates a clearly unfavourable prognosis, the natural consequence is that continued intensive care should be terminated. Even if a certain amount of brainstem function usually entails maintained spontaneous respiration in comatose patients, most patients will die during the following days or weeks, typically from respiratory complications.[6]

8. Summary

Modern treatment methods have improved the survival rate following cardiac arrest, but neurological prognostication has become more complicated by the increasingly advanced and complex care. Although the risk of extensive hypoxic brain injury increases with each day the unsedated patient does not wake up, good recovery may still occur and will require an extended period of treatment. It is important to identify patients with a poor prognosis in order to spare them and their next-of-kin treatment that has no prospect of success. It is presently difficult to formulate an algorithm similar to that found in the AAN guidelines from 2006, where several individual findings were assigned sufficient evidential value. In our opinion, the goal should instead be to gather information using several independent prognostic methods, and the results should thereafter be weighed against each other, as suggested in Table 3. All Swedish hospitals treating cardiac arrest patients should have the capacity to perform cranial CT scans and EEG. Increased availability of SSEP is desirable. In patients treated with hypothermia, prognostic evaluation should be performed no earlier than 72 h after normothermia which is later than previously recommended. If reliable signs of a poor prognosis are absent, we recommend extended observation for another 24 h, at which time further supplementary tests may be considered.

Conflict of interest statement

Tobias Cronberg (TC) and Hans Friberg (HF) are members of the steering committee for Target Temperature Management Trial (TTM, ClinicalTrials.gov Identifier: NCT01020916). HF has received lecturing fees from Care Fusion and Bard Medical. TC participates in a sub-study for TTM that receives support from Care Fusion. Lars Johan Liedholm, Ingmar Rosén, Sten Rubertsson and Christian Rylander have no conflicts to declare.

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