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Temperature management after cardiac arrest, postanoxic injury and neurological recovery

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Anna Lybeck is a specialist in anaesthetics and intensive care at Skåne University Hospital. Her current research, and this thesis, focuses on anoxic brain injury after cardiac arrest.

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Temperature management after cardiac arrest, postanoxic injury and neurological recovery

Anna Lybeck

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Title and subtitle Temperature management after cardiac arrest, postanoxic injury and neurological recovery.

Abstract
In patients admitted alive to hospital after cardiac arrest the most common mode of death is withdrawal of life sustaining therapy due to brain injury. This decicion is preceeed by multimodal neuroprognostication, which includes clinical examination, neurophysiological tests, imagning and serum markers of braininjury. The search for methods to ameliorate the brain injury after cardiac arrest is ongoing. Target temperature manegemnt (TTM) is a neuroprotective stratery recommended by guidelines.

This thesis investigates the characteristics of and neuroprognostic value of time until awakening (I) and clinical seizures (II) at two levels of TTM (33°C vs 36°C). It also investigates the potential bed-side use of simplified continuous electroencephalogram (cEEG) in the ICU (III) and whether electrographic status epilepticus diagnosed on cEEG results in additional brain injury (IV). The thesis is designed to reflect the collaboration between anesthesiologists, neurologists and neurophysiologists in this area of medicine.

Data were collected during the TTM-trial, an international, randomized, parallel group, assessor-blinded trial designed to evaluate outcome in comatose survivors of cardiac arrest after TTM at 33°C or 36°C with no difference in long-term neurological outcome between intervention arms.

Late awakening is common and patients often has a good long-term neurological outcome. Time to awakening was longer in TTM at 33°C than at 36°C. The difference could not be attributed to sedative drugs administered during the first 48 h after cardiac arrest or severity of brain injury. Independent predictors of late awakening were: TTM at 33°C, level of consciousness on admission and clinical seizures. Results may be explained by the effect of body temperature on pharmacokinetics of sedative drugs.

Clinical seizures are common after cardiac arrest and associated with a poor outcome. There were no differences in outcome between early and late onset clinical seizures. Level of TTM did not affect the prevalence or prognostic significance of clinical seizures Good outcomes occur, even in early status myoclonus.

After cardiac arrest, preliminary bedside interpretations of simplified cEEGs by trained ICU physicians may allow earlier detection of clinically relevant cEEG changes and prompt evaluation by an EEG-expert. Bedside interpretation of cEEG by ICU physicians requires awareness of limitations of both the simplified electrode montage and the cEEG interpretations performed by ICU physicians.

After cardiac arrest, ESE is associated with higher levels of serum neurofilament light chain suggesting more severe neuronal injury possibly caused by ESE, which can potentially be mitigated by treatment with antiepileptic drugs. Associations with glial fibrillary acidic protein and glial injury are less clear.

Key words Cardiac arrest, target temperature mangement, outcome, neuroprognostication, seizures, EEG

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Table of Contents

List of publications

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Time to awakening after cardiac arrest and the association with target temperature management. Resuscitation Lybeck A, Cronberg T, Aneman A, Hassager C, Horn, J, Hovednes M, Kjaergaard J, Kuiper M, Stammet P, Wise MP, Ullén S, Friberg H. Resuscitation 126: 166-171 (2018)

II Prognostic significance of clinical seizures after cardiac arrest and target temperature management. Lybeck A, Friberg H, Aneman A, Hassager C, Horn J, Kjaergaard J, Kuiper M, Nielsen N, Ullén S, Wise M, Westhall E, Cronberg T, and the TTM-trial Investigators. Resuscitation. 114:146-151 (2017)

III Bedside interpretation of simplified continuous EEG after cardiac arrest. Lybeck A, Cronberg T, Borgquist O, Düring J, Mattiasson G, Piros D, Backman S, Friberg H, and Westhall E. Acta Anestesiologica Scandinavia. 64:85-92 (2020).

IV Postanoxic electrographic status epilepticus and serum biomarkers of brain injury. Lybeck A, Friberg H, Cronberg T, Rundgren M and Westhall E. In manuscript.

Abbreviations

aEEG	amplitude integrated electroencephalography
ACNS	American Clinical Neurophysiology Society
BIS	bispectral index
cEEG	continuous electroencephalography
CI	confidence interval
CPC	cerebral performance category
CPR	cardiopulmonary resuscitation
CT	computed tomography
ECG	electrocardiogram
EEG	electroencephalography
ESE	electrographic status epilepticus
FPR	false positive rate
GCS	Glasgow coma scale
GCSM	Glasgow coma scale motor score
GFAP	glial fibrillary acidic protein
ICU	intensive care unit
IHCA	in-hospital cardiac arrest
IQR	interquartile range
MRI	magnetic resonance imaging
Nfl	neurofilament light chain
NSE	neuron specific enolase
OHCA	out-of-hospital cardiac arrest
PCAS	post cardiac arrest syndrome

PEA	pulseless electrical activity
RCT	randomized controlled trial
ROSC	return of spontaneous circulation
SSEP	somatosensory evoked potential
VF	ventricular fibrillation
VT	ventricular tachycardia
TTM	target temperature management
TTM33	target temperature management at 33°C
TTM36	target temperature management at 36°C
WLST	withdrawal of life supporting therapies

Background

Cardiac arrest is the cessation of cardiac mechanical activity. The arrest may be reversible or lead to death. If reversed, the arrest may have resulted in anoxic injury to the body. Due to its high metabolic rate and low energy stores, the brain is particularly susceptible to anoxia. This thesis concerns brain injury after out of hospital cardiac arrest in adults.

Cardiac arrest

Aetiology

The cause of the cardiac arrest is most commonly cardiac in origin, e.g. myocardial ischemia and infarction triggering ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). VF/VT may also occur as primary arrhythmias. Other causes of cardiac arrest are massive pulmonary embolus, hypovolemia, hypoxia, severe hypothermia, electrolyte disturbances and drug overdose[1].

Out of hospital cardiac arrest.

Cardiac arrest is often classified as out-of hospital cardiac arrest (OHCA) and in-hospital cardiac arrest (IHCA). The in-hospital location offers rapid access to medical services but the patient suffering the arrest is often critically ill. In OHCA a cardiac cause in a previously rather healthy individual is common. An OHCA carries a better prognosis if it occurs in a public place than if it occurs at home, likely due to availability of bystander CPR and possibly access to automated external defibrillators. The incidence of OHCA with attempted CPR in developed countries is about 50:100 000[1-3]. Over the last 20 years, survival has improved. There has been an increase in patients admitted alive to hospital, and improved 30-day survival, likely due to improved bystander CPR, 30-day survival is about 10% and 90% of survivors are discharged from hospital with a good neurological outcome (CPC1-2)[1, 3].

Pathophysiology of cardiac arrest

Three phases of cardiogenic cardiac arrest have been described. 1) an *electrical phase* lasting for 4 minutes when defibrillation alone may achieve return of spontaneous circulation (ROSC), 2) a longer *circulatory phase* during which chest compressions and the resultant coronary blood flow are required for successful defibrillation and 3) a *metabolic phase* that offers no chance of successful resuscitation. After 20-30 minutes without cardiopulmonary resuscitation (CPR) myocardial changes become irreversible and the heart may manifest this in a final ischaemic contraction resulting in a stone heart[4].

Primary rhythm

The first ECG rhythm seen during an arrest is currently classified as shockable VF/VT or as a non-shockable rhythm, i.e. asystole or pulseless electrical activity (PEA)[5]. A shockable rhythm carries a better prognosis than a non-shockable rhythm[1]. PEA is a rhythm normally associated with cardiac output and may be difficult to differentiate from a low output state. PEA may carry a better prognosis than asystole[6]. There is a continuum of these cardiac rhythms as the amplitude VT/VT or PEA diminishes and asystole occurs. With successful CPR the process may reverse.

Cardiopulmonary resuscitation

The actions linking cardiac arrest with survival are illustrate in the "chain of survival" (fig 1). The current advanced life support algorithm (fig 2) emphasises uninterrupted CPR and early defibrillation. The drugs included in the algorithm improve short term survival but there is no evidence to suggest improved long-term neurological outcome[7].

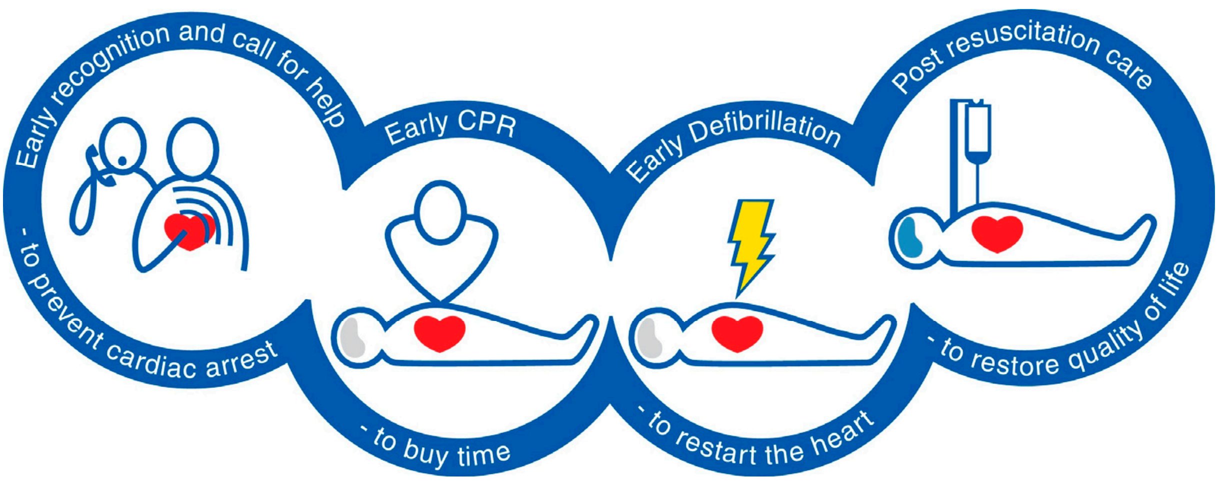

Figure 1: Chain of survival.
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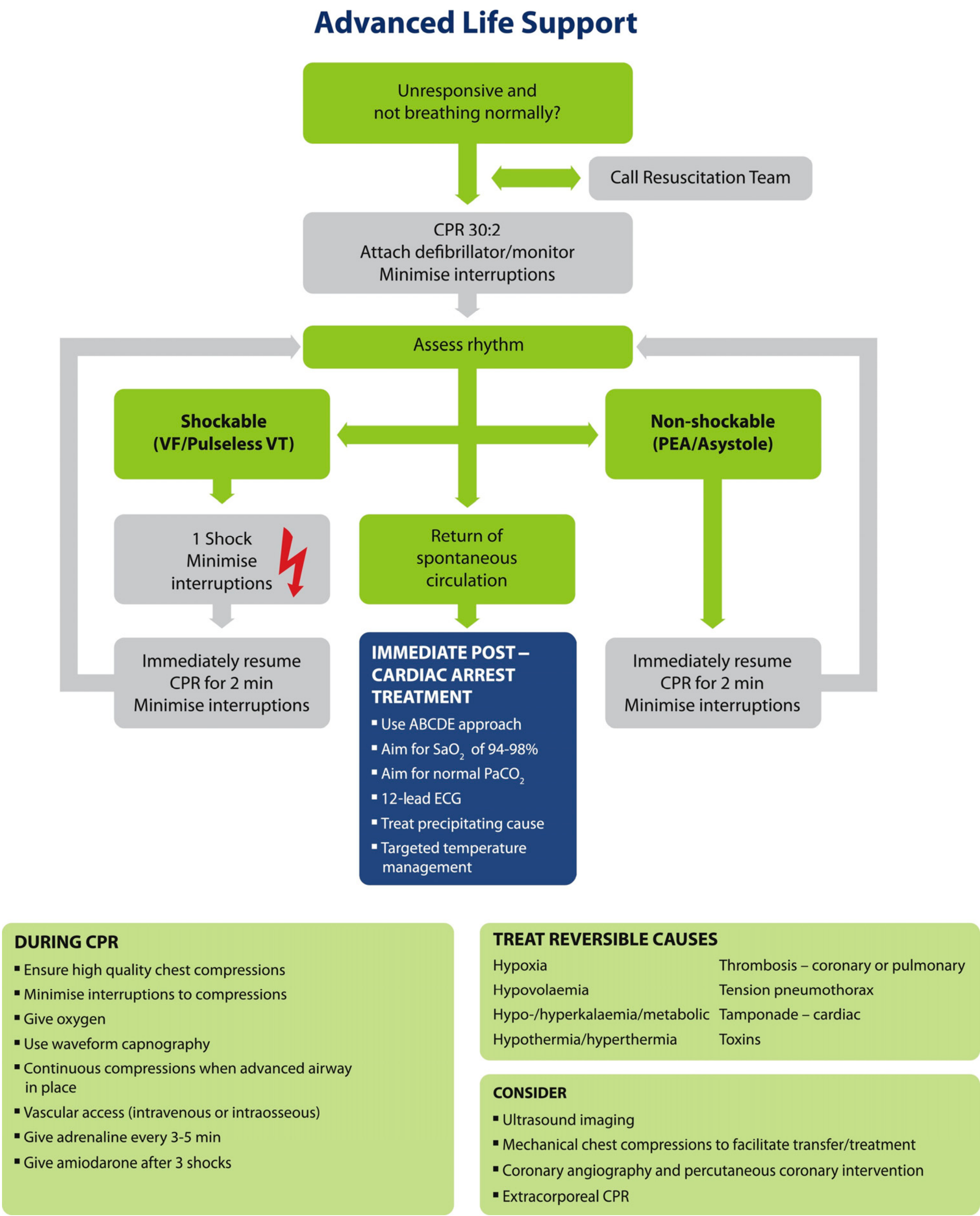


Figure 2. Adult advanced life support algortihm,
European Ressuciation Guidelines 2015. Reprinted with permission.

Post cardiac arrest syndrome

Return of spontaneous circulation (ROSC) after whole-body ischaemia creates a new disease state associated with global ischaemia and the re-perfusion injury caused by resuscitation, the post cardiac arrest syndrome (PCAS)[8].The severity of PCAS will vary with the duration and cause of cardiac arrest and may not occur if the arrest was brief. The pathophysiological processes associated with ischaemia and reperfusion may be considered separate from the process precipitating the cardiac arrest, but clinically the processes overlap and PCAS is considered to have four components:

- post-cardiac arrest brain injury
- post-cardiac arrest myocardial dysfunction
- systemic ischaemia/reperfusion response
- persistent precipitating pathology

Myocardial dysfunction is common after cardiac arrest and typically starts to recover by 2–3 days, although full recovery may take longer. Cardiovascular failure accounts for most deaths on day 1-3, whereas brain injury (see below) accounts for most of the later deaths[9]. The systemic ischaemia/reperfusion after cardiac arrest activates immune and coagulation pathways contributing to multiple organ failure and increased risk of infection. PCAS has many sepsis-like features[10] including intravascular volume depletion, vasodilation, endothelial injury and abnormalities of the microcirculation.

Global anoxic brain injury

The pathophysiology of anoxic brain injury is a “two-hit” model, consisting of primary injury from immediate cessation of blood flow during cardiac arrest and secondary injury occurring after resuscitation. The pathophysiological processes involved in anoxic brain injury has received a lot of research attention aiming at identifying therapeutic targets[11]. Most notably, targeted temperature management (TTM) has been studied rigorously in preventing secondary injury.

Primary brain injury

Compared to other tissues, the metabolism of the brain is heavily dependent on oxygen and glucose. Within 2-3 minutes of cessation of blood flow ATP stores in the brain are almost completely depleted. The lack of ATP results in failure of membrane pumps and loss of membrane potentials, i.e. anoxic depolarisation of neurones. Intra-cellular Ca^{2+} increases due to extracellular influx and release from intracellular stores. Ca^{2+} acts as an intracellular second messenger stimulating release of neurotransmitters including glutamate. As ATP is required for neurotransmitter re-uptake, these substances also accumulate extracellularly. If these excitotoxic mechanisms are not stopped, cell death will result within minutes due to activation of destructive lipases and proteases leading to apoptosis. Additional pathophysiological mechanisms contributing to the primary brain injury are: anaerobic metabolism resulting in lactic acidosis; elevated intracellular Na^{+} levels resulting in cytotoxic oedema, intracellular Ca^{2+} triggering mitochondrial dysfunction (i.e. more problems with ATP formation) and free radical formation[12]. Clinical correlates of primary brain injury are loss of consciousness in 5-10 seconds and isoelectric electroencephalography (EEG) occur within 20 seconds[13, 14].

Secondary brain injury

After ROSC membrane potential and ATP are restored, but apoptosis and necrosis continue for hours or days, suggesting a therapeutic window for neuroprotective strategies. On a cellular level, restoration of blood flow to the brain triggers a secondary cascade of events including endothelial dysfunction (including microthrombi), free radical formation, intracellular Ca^{2+} accumulation, impaired NO, excitatory neurotransmitter release and altered gene expression[12].

The cerebral circulation is also affected after ROSC. Animal studies show that immediately after ROSC there is a short period of multifocal cerebral no-reflow followed by transient global cerebral hyperaemia[15]. During the following 24 hours, there is cerebral hypoperfusion while the cerebral metabolic rate gradually recovers[15]. After cardiac arrest, brain oedema may occur transiently after ROSC but it is rarely associated with clinically relevant increases in intracranial pressure[16].

Further secondary brain injury may be caused by factors affecting oxygen delivery and use[12]:

- Endothelial dysfunction (microthrombi, vasoconstriction, blood-brain-barrier dysfunction) → decreased (inhomogenous) cerebral blood flow, vasogenic oedema
- Cerebral oedema (vasogenic and cytotoxic)→elevated ICP, rarely brain death
- Hyperoxia (O_2 free radicals)→ cell dysfunction and cell death
- Carbon dioxide → vasodilation/vasoconstriction
- Anaemia
- Impaired autoregulation of cerebral blood flow (narrowed and right-shifted)→ cerebral hyperaemia or ischaemia

- Hyperthermia→ increased metabolic rate→ increased O_2 consumption
- Seizures→ increasing O_2 consumption

The above mechanisms are all targets for neuroprotective strategies or interventions during postresuscitation care. More or less evidence based management of these factors is recommended or suggested by guidelines [8, 17] and several neuroprotective interventions targeting these mechanisms have been investigated (see below). Additionally, high blood glucose and high variability in blood glucose are associated with poor neurological outcome[18], but strict control of blood glucose was not beneficial in a RCT[19].

Selective vulnerability of the brain

Structures especially susceptible to anoxic brain injury include the CA-1 (CA=cornu ammonis, shaped as the horn of Amun) region of the hippocampus, thalami, cerebral cortex, corpus striatum, and cerebellum, owing to highly metabolically active tissue[20, 21]. The brainstem is by far the most resistant to injury. The selective vulnerability of the areas of the brain is reflected in the sequential recovery of brain functions in awakening (see below) and in defects in memory among patients who recover[22].

Neuroprotective interventions

In the clinical setting, it is difficult to ascribe the anoxic brain injury to a single pathophysiological mechanism and interventions affecting a single mechanism have all been ineffective: calcium channel blockers[23, 24]; thrombolysis[25]; brain-derived neurotrophic factor[26]; and a caspase-3 (a mediator in apoptosis) inhibitor[27]. A few relatively non-specific interventions have yielded the most promising results: TTM (see below), xenon[28] and mild hypercapnia[29] may improve recovery. Other non-specific interventions have been investigated but no neuroprotective effect found: Coenzyme Q10[30], glucocorticoids[31, 32] and a loading-dose of thiopental[33] or diazepam[34].

Target Temperature Management

In the late 1980s it was reported that mild therapeutic hypothermia, later renamed target temperature management (TTM), improved neurological outcome after cardiac arrest in dogs[35]. Studies in several species on optimal level and timing of TTM followed[36]. However, the mechanisms by which TTM attenuates brain injury remain incompletely understood, several pathways including effects on metabolism, inflammation, gene expression, Ca^{2+} signalling and excitotoxicity may be involved[12].

In 2002 two small clinical trials (n=77 and 275) reported improvement in survival and neurological function when unconscious patients with bystander witnessed OHCA of presumed cardiac origin and initial shockable rhythm, were cooled to 32-34°C for 12- 24 hours[37, 38]. These results received worldwide attention and TTM at 32- 34°C was included in guidelines even for types of cardiac arrest not included in the studies. The International Liaison Committee on Resuscitation (ILCOR)[39] and Cochrane reviews[40] recommended the intervention. However, the optimal target temperature was never defined and it was unclear whether the proposed intervention effect was simply due to fever avoidance as this was not treated in the control groups. Fever is common after cardiac arrest and is associated with poor neurological outcome[41].

In 2012 a systematic review using GRADE methodology reported that the trials on hypothermia were at high risk of systematic error (bias), random errors (play of chance)[42] and the Target Temperature Management-trial (TTM-trial) followed[43]. The TTM-trial randomised 950 patients with OHCA with all types of initial cardiac rhythm to TTM at 33°C (TTM33) or 36°C (TTM36) with no difference in mortality or long-term neurological outcome. Currently guidelines recommend TTM at 32-36°C for at least 24 hours[17, 44] but several questions regarding TTM remain unanswered including whether fever control is a sufficient measure to attenuate brain damage after cardiac arrest. The question is investigated in the ongoing TTM2-trail[45]. A recent trial investigating effect of TTM33 vs targeted normothermia in comatose survivors of cardiac arrest with non-shockable rhythms found a higher percentage of patients with good neurological outcome with TTM33, but number of survivors were small[46].

Awakening

The natural course of recovery

Recovery of neurological function follows a distinct pattern and has been prospectively described in detail[47-50]. First the brain stem recovers with return of spontaneous breathing and cranial nerve reflexes. Extension pattern and defensive movement follows. Eventually consciousness recovers with a gradual return of speech, motor functions, orientation and memory. Most awakening takes place within 3 days after cardiac arrest[51], but has been reported several weeks later[49, 50, 52].

Sedative drugs

Awakening is complicated by sedation required during TTM. In order for the patient to tolerate a lowered body temperature and reduce shivering, sedation is required for the duration of TTM. Drug metabolism is slower and more variable in the critically ill as compared to healthy volunteers [53] and a lowering of the body temperature decreases drug elimination[54, 55]. Hence, sedation may linger after rewarming from TTM and discontinuation of sedation, and possibly delay awakening.

Prognostication

Most deaths in patients who initially survive cardiac arrest are attributed to brain injury, but only 2-10% of these deaths fulfil the criteria for brain death[9]. Instead most deaths result as a consequence of withdrawal of life sustaining therapies (WLST) when a poor neurological outcome is predicted. Accurate neurological prognostication is essential in order to both reduce the risk of a falsely pessimistic prediction and to avoid futile care in those who have no chance of recovery. For this reason a multimodal approach to neuroprognostication (fig 3) is recommended, including clinical examination, neurophysiological tests, imaging and serum biomarkers of brain injury[17, 44, 56].

Many studies on neuroprognostic markers are confounded by the *self-fulfilling prophecy*[57], which is a bias occurring when the treating physicians are not blinded to the results of the outcome predictor and use it to make a decision on WLST. Additionally, TTM has complicated neuroprognostication as sedatives may affect results of both clinical examination and neurophysiological tests[58].

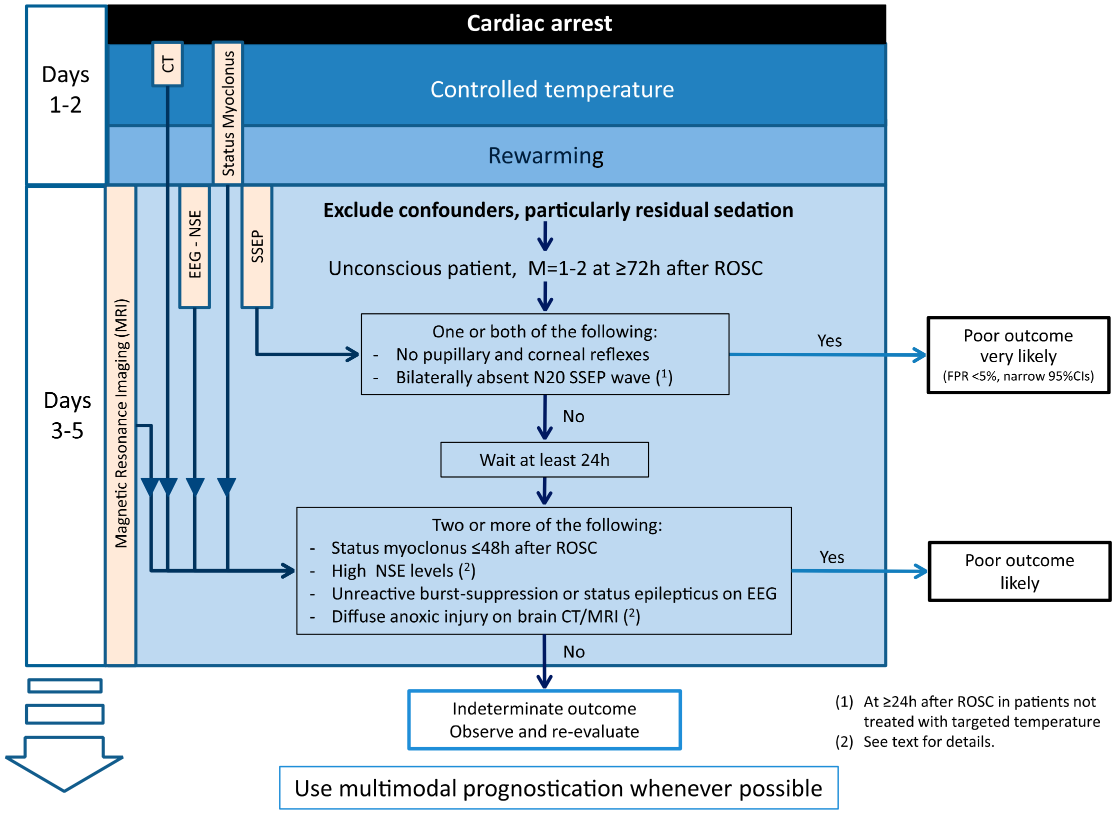


Figure 3 : Suggested prognostication algorithm.
The algorithm is entered ≥72 h after ROSC if, after the exclusion of confounders (particularly residual sedation), the patient remains unconscious with a Glasgow Motor Score of 1 or 2. The absence of pupillary and corneal reflexes, and/or bilaterally absent N20 SSEP wave indicates a poor outcome is very likely. If neither of the features is present, wait at least 24 h before reassessing. At this stage two or more of the following indicate that a poor outcome is likely: status myoclonus ≤48 h; high neuron specific enolase values; unreactive EEG with burst suppression or status epilepticus; diffuse anoxic injury on brain CT and/or MRI. If none of these criteria are met consider continue to observe and re-evaluate From Sandroni C, Cariou A, Cavallaro F, *et al.* Prognostication in comatose survivors of cardiac arrest: an advisory statement from the European Resuscitation Council and the European Society of Intensive Care Medicine. Resuscitation. 2014;85:1779-89. Reprinted with permission.

Clinical examination

Levels of consciousness, brain stem reflexes and presence of clinical seizures are used in neuroprognostication. All these signs may be suppressed by sedatives or neuromuscular blocking drugs.

Absent or extensor motor response at 72 hours after ROSC has a high sensitivity (70-80%) for prediction of poor outcome, but the false positive rate (FPR) is also high (0-50%) in both non-TTM and TTM-treated patients[56]. Still, the high sensitivity of this sign makes it useful to identify the population needing prognostication.

Bilateral absence of pupillary light reflex at 72h after cardiac arrest predicts poor outcome with FPR close to 0 and narrow 95% confidence intervals (95%CI) of

<10% in both TTM- treated and non-TTM-treated patients[56, 59]. The predictive value of bilaterally absent corneal reflexes is similar[56, 59].

Clinical seizures may be myoclonic or tonic-clonic, focal or generalised and are diagnosed in up to one third of comatose survivors of cardiac arrest[60]. Clinical seizures may occur with or without epileptiform activity on the electroencephalogram (EEG). Other involuntary movements such as shivering can be misdiagnosed as seizures[61]. Myoclonic seizures are sudden, brief, involuntary muscle jerks associated with a poor prognosis[62-65]. Status myoclonus is a prolonged period of generalised myoclonus with a grave prognosis[44, 56]. Status myoclonus of early onset was previously considered a reliable sign of poor prognosis, but cases with good outcomes have been reported among patients treated with TTM[63, 65-68]. EEG may help identify cases with good outcomes[65]. Action myoclonus persisting after awakening (Lance-Adams syndrome) is a rare condition occurring mainly after hypoxic cardiac arrest, and compatible with otherwise good neurological recovery[65, 69, 70]. Tonic-clonic seizures are less common than myoclonic seizures and are associated with a poor outcome[71, 72].

Somatosensory evoked potentials (SSEP)

Median nerve SSEP tests the afferent sensory pathways and is elicited by stimulation of the nerve and responses registered along the pathway. The N20-response (contralateral sensory cerebral cortex) reflects thalamocortical projections. As early as 24 hours after cardiac arrest bilaterally absent N20 potentials predict a poor outcome with FPR 0% (95%CI 0-2%), but sensitivity is low (<50%)[56] and cases of false positive SSEP have been reported[73-75]. A study investigating the natural course of comatose survivors of cardiac arrest admitted to neurorehabilitation, found a small number patients with bilaterally absent N20 potentials who recovered over weeks with a good neurological outcome[52]. SSEP is not affected by sedation at doses used during TTM. Interrater variability of SSEP interpretation is moderate to good[75, 76] and affected by noise[75].

Electroencephalography (EEG)

EEG provides immediate examination of the cerebral cortex regarding background activity and seizures. During cardiac arrest the EEG is suppressed (flat) and this pattern may persist for hours or days after ROSC. Recovery begins with intermittent discontinuous cortical activity followed by continuous activity[49, 50]. Body temperature at recommended levels of TTM does not affect the EEG[77] but sedation may suppress both EEG background activity and epileptiform discharges.

Intermittent full-montage EEG (16-21 electrodes according to the international 10-20 system recorded for 20-30 minutes) is the most commonly used tool to assess prognosis after cardiac arrest[78]. Continuous EEG (cEEG) is increasingly used in the ICU (see below). The lack of standardized EEG terminology, both in studies and in clinical practice, is a limitation. Currently the EEG classification proposed by the American Clinical Neurophysiology Society is favoured[79], figure 4. The prognostic value of an EEG recording will be affected by its timing in relation to ROSC and sedation, interpretation is also subject to interrater variability[80].

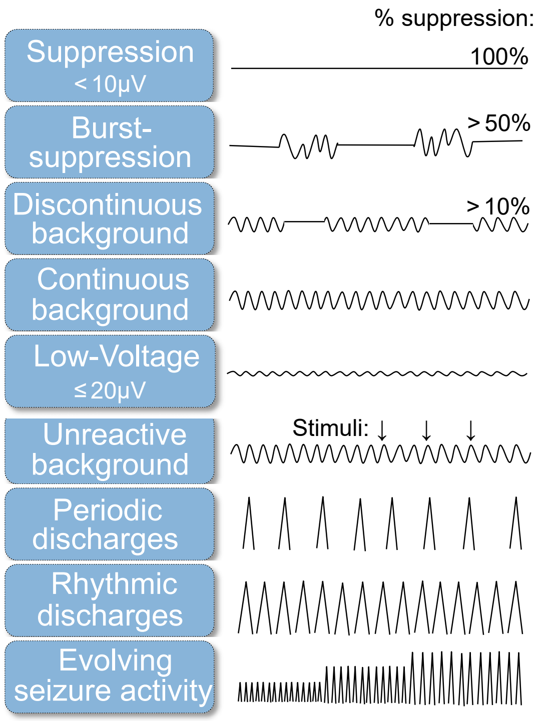


Figure 4 Common EEG features after cardiac arrest.
Criteria for background voltage and suppression-ratio (proportion of recordning that constitutes suppression periods) accordning to ACNS EEG terminology. Reprinted with permission.

<u>Early return of a continuous EEG background</u> is predictive of a good outcome [81-83]. Similarly, a suppressed or low-voltage background >24 hours after cardiac arrest is a marker of poor prognosis[84-87], but studies are hampered by inconsistent definitions of “low-voltage”.

<u>Burst-suppression</u> is usually a transient finding during cerebral recovery. During the first 24–48 h after cardiac arrest burst-suppression is compatible with good neurological outcome in both patients treated with TTM and those not[85, 88, 89]. However, at ≥72 h a persisting burst-suppression pattern is consistently associated with poor outcome[72, 81, 82]. Burst-suppression with identical bursts[90] or in combination with electrographic status epilepticus[81] have a very high specificity for prediction of poor outcome.

<u>Absence of EEG reactivity,</u> predicts poor outcome in many studies [87, 91 88, 92], is associated with higher NSE levels[88] and is included in guidelines on neuroprognostication when it occurs in combination with ESE or burst suppression

background[17, 44]. However, there is a lack of standardized stimulation to provoke EEG reactivity, a high interrater variability in interpretation[80, 93] and high FPRs have been reported (0-30%)[87, 91]. A recent international consensus report on EEG reactivity after cardiac arrest as a prognostic tool concluded that evidence was limited[93]. Early EEG reactivity to external stimuli may be a marker of good outcome[92].

Electrographic status epilepticus (ESE) occurs in up to one third of comatose survivor of cardiac arrest and is associated with poor prognosis[94]. A subgroup of patients recover with a good outcome, these patients have other prognostic markers indicative of a good outcome[59]. There is lack of agreement on the definition of ESE. ACNS has defined periodic and rhythmic patterns that may represent seizures, and strict criteria for unequivocal seizures and ESE[79]. However, in comatose survivors of cardiac arrest no difference in outcome was found between patients with strictly defined unequivocal electrographic status epilepticus and those with possible seizure patterns along the ictal-interictal continuum[95]. ESE is an independent predictor of poor outcome[94, 96]. It may be that ESE is simply a marker of severe brain injury or it may cause further brain injury, e.g. seizures are associated with increased metabolic rate[97] and elevated levels of biomarkers of neuronal injury in cerebrospinal fluid[98] and serum[99]. Treatment of seizures is recommended by expert advice[17, 44], awaiting results from randomized trials[100].

Imaging

All studies on imaging as a tool in prognostication after cardiac arrest had a small sample size, most were retrospective, and imaging was requested at the discretion of the treating physician, which may have caused a selection bias and overestimated their performance. Nevertheless, computed tomography (CT) magnetic resonance imaging (MRI) may serve as adjuctive tools and are included in guidelines[17, 44].

The anoxic brain injury in the grey matter of the cortex, thalamus and basal ganglia can be seen on CT as oedema, which appears as a reduction in the depth of cerebral sulci and an attenuation of the grey matter/white matter interface, due to a decreased density of the grey matter, which has been quantitatively measured as the ratio between the grey matter and the white matter densities. CT is commonly performed[78] and studies suggest that CT head may be an early predictor of outcome [44, 101, 102]. CT can also provide information on structural lesions, e.g. to rule out haemorrhage or a c-spine injury.

Advantages of MRI over brain CT include a better spatial definition and a high sensitivity for identifying ischaemic brain injury[103]. MRI can reveal extensive changes when results of other predictors such as SSEP or ocular reflexes are normal[104]. MRI Diffusion Weighted Imaging (DWI) detects diffusion of water molecules and is sensitive to detection of cytotoxic oedema, which reduces diffusivity. Cytotoxic oedema begins at cardiac arrest, peaks at day 3 and then disappears gradually by day 7-10. MRI Fluid Attenuation Inversion Recovery (FLAIR) employs the water content of tissue, but discards the influence of the cerebrospinal fluid. Therefore, MRI-FLAIR is sensitive to detection of cytotoxic and vasogenic cerebral oedema. FLAIR changes appear on day 1-2 (early vasogenic oedema) and remain for weeks (later changes associated with gliosis).

Biomarkers

Biomarkers of brain injury in serum give a quantitative result and are unaffected by sedative drugs. Disadvantages include lack of clear cut-offs for predicting outcome.

Neuron specific enolase (NSE) is an intracellular enzyme of glycolysis present in neurons and neuroendocrine cells but also in erythrocytes and platelets, which is a source of error in haemolysis. Cut-off levels to predict a poor outcome with 0% FPR varies between studies, mainly due to different sampling time points and laboratory methods[105]. A rise in NSE from 24h to 48h may indicate a poor prognosis[106, 107]. Similarly, a decrease may indicate good prognosis[108]. NSE is included in current guidelines[17, 44].

Several novel biomarkers of brain injury have been investigated including neurofilament light chain (Nfl) and glial fibrillary acidic protein (GFAP). Neurofilament light chain (Nfl) is a novel biomarker of neuronal injury and a robust predictor of poor outcome after cardiac arrest already at 24 hours[109]. After neuronal injury, serum Nfl levels rise rapidly[110] and levels remain elevated for prolonged periods (weeks)[111]. Unlike NSE, Nfl-levels are not falsely elevated by haemolysis. Glial fibrillary acidic protein (GFAP) is a marker of astroglial cell injury with prognostic value after cardiac arrest[112]. Serum GFAP rises rapidly after cardiac arrest[113] and its half-life is long, up to 48 hours[111].

Outcome

Survival is a robust outcome measure, but will be affected by both WLST and the time point at which survival is recorded. WLST will also affect the overall neurological outcome of survivors, as more patients with severe disability will survive without WLST.

Neurological recovery continues for at least 6 months, with most recovery within the first 3 months post-arrest[114]. Neurological outcome is commonly reported using the Cerebral Performance Category (CPC) scale (table 1)[115].

Outcome is often dichotomised (table 1) into good or poor neurological outcome and cut offs have varied over time. According to these definitions, most survivors of cardiac arrest have good neurological outcome, but cognitive defects (memory) and symptoms of depression and anxiety are common[116-118].

Table 1. Cerebral Performance Category (CPC) scale

Outcome	Cerebral Performance Category
Good	CPC1 Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
	CPC2 Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
Poor	CPC3 Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
	CPC4 Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
	CPC5 Dead

cEEG after cardiac arrest

Guidelines recommend use of continuous electroencephalography (cEEG) monitoring in the intensive care unit (ICU)[44, 119-122]. In comatose patients after cardiac arrest, cEEG monitoring may be used for detection of electrographic seizure activity and to assist in neuroprognostication[119, 123]. Full-montage cEEG monitoring in the ICU is challenging[124-126] due to logistic reasons, lack of EEG technicians and EEG-experts especially outside office hours, and high costs[127].

Simplified cEEG methodology

Simplified cEEG can be applied by trained bed-side staff and preliminary cEEG interpretations be performed by ICU physicians awaiting review by an EEG-expert when available e.g. during office hours[128]. For this purpose, various simplified cEEG montages have been proposed[129].

Patients in coma after cardiac arrest may be particularly suitable for a reduced EEG montage despite its impaired spatial resolution, due to the global nature of hypoxic brain injury. Recent studies using simplified cEEG montages after cardiac arrest have shown a high sensitivity (>90%) to detect seizure activity[130-132] and preserved prognostic accuracy[133] compared to a full-lead montage.

Trend analysis

cEEG monitoring generates large amounts of data and quantitative measurements displayed as time-compressed trends have been developed to ease interpretation over longer time-periods. One such measure is amplitude-integrated EEG (aEEG), which has been used in the post cardiac arrest setting[82, 134]. Other quantitative measures investigated after cardiac arrest are suppression ratio (degree of EEG background continuity), bispectral index (BIS)[135-137] and entropy[138]. Recently EEG analysis by machine learning have shown promising results[139, 140].

Aims of the thesis

The overall aim of the thesis was to evaluate neuroprognostic markers used in comatose survivors of cardiac arrest in the ICU. This thesis reflects the close collaboration between the anesthesiologists, neurologists and clinical neurophysiologists.

I To investigate time until awakening after cardiac arrest at two different levels of TTM, including any association between time until awakening and long-term neurological outcome, type, and dose of sedative drugs. Additionally, independent predictors of late awakening were investigated.

II To investigate the incidence and prognostic significance of clinical seizures during the first 7 days after cardiac arrest in the ICU, any interaction with level of TTM and associated EEG findings.

III To investigate whether basic features of a simplified cEEG can be interpreted by an ICU physician after a short training, and whether acceptable interrater agreement compared to an EEG-expert can be achieved.

IV To explore the effects of postanoxic status epilepticus on serum levels of biomarkers of brain injury.

Materials and methods

All four papers included in this thesis used data collected during the TTM-trial[43]. Details of materials and methods are described in each paper.

Table 1. Overview of study design

Paper	I	II	III	IV
Design	Post hoc analysis of a multicentre, randomised trial	Post hoc analysis of a multicentre, randomised trial	Prospective	Post hoc analysis of a multicentre, randomised trial
Study population	OHCA of presumed cardiac cause, managed with TTM at 33°C or 36°C 2010-2013 n=939			
	Patients who awoke	All	Monitored with cEEG at 3 trial sites	Monitored with cEEG and serum biomarkers samples at 5 trial sites
Participants	n=496	n=939	71 cEEG (37 patients) 5 ICU-physicians 1 EEG-expert	n=128

The TTM-trial

The TTM-trial[43], was an international, randomized, parallel group, assessor-blinded trial designed to evaluate outcome in comatose survivors of cardiac arrest after TTM at 33°C. or 36°C. It enrolled 950 adult (≥18 years) patients in 26 months 2010–2013. The modified intention to treat group included 473 patients at 33°C and 476 at 36°C. Trial data were obtained from 36 intensive care units in Europe and Australia with no difference in end-of-trial mortality or 180-day neurological outcome between intervention arms.

Ethics

For the main TTM-trial ethical approval was obtained in each country. Consent was obtained or waived according to local regulations. The trial was monitored according to Good Clinical Practise. For III additional ethical approval was sought.

Patients

Adult unconscious survivors of cardiac arrest. Inclusion criteria in the TTM-trial were: ≥18 years; OHCA of presumed cardiac origin; GCS>8; sustained ROSC (<20 min). Exclusion criteria were: pregnancy, known bleeding diathesis, suspected or confirmed intracranial bleeding, suspected or confirmed acute stroke, unwitnessed asystole, known limitations in care, known disease making 180 day survival unlikely, pre-arrest CPC3-4, >240 minutes since cardiac arrest, temperature <30 °C, systolic blood pressure < 80mmHg despite fluid, vasopressor, inotropes or aortic balloon pump.

Protocol

The TTM-trial study protocol time-line for the first 108 hours is summarised in figure 5. After randomisation to TTM33 or TTM36, patients were sedated, endotracheally intubated and mechanically ventilated. Choice of sedative was not protocolized. Temperature was managed with an external or internal device. Patients randomised to TTM33 were cooled as rapidly as possible using cold-fluids, ice packs or a cooling device. Patients randomised to TTM36 who initially had a lower temperature, was allowed to rewarm passively. After the intervention period patients were re-warmed at ≤0.5 °C/hour. After rewarming sedation was stopped, unless required for other medical reasons. A body temperature of <37.5°C was maintained for unconscious patients.

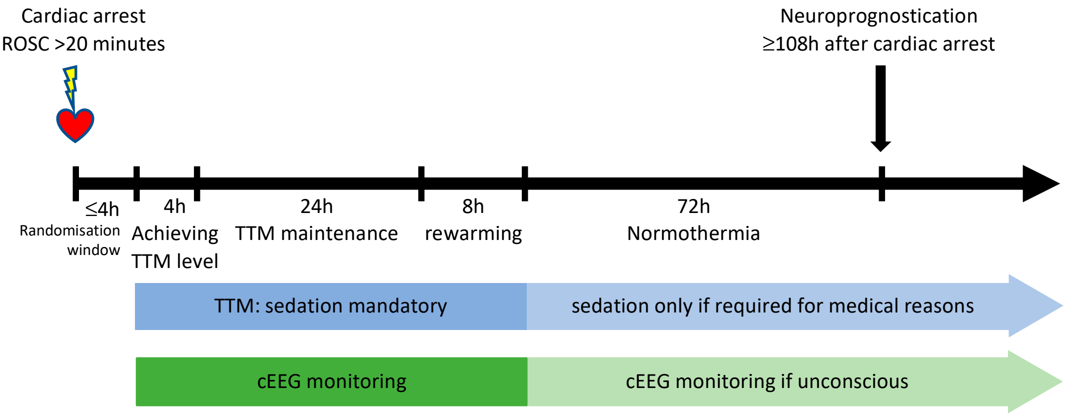


Figure 5 TTM-trial study protocol time-line 0 to 108 hours
After ROSC (defined as 20min of spontaneous circulation) there was a 4 h inclusion window. The intervention period was divided into 3 periods: (a) achievement of target temperature (4 h), (b) maintenance of target temperature (24 h) and (c) rewarming to 37 °C (8 h). After 36 h, sedation was stopped unless continued for medical reasons, at the discretion of the treating physician. cEEG-monitoring was started after patients were stabilized in the ICU.

Neuroprognostication and WLST

In the TTM-trial there was strict criteria for WLST. All patients were actively treated until 72 hours after normothermia (108 hours after randomization). Neuroprognostication was protocolized and performed by a physician blinded to level of TTM. Serum biomarkers were not part of neuroprognostication.

At 72 hours after normothermia, WLST was permitted in:

1. persisting coma with GCS-M 1-2 and bilateral absence of N20-peaks on SSEP.
2. persisting coma with a GCS-M 1-2 and a treatment refractory status epilepticus

Earlier WLST was permitted in:

1. Brain death due to cerebral herniation.
2. Status myoclonus in the first 24 hours after admission and a bilateral absence of N20-peak on median nerve SSEP.
3. Ethical reasons (e.g. previously unknown information about disseminated end-stage cancer or refractory shock with end-stage multiorgan failure)

Patients with GCS-M 1-2 at 72 h after normothermia who had preserved N20-peak on the SSEP, or in hospitals where SSEP was not available, were re-examined daily and limitations in care/WLST considered if GCS-M did not improve and metabolic and pharmacological effects were ruled out.

Long-term neurological outcome

180-day neurological outcome was assessed by a face-to-face interview using the CPC scale. Survival status was obtained from hospital or civil registers. A poor outcome was defined as CPC3-5.

Awakening (I)

Awakening in the ICU was defined as GCS motor score 6, i.e. obeying command, which was registered daily in the ICU. In patients who awoke after ICU discharge, no exact day of awakening was available. Instead, the CPC score collected at hospital discharge and at 180-days were used, CPC 1–3 was considered awake. Early awakening was defined as awakening on day 1–4, before the time of the scheduled neurological prognostication. Awakening on day 5 or later was defined as late awakening.

Sedation (I)

Choice of sedative drugs, neuromuscular blocking agents and sedation monitoring scales were not protocolized. Data on sedative drugs and use of sedation monitoring scales were retrospectively collected from trial sites via online questionaires (2015–2016). Cumulative doses of sedative drugs were collected at 12, 24 and 48 h.

Clinical seizures (II)

Clinical seizures were reported on a daily basis during day 1–7 in the ICU. In the electronic case report form seizures were classified as myoclonic or tonic-clonic, focal or generalised, and duration of seizure as less than or more than 30 minutes. Treatment of seizures was not protocolized but recorded daily and separately for myoclonic and tonic-clonic seizures. Status myoclonus was defined as generalised (face and extremities) myoclonic convulsions of >30 minutes duration and tonic-clonic status as generalised tonic-clonic seizures of >30 minutes duration.

Biomarkers (IV)

Serum samples were collected at 24, 48, and 72 hours after return of spontaneous circulation (ROSC). All samples were preanalytically processed at trial sites, aliquoted, and frozen to −80°C before shipment to the Integrated BioBank of Luxembourg for batch analysis after trial completion. For details on individual biomarker analysis, see paper IV.

Full-montage cEEG (II)

A full-montage EEG) was recorded in patients remaining in coma 12–36 h after rewarming and when clinically indicated. The EEG was recorded using 16 electrodes+reference+ground, for 20-30 minutes with testing for reactivity. Interpretations of the EEG recordings were done by the local EEG-experts at the trial sites and reported prospectively.

Simplified cEEG (III, IV)

Monitoring with simplified cEEG was performed at six European trial-sites. cEEG-monitoring was started by the ICU staff after patients were stabilized in the ICU. ICU staff were blinded to the cEEG recording. Patients were monitored with Nicolet One monitors (Viasys Health care) with a simplified cEEG montage displaying two bipolar channels according to the 10–20 system (F3-P3 and F4-P4 (figure 6). All EEG interpretation was performed by review of the original EEG-signal.

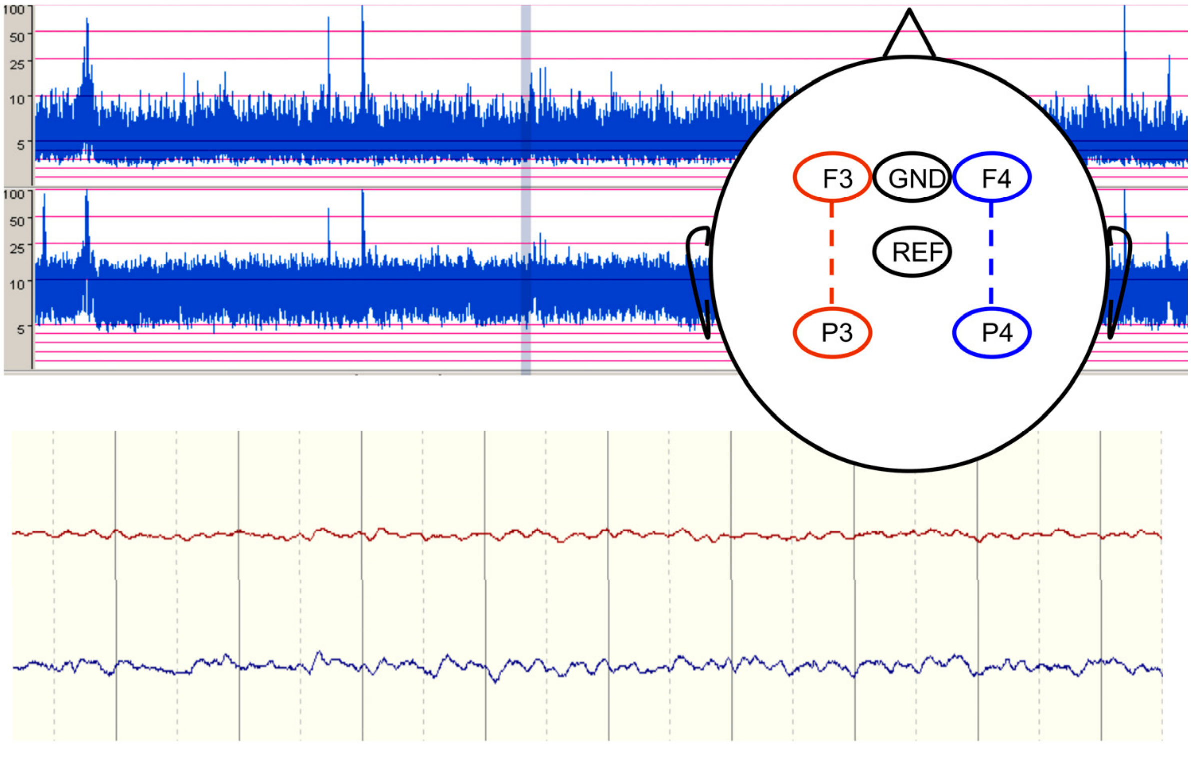


Figure 6 cEEG montage with an example of simplified continuous EEG recording:
F3, P3, F4, P4, reference Cz, ground Fz. The upper curves display the left and the right time-compressed aEEG, the y-axis displays the semilogarithmic µV scale. The shaded aEEG marks the time span of the aEEG corresponding to the original EEG below. The lower part displays the original EEG recording from the left and the right hemispheres; each division represents 1 sec.

Electrographic status epilepticus (IV)

An EEG-expert interpreted cEEG at 12, 24, 36, 48, 60 and 72 hours after cardiac arrest. ESE was defined as:

- Regularly appearing (=periodic or rhythmic) epileptiform discharges at ≥1Hz continuously (≥90%) appearing during a 30-minute-period.
- Unequivocal electrographic seizure activity, constituting <50% of a 30-minute-period (≥10 second duration generalized rhythmic epileptiform discharges ≥3Hz) OR clearly evolving discharges of any type reaching >4Hz, according to the EEG criteria of the American Clinical Neurophysiology Society 2012 version.
- Unequivocal electrographic status epilepticus with unequivocal seizure activity constituting ≥50% of a 30-minute-period.

For patients with ESE, a control group matched for severity of brain injury was found by propensity score matching using known early (before onset of ESE) independent predictors of neurological outcome.

Interpretation of simplified cEEG by ICU physicians (III)

Five ICU physicians received training in interpretation of simplified cEEG - total training duration 1 day. The ICU physicians then interpreted 71 simplified cEEG recordings from 37 comatose survivors of cardiac arrest, from 3 TTM-trial sites. Patients were included if motor phenomena indicating possible seizures were observed during the first two days after cardiac arrest, type of suspected seizure movement was not reported. This selection was made primarily for statistical reasons to increase the number of cEEG recordings with electrographic seizures, but also mimicking the set of patients to whom the physician is called bedside to evaluate motor phenomena, a common task during postresuscitation care.

The cEEG included amplitude-integrated EEG trends and two channels with original EEG-signals. Basic EEG background patterns and presence of epileptiform discharges or seizure activity were assessed on 5-grade rank-ordered scales based on standardized EEG terminology (figure 7). Reported cEEG background patterns were also dichotomized as continuous/nearly continuous background versus the non-continuous background patterns discontinuous, burst-suppression or suppressed background, reflecting likely good or poor neurological outcome. Similarly, reported discharge patterns were dichotomized to include patterns indicating possible or definitive electrographic seizures versus patterns without seizures. An EEG-expert was used as reference. Interrater statistics were used.

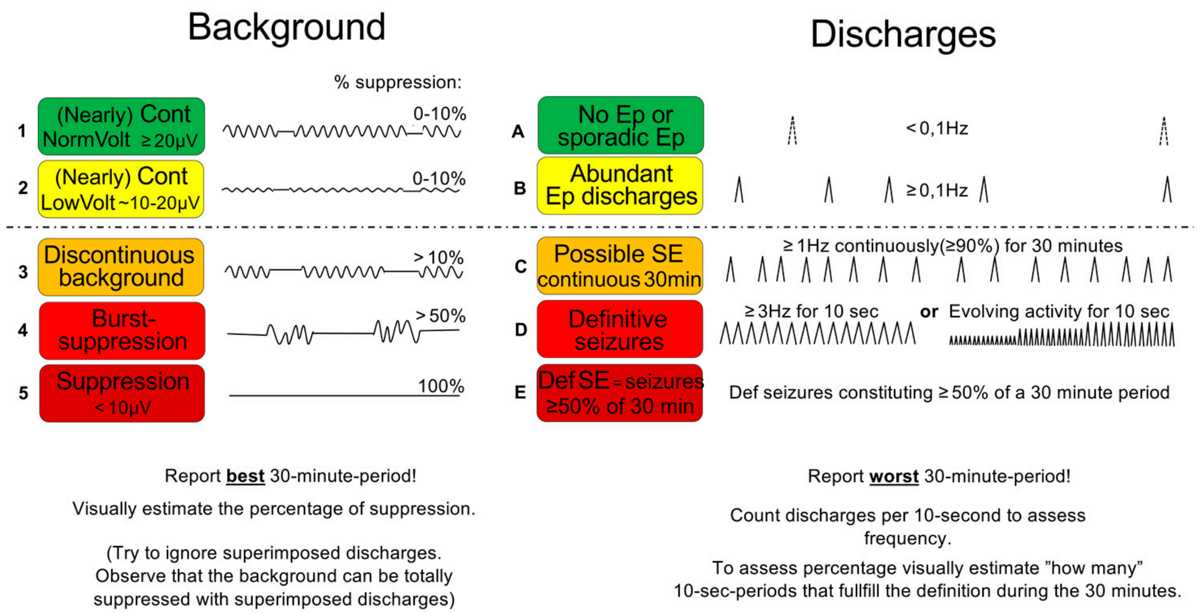


Figure 7 Pre-specified, rank-ordered cEEG patterns

Background (with or without superimposed discharges): 1) Continuous or nearly continuous normal-voltage background >20µV constituting ≥90% of the 30 minute-period (includes nearly continuous background with suppression periods constituting <10% of the recording); 2) Continuous or nearly continuous low-voltage background with most or all activity 10-20µV; 3) Discontinuous background (suppression periods <10µV constituting 10-49%);4) Burst-suppression (suppression periods <10µV constituting 50-99%); 5) Suppression with extremely low-voltage EEG background (peak-to-peak amplitude <10µV in both channels, 100% of the 30-minute-period).

Epileptiform discharges: A) No discharges or sporadic epileptiform discharges, i.e. sharp waves and spikes, at <0.1Hz; B) Abundant epileptiform discharges ≥0.1Hz during a 30-minute-period; C) Possible electrographic status epilepticus = Regularly appearing (=periodic or rhythmic) epileptiform discharges at ≥1Hz continuously (≥90%) appearing during a 30-minute-period; D) Unequivocal electrographic seizure activity, constituting <50% of a 30-minute-period (≥10 second duration generalized rhythmic epileptiform discharges ≥3Hz OR clearly evolving discharges of any type reaching >4Hz); E) Unequivocal electrographic status epilepticus with unequivocal seizure activity constituting ≥50% of a 30-minute-period.

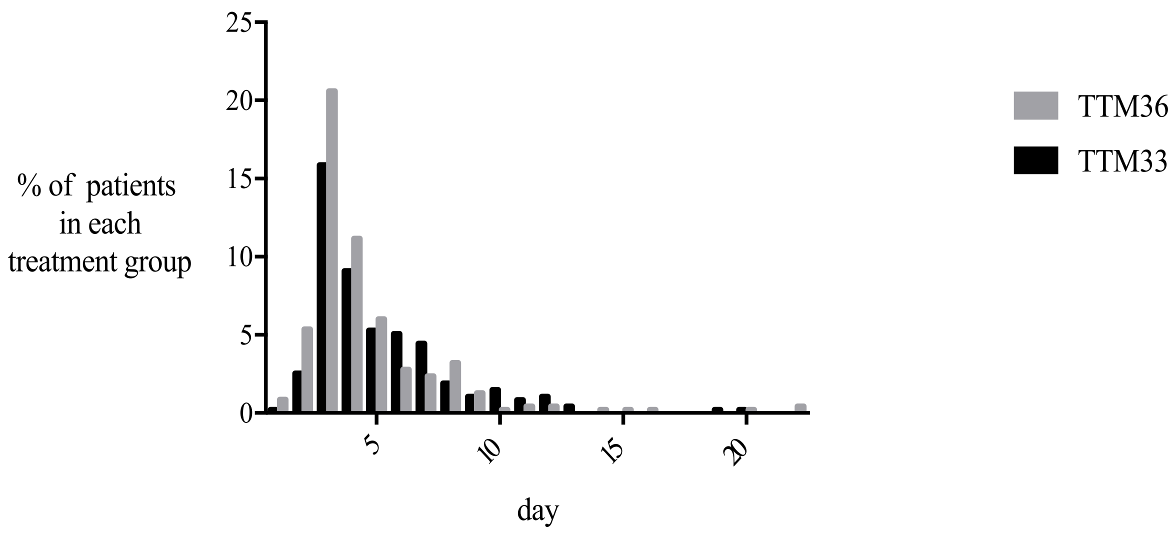
Results

Paper I

539 patients awoke (262 managed at TTM33 and 277 at TTM36), of whom 496 patients had registered day of awakening in the ICU (235 managed at TTM33 and 261 at TTM36). 43 patients awoke after discharge from ICU with no exact day of awakening available.

TTM33 vs TTM36

Awakening occurred later in TTM33 (median 4, IQR 3–6) than in TTM36 (median 4, IQR 3–5), p=0.002 (figure 8), these results remained when a competing risk analysis for risk of awakening including risk of death was performed.



Figur 8 Daily awakening in patients treated at TTM33 and TTM36

Early vs late awakening

Among 496 patients with registered day of awakening, 188 (38%) had a late awakening (≥day 5), the last awakening was on day 22 (figure 9). Life table survival analysis shows decreasing chances of awakening during day 1–22 (figure 10). The following independent predictors of late awakening were identified by multivariate analysis: TTM33 (p = 0.006), clinical seizures before awakening (p = 0.004) and lower level of consciousness on admission before administration of sedatives (p=0.03). Age was not an independent predictor of late awakening (p=0.08). BMI and renal failure on admission (eGFR<60) were not predictors of late awakening.

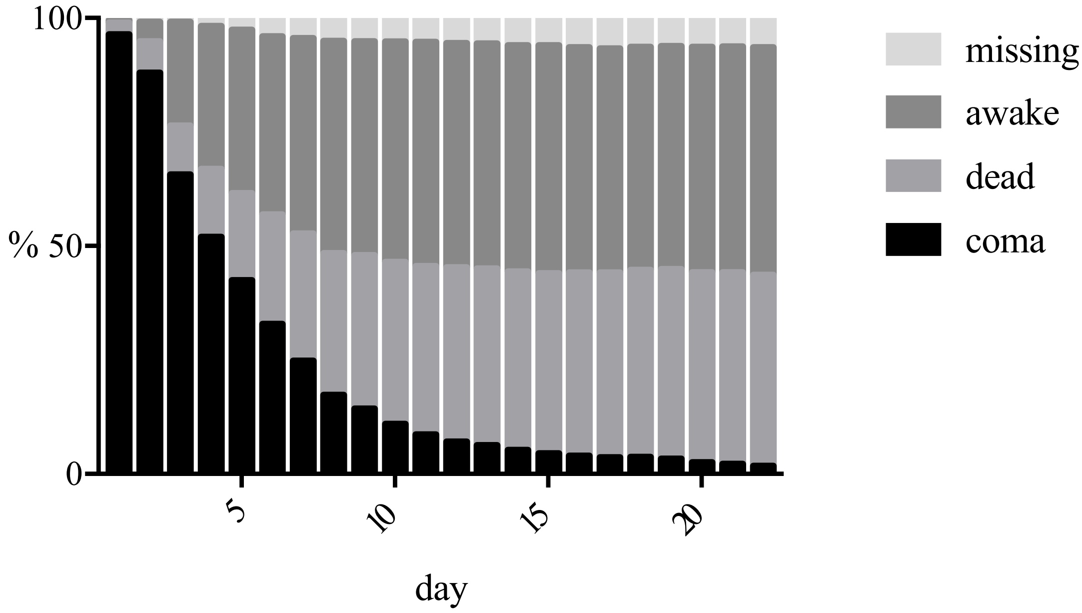


Figure 9 Daily status of TTM-trial patients (n = 939): coma, awakening and death on day 1- 22.

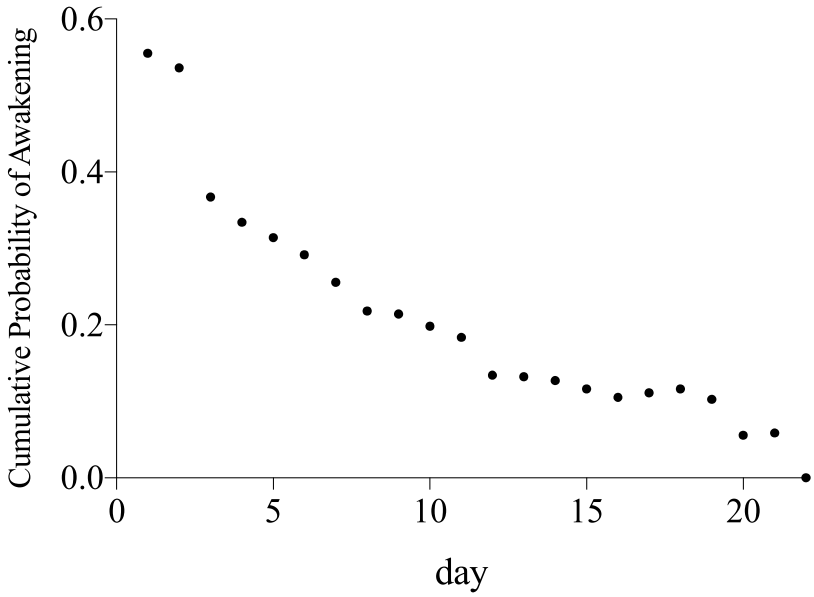


Figure 10 Cumulative probability of awakening, i.e. chances of awakening after this day.

Awakening and long-term neurological outcome

In patients who awoke, there was no significant difference in long-term neurological outcome between TTM33 and TTM36, p=0.12. The Spearman correlation between day of awakening and neurological outcome was 0.20 (95%CI 0.12–0.29), p<0.001. A good long-term neurological outcome was more common among patients with early awakening, 275/308 (89%), as compared to those with late awakening 142/188 (76%) (p<0.001). Seven patients awoke on day 15–22, three had a good neurological outcome. In patients who awoke, neuroprognostication was more commonly performed in the group managed at TTM33 (46/261, 18%) than TTM36 (29/278, 10%). At neuroprognostication, a recommendation to continue active care was issued in 39/46 (85%) patients managed at TTM33 and 26/29 (90%) at TTM36.

Sedation

Data on sedative drugs and sedation monitoring scales were collected from 21/36 trials sites in 352/496 (71%) patients. From sites with reported sedation, data was available for 352/381 patients (92%). There were no statistically significant differences in cumulative doses of the main sedatives used (propofol, midazolam, morphine, fentanyl or remifentanil) at 12, 24 or 48 h between TTM33 and TTM36. 19/20 trial-sites reported use of sedation monitoring scales.

Paper II

Patients with clinical seizures were older, less likely to have a witnessed arrest, receive bystander cardiopulmonary resuscitation (CPR), and have a first monitored shockable rhythm and their time to ROSC was longer.

TTM33 vs TTM36

In patients with clinical seizures, there were no differences in background characteristics, frequency of clinical seizures (table 2) or outcome between the two intervention groups TTM33 and TTM36 regardless of seizure subtype.

Incidence of seizures

Table 2. Frequency of clinical seizures.
Some patients exhibited a combination of myoclonic and tonic-clonic seizures, hence the sum of patients with tonic-clonic and myoclonic seizures is greater than the total number of patients with seizures. Status was defined as generalised seizures of >30 minutes duration.

Seizure type	TTM33 (n=473)	TTM36 (n=466)	All (n=939)	p
Any seizure	147 (31%)	121 (26%)	268 (29%)	0.08
Myoclonic	132 (28%)	108 (23%)	240 (26%)	0.10
Status myoclonus	37 (8%)	36 (8%)	73 (8%)	1.00
Focal myoclonus	48 (10%)	33 (7%)	81(8%)	0.10
Tonic-Clonic	37 (8%)	34 (7%)	71 (8%)	0.81
Tonic-clonic status	12 (3%)	8 (2%)	20 (2%)	0.50
Focal tonic-clonic seizures	6 (1%)	5 (1%)	11 (1%)	1.00
Combination[1]	22 (5%)	21 (5%)	43(5%)	1.00

Outcome and prognostic value

A poor 180-day neurological outcome occurred more often in patients with myoclonus than tonic-clonic seizures (178/197 (90%) vs. 20/27 (74%), p=0.02). Patients with a combination of seizure types had a similar rate of poor outcome as those with isolated myoclonic seizures (40/43 (93%), p = 0.77). Twenty-nine of 268 patients (11%) with seizures had a good outcome. One patient had early onset status myoclonus and a good 180-day neurological outcome. For predictive values, see table 3.

The Kaplan–Meier survival-curves for patients with different seizure types differed (figure 11). Eighteen patients with status myoclonus had WLST due to early status myoclonus and bilaterally absent N20 potentials.

Table 3. Seizures to predict a poor neurological outcome (CPC3-5)
Data are given in numbers and percentages. CPC, cerebral performing category; CI, confidence interval; FPR, false positive rate; TP, true positive; FP, false positive; TN, true negative; FN, false negative. a) First seizure on day 1–2. b) First seizure on day 3–7.

Seizure type	Tested patients (n)	TP (n)	FP (n)	TN (n)	FN (n)	Sensitivity % (95%CI)	FPR % (95%CI)
Any seizure	933	238	29	411	255	48.2% (43.8- 52.8)	6.6% (4.6-9.3)
Early seizures[a)]	933	121	12	480	372	24.5% (20.8-28.6)	2.7% (1.5-4.8)
Late seizures[b)]	933	117	17	423	376	23.7%(20-27.7)	3.9% (2.4-6.1)
Myoclonus (non-status & status)	933	178	19	421	315	36.1% (31.9-40.5)	4.3% (2.7-6.7)
Status myoclonus	933	60	1	439	433	12.2% (9.4-15.3)	0.2% (0.0-1.0)
Early status myoclonus	933	28	1	439	465	5.7% (3.8-8.1)	0.2 % (0.0-1.4)
Tonic-clonic seizures (non-status & status)	933	20	7	433	473	4.1% (2.5-6.2)	1.5% (0.7-3.3)
Tonic- clonic Status	933	9	0	440	484	1.8% (0.8-3.4)	0% (0-1.0)
Combination of seizure types	933	40	3	437	453	8.1% (5.9-10.9)	0.7% (0.1-2.1)

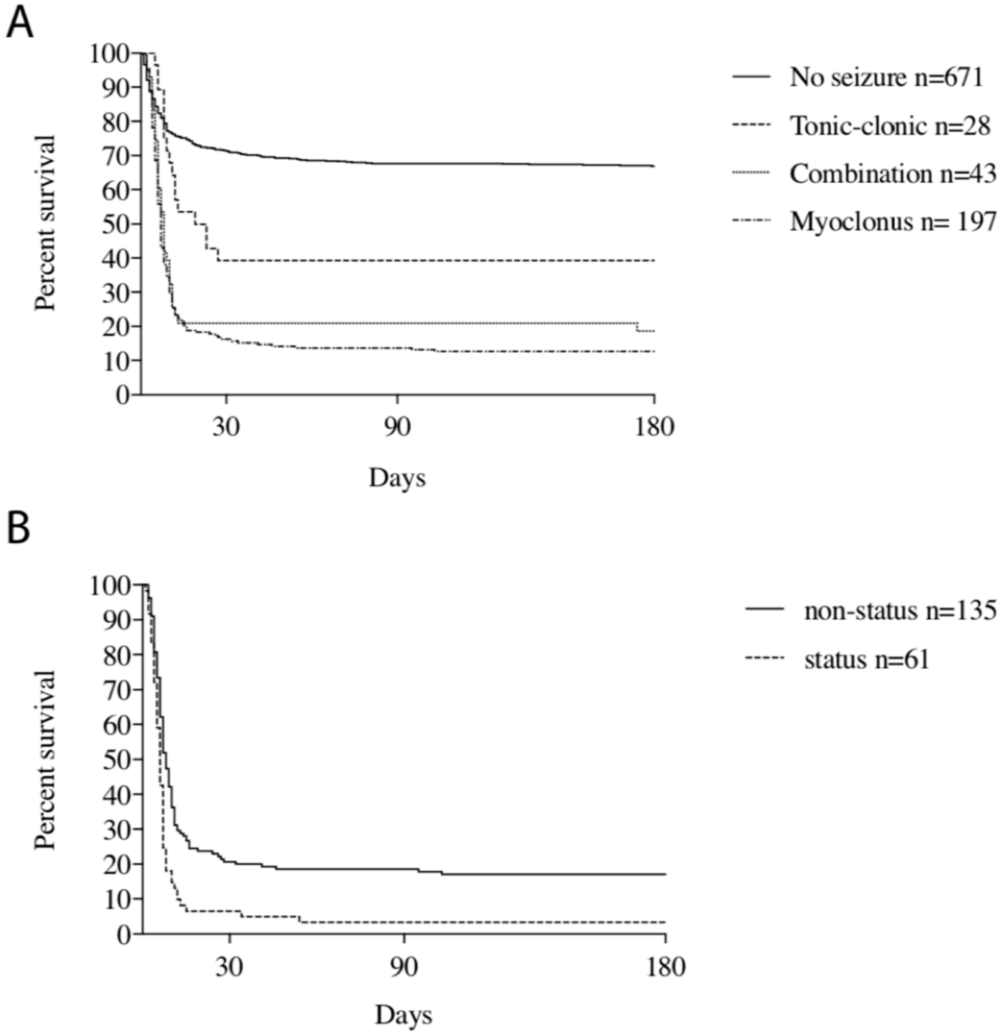


Figure 11 Kaplan–Meier survival curves.

(A) Kaplan–Meier Survivial Curve of all TTM-trial patients. Overall, curves differ significantly (p<0.0001). Curves for combination and myoclonus are similar (p=0.33). (B) Kaplan–Meier Survival Curves of patients with myoclonus (excl. patients with a combination of seizure types). Curves differ significantly (p<0.0001).

EEG

EEG was available for 187/268 (70%) patients with clinical seizures. EEG interpretations were similar in patients with myoclonic, tonic-clonic and a combination of seizure types (p=0.48). The most common EEG finding was an epileptiform EEG found in 83/187 (44%) patients. An unreactive EEG was a common finding among patients with myoclonus status or tonic-clonic status. Patients without EEG (69/268, 26%) had a lower end-of- trial-mortality, less often seizures of >30 min duration.

Treatment of seizures

Myoclonus and tonic-clonic seizures received similar treatment consisting f increasing ongoing sedatives, addition of other sedatives and addition of antiepileptic agents. The most commonly used drugs were: propofol, midazolam and fos-phenytoin.

Paper III

cEEG findings

Table 4. Frequency of reported cEEG findings

Reported findings	EEG-expert		5 ICU physicians, median (range)	
	n	%	n	%
EEG Background				
1. Continuous >20µV	31	44%	35 (26-37)	49% (37-52%)
2. Continuous 10-20µV	5	7%	7 (5-8)	10% (7-11%)
3. Discontinuous	13	18%	8 (4-14)	11% (6-20%)
4. Burst-Suppression	16	23%	15 (10-17)	21% (14-24%)
5. Suppression	6	8%	10 (5-15)	14% (7-21%)
Epileptiform discharges				
A. No or sporadic discharges	37	52%	39 (30-47)	55% (42-66%)
B. Abundant discharges	16	22%	13 (11-22)	18% (15-31%)
C. Possible status epilepticus	10	14%	9 (6-12)	13% (8-17%)
D. Definitive seizures	6	8%	5 (2-8)	7% (3-11%)
E. Definitive status epilepticus	2	3%	3 (1-5)	4% (1-7%)

Interrater agreement – ICU physician versus neurophysiologist

Interrater agreement for the prespecified categories is presented in table 5. Identification of a continuous EEG background yielded substantial agreement (κ0.69) and was detected with median sensitivity 86% (95%CI 71-95%) and specificity 74% (95%CI 57-88%). For detection of epileptiform patterns representing possible or definitive seizure activity agreement was fair (κ 0.39), these patterns were detected with median sensitivity 50% (95% CI 44-65%) and specificity 87% (95% CI 82-90%).

Table 5. Interrater agreement of ICU physicians versus neurophysiologist.

N=71 cEEGs. Percentage agreement and kappa (κ) for the reported prespecified EEG patterns, presented as median (range) among the 5 pairs formed by the 5 ICU physicians and the neurophysiologist. [a] ICU physician reported a pattern in an adjacent rank-ordered category, e.g. the neurophysiologist reported burst-suppression and the ICU physician reported either discontinuous or suppressed background [b] continuous EEG background vs non-continuous (discontinuous, burst-suppression or suppressed) background. [c] possible status epilepticus, unequivocal seizures or unequivocal status epilepticus vs none to abundant discharges (<1Hz).

	Percent agreement 5 pairs median (range)	Kappa 5 pairs median (range)	Strength of interrater agreement (kappa)
Background EEG pattern			
Identical pattern	69 % (60-73%)	0.69 (0.61-0.73)	Substantial
Adjacent pattern[a]	87% (80-89%)	-	-
Identification of continuous EEG background[b]	85% (77-90%)	0.69 (0.57-0.80)	Substantial
Epileptiform discharges			
Identical discharge pattern	62% (56-63%)	0.43 (0.38-0.49)	Moderate
Adjacent pattern [a]	83% (82-87%)	-	-
Identification of patterns consistent with status epilepticus[c]	79% (73-83%)	0.39 (0.31-0.57)	Fair

Interrater agreement – among ICU physicians

Among the five ICU physicians there was substantial agreement κ 0.63 (range 0.44-0.73) for reporting identical background patterns and moderate agreement κ 0.54 (range 0.45-0.62) for classification of epileptiform discharges. When background was dichotomized into continuous versus non-continuous background agreement was substantial κ 0.68 (range 0.43-0.72). Epileptiform discharges representing possible or definitive seizure activity), were detected with moderate agreement κ 0.54 (range 0.42-0.68)

Paper IV

At the six trial sites with cEEG monitoring, 134/302 patients were monitored with cEEG. Nfl and GFAP were analyzed in 128/134 patients, not all 128 patients had biomarkers sampled and analyzed at all time points. 26/128 patients developed ESE. 18 patients developed ESE by 24 hours, 6 at 24-48 hours and 2 by 48-72 hours.

Nfl

In multivariate analysis ESE was an independent predictor of serum Nfl levels at 72 hours ($p<0.001$). When compared to the matched control group, serum levels of Nfl were significantly higher in patient with ESE at 72 hours after cardiac arrest (median 4358 (IQR1720-5364) vs 142 (43-2661) pg/mL, $p=0.03$, figure 12). Although numerically higher, statistical significance was not reached at 24 hours (2227 (1341-4760) vs 391 (38-3286), p=0.30) or 48 hours (3803 (1647-8035) vs 130 (39-8144), p=0.40) (figure 12).

GFAP

In multivariate analysis, ESE was not an independent predictors of serum GFAP at 72 hours. When compared to the matched control group, serum levels of GFAP were significantly higher in patient with ESE at 72 hours after cardiac arrest (median 117 (IQR 71-305) vs 106 (31-965) ng/mL, p=0.04, figure 12). Levels were not significantly higher at 24 hours (76 (53-145) vs 106 (31-965), p=0.64) or 48 hours (122 (82-229) vs 95 (19-723), p=0.40) (figure 12).

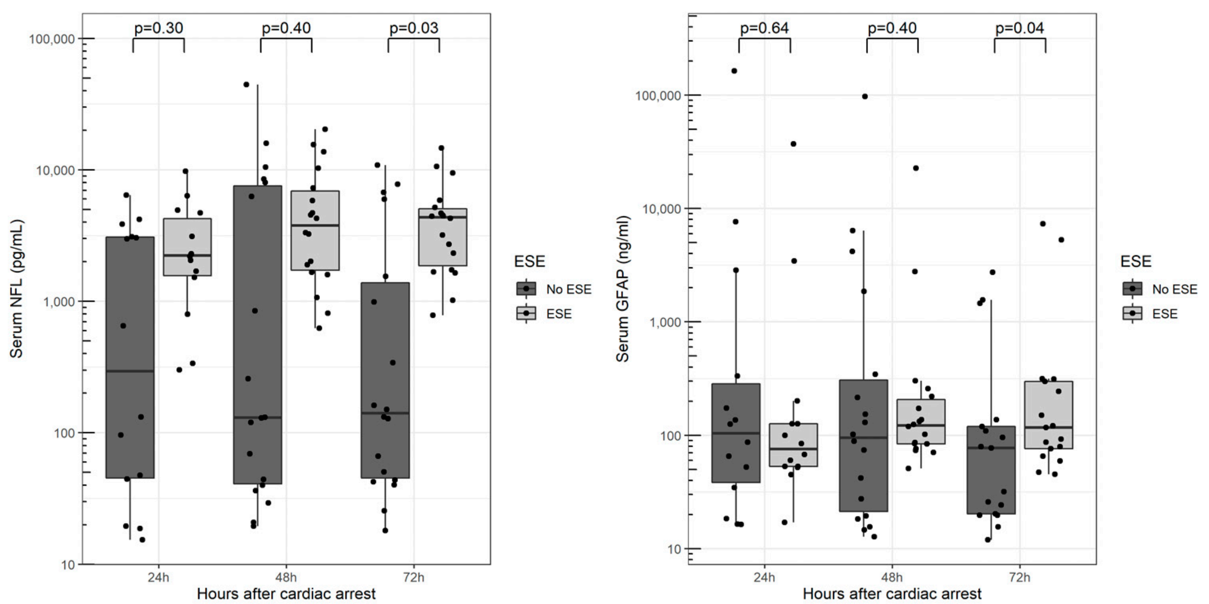


Figure 12 Serum levels of Nfl and GFAP (pg/mL) at 24, 48, 72 hours after cardiac arrest in patients who have developed ESE before time point of blood sample vs their matched controls.

The lower boundary of the boxes indicate the 25th percentile; horizontal line within the box, median; higher boundary of the box, 75th percentile; error bars, 90th and 10th percentiles.

Discussion

Paper I-IV all use data collected during the TTM-trial. Results are strengthened by the large number of patients in the multicentre TTM-trial, the extensive prospective data collection and strict criteria for WLST.

Awakening

Paper I is the largest prospective study on awakening after cardiac arrest and TTM. Awakening was delayed (≥day 5) in 38% of patients who awoke and neurological outcome was good in 76% of late awakeners.

Awakening occurred later in TTM33 than in TTM36, confirming results of an earlier, smaller study[141]. Additionally, in multivariate analysis, TTM33 was an independent predictor of late awakening. If sedation is not prolonged for medical reasons, time of awakening after cardiac arrest will vary due to severity of brain injury, duration of TTM including the re-warming phase, type and dose of sedation and effects of TTM on pharmacokinetics of sedative drugs. The background variables analyzed in paper I did not suggest a more severe brain injury as the cause of later awakening in TTM33 and there were no differences in administered sedative drugs at 0-48 hours. These results suggest that the slowing effects lower body temperature on pharmacokinetics[54] may contribute to the later awakening in TTM33.

Delayed awakening may put patients at higher risk of WLST, stressing the importance of timely multimodal neuroprognostication[17, 44]. Indeed, neuroprognostication was more commonly performed in TTM33, but recommendation to continue active intensive care was also more commonly issued for these patients. This is consistent with previous data from the TTM-trial[43] and makes an effect on outcome of the later awakening in TTM33 unlikely.

The daily cumulative probability of awakening illustrates the decreasing chances of awakening with duration of coma. Most patients who awoke had a good neurological outcome, consistent with a previous study[142]. There was a significant but weak correlation between time until awakening and long-term neurological outcome, suggesting an association between early awakening and less brain injury.

The correlation analysis of time to awakening and neurological outcome yielded a low value of the correlation coefficient, likely due to the large inter-individual variation of day of awakening in patients with good neurological outcome.

GCS-M on admission and clinical seizures were also independent predictors of late awakening. Both are markers of severity of brain injury, consistent with day of awakening correlating with long-term neurological outcome. A recent retrospective single-centre study found late awakening to be associated with markers of more severe brain injury: discontinuous (vs continuous) EEG background was more common and NSE levels were higher[143]. Clinical seizures in the TTM-trial were commonly treated with additional sedative drugs[144], likely further contributing to late awakening. Previous studies have found other predictors of late awakening[141, 145, 146]. These studies used both different sets of patient characteristics in their multivariate analyses and different sedation regimens, both likely to affect identified predictors. In paper I, age did not reach statistical significance as an independent predictor of late awakening but age is yet likely a clinically important predictor. Prolonged effects of sedatives may be observed in older age since renal function, activity of cytochrome enzyme P450 and hepatic blood flow all decrease with older age[147]. Renal failure on admission was not an independent predictor of late awakening in our data. However, certain drugs, e.g. midazolam, its active metabolite α-hydroxy-midazolam and morphine's active metabolite morphine-6-glucuronide, will accumulate in renal failure[148, 149].

Clinical seizures

This study is the largest prospective study on clinical seizures after cardiac arrest and the first compare two levels of TTM. Rates of seizures were similar to those reported after the introduction of TTM, supporting previous findings[60, 62-64, 72] and the outcomes for patients with clinical seizures (including FPR to predict a poor outcome) in this study are also similar to more recent studies[62-64, 72, 150], suggesting generalizability the results in the present study.

Overall myoclonus is a sign of poor outcome after cardiac arrest. If the myoclonic seizures are less explicit, e.g. non-status myoclonus in this study, their prognostic significance is less clear. This may be explained by a less severe brain injury, misdiagnosis of other movement and myoclonus due to other causes. The group of patients with non-status myoclonus likely also contained cases with more severe myoclonus suppressed by sedative medication[151]. This study reported two survivors with status myoclonus, one of whom had an early status myoclonus and a good neurological outcome. The American Academy of Neurology guidelines on neuroprognostication after cardiac arrest[67] state that a status myoclonus on day 1 post-arrest was predictive of a poor outcome with an FPR of 0%. Since the publication of the guidelines, several cases of early-onset status myoclonus and good neuro-logical outcome have been reported in hypothermia treated patients[63, 65, 66, 68]. Additionally, Lance-Adams syndrome (action myoclonus persisting after awakening compatible with otherwise good outcome) may occur on rare occasions mainly, but not exclusively, after cardiac arrest of primarily hypoxic origin. This study only included patients with a presumed cardiac cause of arrest and there was no evidence of chronic myoclonus the two survivors, suggesting that good outcome is possible also from other forms of status myoclonus.

Studies from the pre-TTM era, generally report a higher incidence of clinical seizures than later studies in which patients received TTM and sedation[71, 152, 153] but most studies were small with a varying time-span for recording seizures. This study found no difference in frequency of seizures between patients managed at TTM33 and TTM36, suggesting that differences between older studies and the present one may be explained by factors other than temperature management, e.g. improvements in ICU care and masking seizures by sedative and muscle relaxant drugs during TTM.

Previous EEG-data suggest that later onset electrographic seizures have a better prognosis than early onset seizures[81, 154], a finding that was not reproduced in this study on clinical seizures. In this study the timing of clinical seizures in relation to timing of normothermia, the effect of sedative medication and potential misdiagnosis of shivering are not known, limiting conclusions.

cEEG as a bedside-tool in the ICU

This is the first study to investigate the interrater variability of a trained non-expert versus an EEG-expert using simplified cEEG specifically in comatose survivors of cardiac arrest, a type of patient frequently cared for in the general ICU.
Several previous studies have investigated the interrater agreement among EEG-experts reading full-montage EEG. In post-cardiac arrest patients, substantial agreement was reported on EEG background continuity and voltage, similar to the agreement between ICU physicians and an EEG-expert in III [80]. In the same study agreement for classifying periodic or rhythmic patterns was only moderate, again similar to the results of III. Interrater agreement for detection of seizures among EEG-experts reading shorter sequences (10-60 seconds) of full-montage EEG has been reported as substantial or near perfect, but was lower for seizure characteristics such as frequency[155-157]. The differences in interrater agreement for seizure detection in previous studies may reflect differences in study-design, e.g. type of patients,

length of EEG recording, level of experience of the EEG-experts or definition of electrographic seizures used.
It is possible that the ICU physicians would have performed better with more training and exposition. A much smaller study with more extensive training of ICU-physicians, reported more accurate identification of seizures[158]. However, another small study compared trained ICU physicians' interpretations of single-channel aEEG with those of an EEG-expert (who had additional access to the single raw-EEG-channel)[159], reported sensitivity of 40% and specificity of 89% for identifying electrographic seizures in patients with recent clinical seizures, similar to the results of III[159].

Considering results of previous studies in combination with the clinical reality of limited access to EEG-expertise outside office-hours, the ICU physicians' interpretation of cEEG in patients post-cardiac arrest may be of value as a preliminary interpretation awaiting review by an EEG-expert. For access to EEG-expertise, cEEG monitors may be connected with neurophysiology departments off-site. Additionally, improving the ICU physicians' knowledge of EEG may facilitate communication and collaboration between ICU physicians, neurophysiologists and neurologists.

Electrographic status epilepticus and serum biomarkers of brain injury

To our knowledge this is the first study aiming to investigate secondary brain injury in postanoxic ESE using serum levels of biomarkers of brain injury. It has not previously been shown whether postanoxic ESE causes further secondary brain injury or is simply a marker of severe encephalopathy in which treatment would be futile. Because epileptic activity can increase the metabolic demand [97, 160] and thereby may inflict further neuronal injury, treatment of seizures is generally recommended[44]. These recommendations are based on expert advice awaiting evidence from an ongoing randomized trial[100].

Postanoxic ESE was found to be an independent predictor of serum Nfl-levels at 72-hours after cardiac arrest and patients with ESE had higher levels of serum Nfl at 72-hours compared to a control group matched for markers of primary brain injury. These results suggest additional neuronal injury in patients with ESE and are consistent with an earlier study where ESE was found to be an independent predictor of death[94], however this study lacked a protocol for WLST putting results at risk of the self-fulfilling prophecy[161]. ESE was not an independent predictor of serum GFAP at 72-hour, although GFAP-levels in patient with ESE were higher at 72-hours compared to matched controls. The shorter half-life of GFAP may have contributed to the observed lower levels. However, the difference in results between the two biomarkers of brain injury in this study may also be explained by their different cellular origin and postanoxic ESE predominantly injuring neurons as opposed to glial cells.

In an attempt to answer the question of what comes first, the ESE or the secondary brain injury, a control group matched for predictors of poor neurological outcome was identified among patients without ESE. The variables used for matching were arrest variables suggesting a similar primary brain injury, but also similar risk factors for developing secondary brain injury due to reperfusion injury, fever, hyperglycemia, hypoperfusion or seizures.

The serum biomarkers of brain injury Nfl and GFAP were chosen due to their quick release and prolonged presence in serum after brain injury[111], making elevated levels in subsequent samples more likely to represent additional injury compared to biomarkers of brain injury with shorter half-lives. At 72 hours after cardiac arrest, serum Nfl and GFAP levels were significantly higher in patients with ESE compared to matched controls suggesting that ESE may cause additional secondary brain injury.

The study design is only an attempt to correct for secondary brain injury other than ESE, and cannot exclude these other mechanisms of secondary brain injury as a cause for the elevated levels of serum Nfl and GFAP. The lack of negative result in this study is also important, if no difference in serum biomarkers of brain injury had been found between the group with ESE and their matched controls, this would have suggested that postanoxic ESE does not contribute to further brain injury after and futility of treatment.

Limitations

Only patients with cardiac arrest of presumed cardiac origin were included, results may not be applicable to patients with cardiac arrest of other causes.

Outcome assessors were blinded to level of TTM, while ICU staff was not. ICU staff was instructed to treat patients in the two intervention arms equally. But awareness of level of TTM may have affected all patient management including choice of treatment and assessment of clinical variables.

The TTM-trial was not primarily designed to investigate awakening, clinicals seizures or serum biomarkers in postanoxic ESE, e.g. exact timings of some variables were not available, e.g. awakening, cessation of sedative administration, seizure and antiepileptics. Sampling of serum biomarkers was not timed to onset of ESE. For variables recorded daily during the trial, the varying duration of day 1 may have contributed to error. Neither sedation nor antiepileptic management was protocolized.

The study design of III did not entirely reflect the daily clinical practice of cEEG interpretation bed-side in the ICU, e.g. all cEEGs were presented within a short time frame without distracting tasks. The aim of this study was to assess the ICU physicians' interpretations of EEG, therefore an interrater-assessment among neurophysiologists was not performed. Intra-rater agreement was not assessed. All 5 ICU physicians had no prior formal training in cEEG interpretation but, worked in ICUs were cEEG was routinely monitored but only interpreted by neurophysiologists.

Conclusions

Awakening

- Late awakening is common and patients often have a good long-term neurological outcome.
- Time to awakening was longer in TTM33 than in TTM36. The difference could not be attributed to sedative drugs administered during the first 48 h after cardiac arrest.
- Independent predictors of late awakening were: TTM33, level of consciousness on admission and clinical seizures.

Clinical seizures

- Clinical seizures are common after cardiac arrest and associated with a poor outcome.
- Good outcomes occur, even in early status myoclonus.
- No differences in outcome between early and late onset clinical seizures.
- Level of TTM does not affect the prevalence or prognostic significance of seizures.

cEEG as a bedside-tool in the ICU

- After cardiac arrest, preliminary bedside interpretations of simplified cEEGs by trained ICU physicians may allow earlier detection of clinically relevant cEEG changes.
- Earlier diagnosis may prompt changes in patient management as well as additional evaluation by an EEG-expert.
- Bedside interpretation of cEEG by ICU physicians requires awareness of limitations of both the simplified electrode montage and the cEEG interpretations performed by ICU physicians.

Postanoxic ESE and serum biomarkers of brain injury

- After cardiac arrest, ESE is associated with higher levels of serum Nfl suggesting more severe neuronal injury possibly caused by ESE, which can potentially be mitigated by treatment with antiepileptic drugs.
- Associations with GFAP and glial injury are less clear.

Future directions

Sedatives and TTM

The later awakening in patients managed at TTM33 vs TTM36 without any difference in administered sedation, suggests an effect of level TTM on pharmacokinetics of sedative drugs. Lingering sedation may also affect neuroprognostication. A study is ongoing as part of the TTM2-trial.

Bedside use of cEEG

Bedside interpretation of cEEG may not be restricted to physicians. Nurses and assistant nurses spend more time bedside and may identify changes in cEEG earlier. Interpretation by nursing staff would also require validation, eg by a study similar to paper III. In the future, computer-assisted EEG interpretations [162, 163] may further aid cEEG implementation, e.g. by alerting staff to changes in EEG.

Postanoxic ESE

Effects of treatment with antiepileptic drugs are being investigated in an ongoing randomized trial[100].

Neuroprognostication

Many prognostic markers included in guidelines[17, 44] were not studied with blinded assessors and often without a protocol for WLST. Also, the added value of different neuroprognostic markers has not been validated.

Populärvetenskaplig sammanfattning

Varje år påbörjas hjärtlungräddning (HLR) vid ca 3500 hjärtstopp utanför sjukhus i Sverige. De senaste 20 åren har överlevnaden förbättrats, sannolikt p.g.a. större medvetenhet hos allmänheten som kan påbörja HLR, ringa 112 och kanske även har tillgång till en automatisk defibrillator. Larmoperatören på 112 kan larma ut räddningstjänsten, som ofta har kortare inställelsetid än ambulans. I några delar av Sverige larmas även ”sms-livräddare” (personer i allmänheten med kunskap i HLR) som befinner sig i närheten av hjärtstoppet.

Av de 3500 där HLR påbörjas, överlever 1300 patienter själva hjärtstoppet. Under hjärtstilleståndet upphör den normala blodcirkulationen. Som en följd drabbas kroppen av syrebrist, vilket främst påverkar det känsliga organet hjärnan. Vid hjärtstilleståndet blir patienten medvetslös och inom några minuter uppstår hjärnskada till följd av syrebrist. Ofta påverkas hela kroppen av syrebristen och flera organ kan svikta. Patienterna behöver vårdas på en intensivvårdsavdelning, där de t.ex. behöver hjälp att andas i respirator. Av de patienter som läggs in på en intensivvårdsavdelning överlever sedan cirka hälften, de som avlider dör p.g.a. att flera organ sviktar (kroppen orkar inte mer) eller p.g.a. hjärnskadan.

När en patient avlider p.g.a. hjärnskadan, sker detta oftast efter beslut om att avsluta livsuppehållande behandling t.ex. genom att respiratorn stängs av. Detta stora beslut grundas på en prognosbedömning av hjärnskadan – kommer patienten kunna vakna igen utan grava handikapp? I bedömningen ingår klinisk undersökning av patienten, tester av funktionen av patientens nervsystem (neurofysiologiska tester), röntgen av hjärnan och blodprover i vilka markörer för hjärnskada analyseras. Flera olika behandlingar har testats för att försöka minska hjärnskadan efter hjärtstopp. Den hittills mest framgångsrika behandlingen har varit kylbehandling.

Avhandlingen handlar om bedömning av hjärnskada efter hjärtstopp, i två av studierna jämförs effekten av kylbehandling vid två olika temperaturer (33°C och 36°C). De viktigaste fynden är:

- Av de patienter som vaknar upp igen, vaknar de som kylbehandlats vid lägre temperatur (33°C) senare, kanske för att de påverkas av sömnläkemedel under längre tid.

- Kliniska kramper (likande epileptiska anfall), medför oftast en dålig prognos men undantag finns. Det är därför viktigt att göra av samlad bedömning av flera olika undersökningar. Ingen skillnad i prognosvärdet sågs vid kylbehandling vid två olika temperaturer.
- Intensivvårdsläkare är tillgängliga för patienterna dygnet runt. Efter en kort utbildning kunde intensivvårdsläkare tolka registrering av hjärnbarkens elektriska aktivitet (elektroencefalogram, EEG). Detta kan innebära snabbare behandling än om EEG tolkas av specialister som endast är tillgängliga dagtid.
- På EEG kan man se krampanfall som pågår i hjärnan utan att kroppen rycker. Krampanfall som syns på EEG följs utav förhöjda nivåer av markörer för hjärnskada i blodprov. Dessa kramper bör behandlas med läkemedel för att undvika att de orsakar ytterligare hjärnskada.

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