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Early multimodal predictors of outcome in out of hospital cardiac arrest patients treated with normothermia

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Early Multimodal Predictors of Outcome in out of Hospital Cardiac Arrest Patients Treated With Normothermia.

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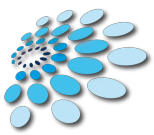

Because, you make my day.

This is dedicated to those who pursue a dream in life,
to the tenacious, stubborn and willful,
to those who fall and always gets up,
those who always seek and those who never give up,
because they look forward,
they always experience,
they believe in the future and will never stop dreaming.

This is for you, my girls.

Content

List of publications

I. Clinical and EEG characteristics of patients with preserved cortical SSEPs after post anoxic coma. Leda Nobile, Erik Roman-Pognuz, Andrea Rossetti, Verginella Francesca, Nicolas Gaspard, Jean-Louis Vincent, Mauro Oddo, Fabio Taccone. Crit Care Med 2016 • Volume 44 • Number 12 (Suppl.) doi: 10.1097/01.ccm.0000508937.19310.20

II. Clinical and electrophysiological correlates of absent somatosensory evoked potentials after post-anoxic brain damage: a multicentre cohort study. Leda Nobile, Erik Roman-Pognuz et. al Intensive Care Medicine experimental 2016, 4 (Suppl. 1):28 doi: 101188/s40635-016-0100-7

III. SSEP N20 amplitude as an early predictor of neurological outcome in cardiac arrest survivors treated with therapeutic hypothermia. Erik Roman-Pognuz, Barbara Penolazzi, Walter Gerbino, Paolo Manganotti, Fabrizio. Monti and Giorgio Berlot.

TSPC2016: Proceedings of the Trieste Symposium on Perception and Cognition, November 4th 2016", Trieste, EUT Edizioni Università di Trieste, 2016, p. 82.

IV. Omeostasi termica perioperatoria. Edizioni Minerva Medica. Capitolo 14: Ipotermia terapeutica e temperature management dopo arresto cardiaco. E. Roman-Pognuz, A. Peratoner

V. ISBN 978-88-7711-888-2;Impact of European Emergency Number (112) in out of hospital Cardiac Arrest: Trieste experience. Giuseppe Davide Caggegi, Carlo Pegani, Perla Rossini, Michele Zuliani, Erik Roman Pognuz, Davide Durì, Matteo Danielis Alberto Peratoner.

Resuscitation 2018 • Volume 130 • Supplement 1, Page e132

VI. Markers of cardiogenic shock predict persistent acute kidney injury after out of hospital cardiac arrest. Erik Roman Pognuz, Jonathan Elmer, Jon Rittenberger, Francis X Guyette, Giorgio Berlot, Alberto Peratoner, Silvia de Rosa, Blanca Martinez de Arrabye, Umberto Lucangelo, Clifton W Callaway.

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Abbreviations

AAN American Academy of Neurology

ACNS American Clinical Neurophysiology Society

ATP Adenosine triphosphate

CA Cardiac arrest

CT Computed tomography

CI Confidence intervals

CPC Cerebral Performance Categories scale

CPR Cardiopulmonary resuscitation

EEG Electroencephalography

ESE Electrographic status epilepticus

ERC European Resuscitation Council

EMS Emergency medical system

ESICM European Society of Intensive Care Medicine

FPR False positive rate

GCS Glasgow coma scale

ICU Intensive care unit

ILCOR International Liaison Committee on Resuscitation

IHCA In Hospital Cardiac Arrest

IQR Interquartile range

MRI Magnetic resonance imaging

N20 Cortical peak in median nerve somatosensory evoked potentials

NCSE Non-convulsive status epilepticus

NSE Neuron specific enolase

OHCA Out-of-hospital cardiac arrest

PCAS Post cardiac arrest syndrome

PEA Pulseless electrical activity

ROSC Return of spontaneous circulation

SSEP Somatosensory evoked potentials

VF Ventricular fibrillation

VT Ventricular tachycardia

TTM Targeted temperature management

WLST Withdrawal of life-sustaining therapy

Background, Epidemiology and Pathophysiology

Cardiac arrest (CA) is a dramatic event defined as the sudden cessation of cardiac activity, breathing and consciousness that requires electric shocks and chest compressions for the return to spontaneous circulation (ROSC).

CA is one of the leading causes of death and disabilities worldwide. It accounts for about 375,000 fatalities in Europe, of which 55,000 occur in Italy, every year. Because of its incidence and the increasing economic burden for healthcare systems, the identification of early prognostic indicators able to predict the residual brain performance has become essential.

Preservation of life is no longer the only goal in the management of such a dramatic event. The primary endpoint is quality of life.

Therapeutic hypothermia (HT) and Target Temperature Management (TTM) are treatments aimed at the preservation of brain functions after an anoxic insult. The refinement of therapeutic cooling techniques is due to studies conducted in recent decades, but the very concept of the benefit that the reduction of temperature can have in certain cases, was already reported in distant times. According to historical evidence, Hippocrates knew that in the cold winters, soldiers affected by head injury in battle survived better than those who fell in the milder seasons. The hypothermia as we know it today, from a scientific point of view, is due to the early rudiments of cardiopulmonary resuscitation at the beginning of the 19th century. From that moment on, hypothermia has had moments of light and shadows, until the beginning of the last century, when Britton and collegues, brought to light in an article, how potentially extreme hypothermia would benefit patients after apparent death. [1] In the '50s the studies began to take a scientific aspect. Williams first and Benson later, focused the advantage that hypothermia can give on cardiac arrest. The first randomized trials date from the 1990s, but it is only on 2002 that two randomized

controlled Trials (RCTs) described clearly the therapeutic efficacy of hypothermia in the preservation of post-anoxic brain damage following cardiac arrest (CA). [1,2,3]

In 2002 Bernard et al published in New England Journal of Medicine (NEJM) a study conducted on 77 patients. A moderate hypothermia (33 ° C) was applied for 12 hours to the treated group (43 people), the remainder constituting the control group. The data clearly shows that 48.8% of patients treated with hypothermia had a good neurological outcome compared to the control group (26.5%). The second study was conducted by the European Hypothermia After Cardiac Arrest Study Group (HACA), published the same year on NEJM. The trial includes 273 patients. In this study the hypothermia period was extended to 24 hours, (12 more than the previous study) with a thermal target between 32-34 ° C. This work showed that 55.2% of patients treated with therapeutic hypothermia had a good neurological outcome compared to 39.4% of the untreated group. These two trials represented a landmark in the treatment of cardiac arrest, introducing the concept of post-arrest syndrome. Cardiac arrest develops a process that progresses and expands well beyond the return to circulation (ROSC) and is not limited to myocardial dysfunction but involves brain damage and the cytokine storm linked to ischemia and subsequent reperfusion. The complexity of this cascade of events suggests the identification of a therapeutic window driving which Hypothermia could hit the reversible factors influencing the final outcome.

Initially the use of hypothermia as a neuroprotective factor was attributed to the reduction of cell metabolism.

Currently, the most reliable hypotheses suggests hypothermia would reduce the oxygen demand to tissues, reducing the harmful effects of ischemia. Cells need O2 to generate adenosine triphosphate (ATP) to generate energy. The ATP, in turn, is used to activate the cellular import and export. In oxygen debt the amount of ATP needed to regulate the ionic levels would be unavailable defining what is called "intracellular pollution". In this context, hypoxemia, caused by cardiac arrest, would result in the cell's inability to generate ATP to maintain ion cell homeostasis. Although HT seems to guarantee a cellular membrane stability after the ischemic insult, this effect does not seem to be related to the depth of hypothermia.

The thermal control is also crucial in the reperfusion damage by oxidative stress which involves the transport of inflammation mediators during the restoration of the circulation (ROSC).

Hypothermia seems to act by counteracting the immune-inflammatory response and determining the reduction of its harmful effects.

Since 2010, therapeutic hypothermia and thermal control have been recommended by international guidelines (AHA, ERC) for patients with ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) (class I, Level of Evidence B), and for patients with asystole and pulseless electric activity (class II, Level of Evidence B).[4] In 2012 a Cochrane review gave added weight to these conclusions. [5]

The epidemiological characteristics are difficult to determine with precision. Survival from cardiac arrest is poor and fraught with complications across many organ systems due to post cardiac arrest syndrome (PCAS). Over the past decade a number of factors have contributed to an overall increased of survival rates in many countries, although survival to hospital discharge varies globally.[6,7,8,9]

Progress in advanced life support (ACLS), target temperature management (TTM), persistent support to cerebral perfusion and mitigation to organ insult like hyper glycemia or infection have contributed to an increase of percentage of survivors with good neurological recovery after cardiac arrest. This progress supports an increasingly optimistic expectation to have an earlier prediction of long term outcomes.

To date, the early prognosis of neurological outcome represents the research frontier for the evaluation of neurological performance following hypoxic-ischemic cerebral injury.

The aim of the study is to evaluate the early neurophysiological changes from different perspectives.

Etiology

Cardiac arrests are generally divided in Out of Hospital (OHCA) and In Hospital (IHCA) incidents according to the location of the occurrence. There are four electrical mechanisms leading to CA: ventricular tachycardia (VT), ventricular fibrillation (VF), asystole and pulseless electrical activity (PEA). The most common immediate presenting electrocardiographic rhythms of CA are the ventricular fibrillation (VF) and the pulseless ventricular tachycardia (VT). According to the treatment these rhythms are called "shockable" and they are associated with better survival than the "non shockable" rhythms (Pulsless Electrical activity (PEA) and Asystole). [8]

The exact causes of collapse are often complex, but generally they are divided into cardiac and non-cardiac causes. [10] However, a life-threatening arrhythmia usually develops in a person with a pre-existing heart condition, such as a coronary artery disease (CAD), an acute Myocardial infarction (MI) or a Cardiomyopathy where heart tissue damage caused these arrhythmias.

In children, CA is mainly due to a congenital heart disease. Furthermore, there are few primary rhythm abnormalities conditions such as Brugada's syndrome and long QT syndrome, that are involved in the development of CA arrhythmias. Several risk factors are often linked with coronary artery disease including:

- A family history of coronary artery disease
- Smoking
- Hypertension
- Hypercholesterolemia
- Obesity
- Diabetes

Other factors that may increase risk include:

- Family history of cardiac arrest
- Family history heart disease, rhythm disorders, congenital heart defects, heart failure and cardiomyopathy
- Age
- Using of cocaine or amphetamines
- Nutritional imbalance, such as low potassium or magnesium levels

Cardiac causes has been reported in more than ⅔ of OHCA and Coronary disease has been reported as the underlying causes in more than ½ of patients. [11,12,13]

The most common non-cardiac causes are trauma, bleeding (such as GI bleeding, aortic rupture or intracranial hemorrhage), an overdose of drugs, drowning and pulmonary embolism.

Non primary cardiac causes account for less than ⅓ of CA .[14]

Out-of-Hospital Chain of Survival

The chain of survival (Fig A) is a system of care that have been used for almost 25 years as an essential requirement for OHCA and IHCA to achieve the ROSC after a cardiac arrest. In 2015, resuscitation guidelines separated the original chain into OHCA and IHCA systems of care. The Chain has been made and developed to reduce time of arrest that is a fundamental for survival and positive neurological outcome. [15-16]

The Chain of Survival consist of four links that include early recognition and activation, early CPR, rapid defibrillation, effective advanced life support (ALS), and integrated post–cardiac arrest care.

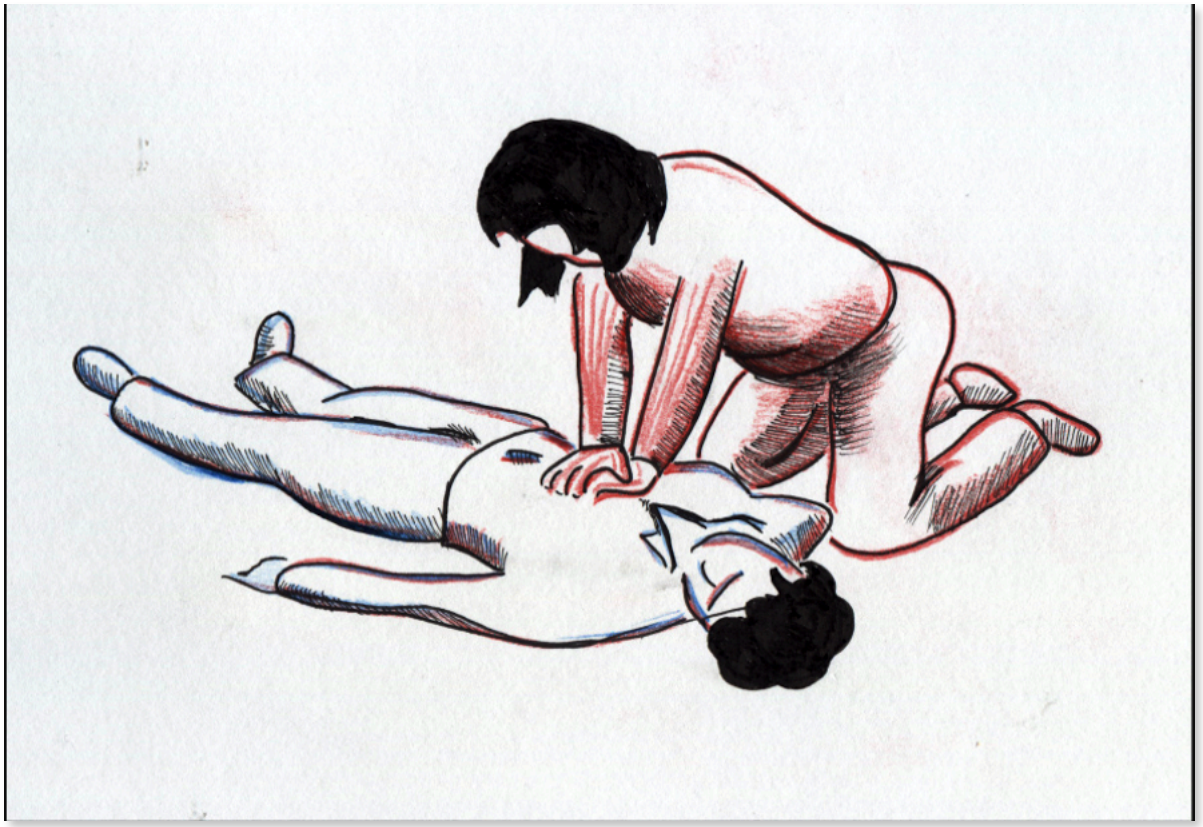
Fig.A The chain of survival

Time remain an essential constraint in pursuit of high quality cardiopulmonary resuscitation, maintaining cerebral perfusion and promoting the restoration of spontaneous circulation .

After recognizing a CA, chest compressions should be initiated immediately in order to allow better delivery of the oxygen that is already present in the lungs and arterial circulation to the heart and brain. Adequate cerebral and coronary perfusion pressure is essential for the success of resuscitation and restoration of neurological functions. [17,18]

After a cardiac arrest, patients are generally comatose and brain stem and cerebral function are absent. The Brain stem is more resistant to anoxic-ischaemic damage than the cerebral cortex and, after the circulation has been re-established, the brain

stem reflexes will be gradually restored. Consciousness, after awakening, as such as verbal and motor responsiveness, eye-orientation, speech and memory depends on the cortical function recovery. [19]



Courtesy of Anna Baldo

Post-cardiac arrest syndrome

Approximately ⅔ of patients who received successful cardiac resuscitation die before hospital discharge due to the post cardiac arrest syndrome (PCAS), described and defined by the International Liaison Committee on Resuscitation (ILCOR) in 2008.
This complex pathophysiological process involves all the organs and depends on both CA ischemic damage and the following reperfusion and re-oxygenation after ROSC. [20]

The Key elements composing the syndrome are:

- Cerebral dysfunction and the resulting post anoxic damage leading to reduced cerebral perfusion, edema and neuro degeneration.
- Myocardial dysfunction due to acute coronary syndrome and myocardial stunning.
- Systemic ischemia and reperfusion response causeing generalized activation of immunological and coagulation pathways, increasing the risk of multiple organ failure and infection.
- Persisting acute pathology that caused or contributed to the cardiac arrest itself

Myocardial dysfunction occurs from the first hours up to the first post arrest days and is the leading cause of early death after resuscitation.[21,22]
Brain damage, on the other hand, affects the final outcome of post arrest patients, representing the main cause of death. [23]

Targeted temperature management (TTM)

Despite the hypothermia research begun during the first half of the 20th century, in the early 1960s Peter Safar and colleagues at the University of Pittsburgh, were among the first to suggest the use of deep hypothermia (28-32 °C) in humans for brain protection after cardiac arrest. Unfortunately side effects resulting from exposure to temperatures below 30°C forced thermal treatment to be abandoned for years.[24]

In 2002, the HACA group and Bernard's Australian group published two randomized controlled trials (RCTs) that demonstrated therapeutic hypothermia promoted improved survival and neurological recovery in a selected population of patients with CA [4-15]. Since then, the thermal treatment has gained wide acceptance and is currently recommended in the guidelines [11]. No RCTs have been conducted for more than 10 years, but a numerous single-center studies have reported how the enforcement of hypothermia has improved survival.[25]

In 2013 the Niklas Nielsen and colleagues, evaluated in the TTM trial the effects of temperature management at 33 ° C vs. 36 ° C showing no difference in outcome between the two intervention groups.[26] However, they have shown how it is important to implement a strict temperature control to avoid hyperthermia, regardless of the set target temperature. From this perspective, the term "therapeutic hypothermia" has been replaced with "target temperature management" to underline the importance of the management of temperature even after the treatment 19,20

As a consequence, ILCOR guidelines in 2015, recommend the use of TTM between 32°-36 °C for at least 24 hours post-arrest. [27] These suggestions led many individual centers to perform a temperature control at 36°C avoiding any hypothermia side effects.

The therapeutic hypothermia mechanisms of action are multiple and not yet clearly understood. (Fig.2)

Anti-apoptotic action seems to play a relevant role. The pathways involved inhibit the influx of Ca^{2+} ions into the cell diminishing the cytoplasmatic accumulation and limiting the mitochondrial damage.

Moreover, hypothermia limits intra and extracellular acidosis and the release of glutamate and glycine reducing cerebral excitotoxicity, inflammation and the production of nitric oxide and free radicals.

Among the many described mechanisms believed responsible for the neuroprotective effects of hypothermia are: [28]

- A decrease in cerebral metabolism
- A reduction of apoptotic mechanisms including mitochondrial dysfunction
- Slowing of the cerebral excitatory cascade
- A decrease of the inflammatory response
- Reduced production of oxygen free radicals
- Decrease of vascular and membrane permeability

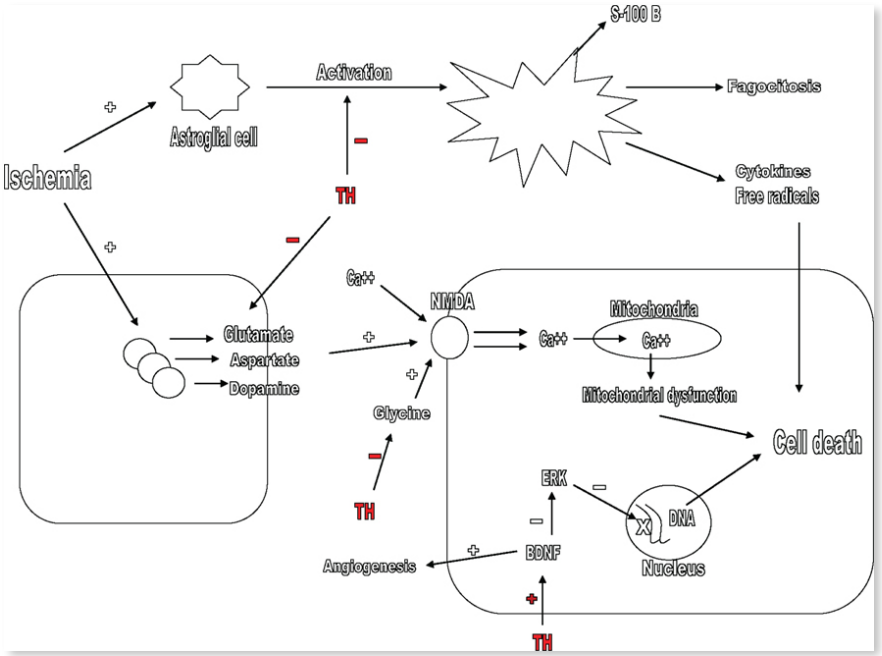


Fig. 2 hypothermia mechanisms of action

Neurological prognostication in comatose CA survivors

In patients who remain comatose several days after resuscitation, the prognosis remain challenging and the evaluation of brain damage is crucial for neurological prognostication. In these situations, when there are few certainties, the role of the physician is to provide informations in order to guide the treatment, to inform the family doctor and relatives about prognosis and to ensure ethical distribution of resources and intensive care, while avoiding futile care of those for whom the vegetative state or death are inevitable.

In 2006, a landmark review from the American Academy of Neurology (AAN) recommended an algorithm to predict poor neurological outcome in comatose survivors after cardiac arrest.

According to the algorithm the following can predict a poor outcome:

- the presence of myoclonus status epilepticus on day 1
- the bilateral absence of the N20-response of the somatosensory evoked potentials (SSEPs) coupled with blood concentration of neuron specific enolase (NSE) above 33 µg/ L at days 1–3
- absent pupillary and corneal reflexes or a motor response no better than extension (GCS M1–2) at day 3

However, these recommendations were based on studies conducted before the introduction of TTM, which is now a gold standard of treatment in post-arrest coma. Moreover, the AAN algorithm did not include predictors such as electroencephalography (EEG) and imaging studies, still in development at that time.

Since the beginning of the thermal treatment and the utilization of sedatives, the indicators of poor neurological prognosis previously used were no longer reliable. [29,30]

Hypothermia, the use of sedative and analgesic drugs as well as their reduced metabolism, possibly masked epilepsy and, moreover the delay in the development and repair of anoxic damage.

The European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM) recently issued updated guidelines including the four main prognostication modalities (clinical examination, electrophysiology including EEG-based predictors, biomarkers, and imaging studies) with the recommendation that these modalities should be combined whenever possible.[31,32,33]

The recent ERC guidelines emphasize the need to use a multimodal strategy for prognostication as well as allowing sufficient time for neurological recovery and metabolism. The suggested prognostication strategy is to start the prognostication process at a minimum of 72 hours post-arrest in patients who are still comatose and where confounders have been excluded. Importantly, the guidelines emphasize that only ocular reflexes and SSEP are reliable marker of prognosis at that time. (figure 2)

In patients who do not regain consciousness, the chances of a poor prognosis increase with the passing of the days in a comatose state. However, since the introduction of therapeutic hypothermia, cases of recovery of consciousness with good neurological recovery have been observed even after many days.

Each of the individual prognostic elements listed above are factored to account by a percentage of false positives.

The aim of a multimodal approach is to refine the predictive power by combining the results of several prognostic indicators.

Multimodal prognostication

Neurological recovery is related to the severity of brain injury and follows certain progressive steps. Since brainstem is less sensitive to hypoxia than other structures, initially there is a return to brainstem functions with the restoration of cranial nerve reflexes and spontaneous breathing. Afterwards, the structures which control deeper functions, like reactivity and consciousness, speech, motor function and memory will later return to activity.
Several methods for predicting the long term outcome have been reported. For a reliable prognostication a combination of multiple predictors is needed.[30]

The multimodal approach makes use of the following elements: [29] (Fig.3)

1. Clinical neurological examination

- pupillary reflex
- corneal reflex
- motor reaction to stimulation (motor GCS)

2. Neurophysiological:

- Electroencephalography EEG
- Somatosensory evoked potentials (SSEP)

3. Biomarkers:

- specific neuron enolase (NSE)

4. Neuroimaging:

- Brain CT scan
- Magnetic resonance (MRI)

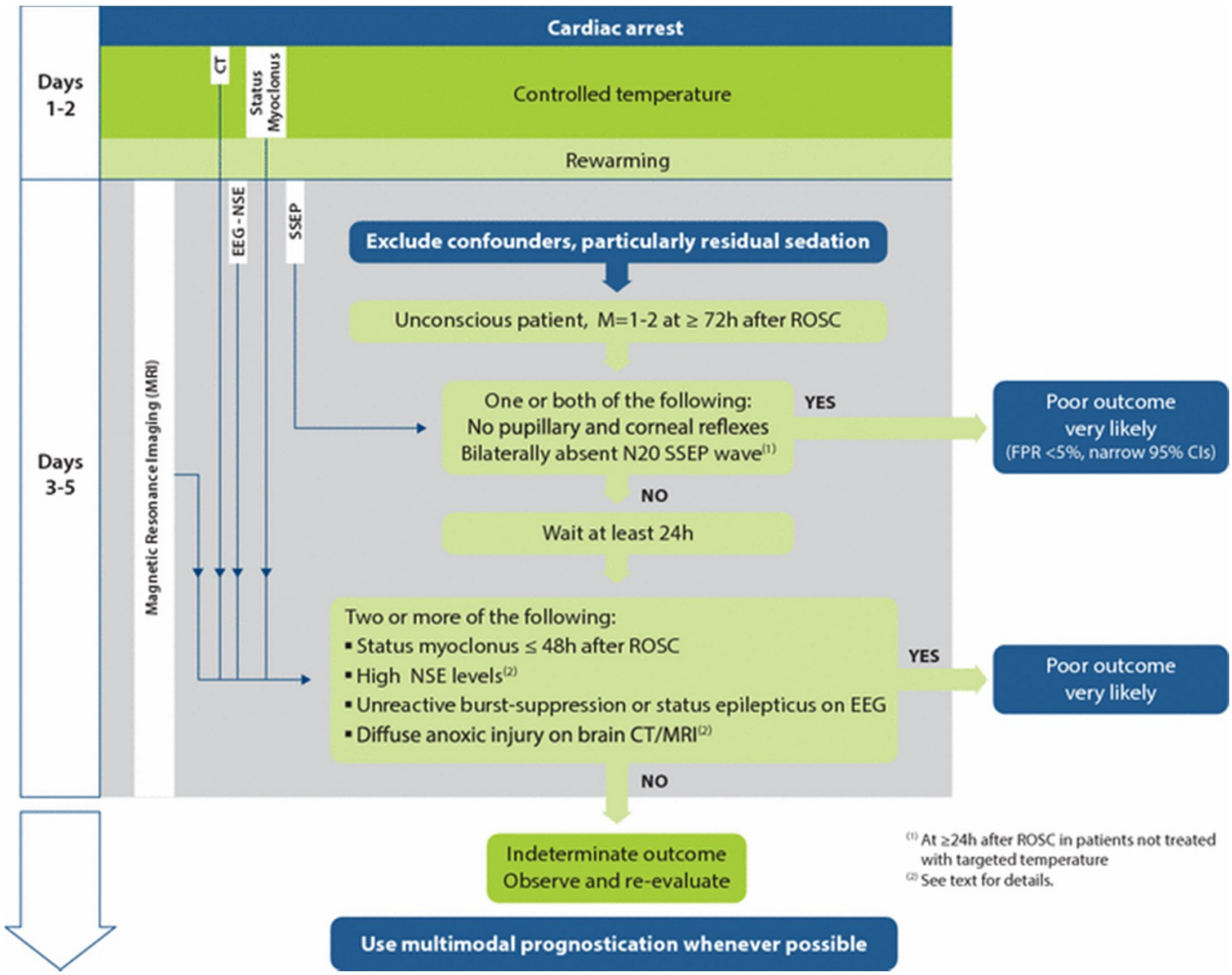


Fig. 3 Prognostication strategy algorithm. From Nolan JP, Soar J, Cariou A, et al. European Resuscitation Council and European Society of Intensive Care Medicine 2015 guidelines for post-resuscitation care. Intensive care medicine 2015;41:2039-2056. Reprinted with permission.

Clinical neurological examination

After the thermal treatment and the clearance of sedative drugs all the patients should undergo to a neurological evaluation.

Before the TTM era, the the lack of pupillary and corneal reflexes and GCS motor score ≦ 2 on day 3 after CA were reliable predictors of poor outcome. [34]

Clinical neurological examination presented high rates of false positives in predicting a poor prognosis, particularly in the first days after sedation suspension.

In 2010, Rossetti et colleagues in a large prospective study using the AAN algorithm for prognostication, found a high false predictive rate for motor response in TTM treated patients, concluding that clinical test should be carefully interpreted for predicting poor outcome.

Similarly in 2011, Samaniego and colleagues investigated on the effects of sedation on the accuracy of clinical examination for predicting outcome in TTM patients. [35]

Clinical neurological evaluation should include:

- brainstem reflexes
- motor response
- presence of myoclonus.

The coexistence of absence of pupillary and corneal reflexes, GCS motor score ≤2 (absent or extended motor reactivity) after the restoration of normothermia (~ 3-5 days after ROSC) indicates an unfavorable prognosis.

In the event of suspicion of sedation or residual paralysis it suggested to prolong the clinical observation beyond the 72h post-ROSC. [29]

Neurophysiology

EEG

EEG signal is a non-invasive and inexpensive investigation that provides a real-time examination of cortical and subcortical structures.

It has been used routinely for decades in coma prognostication, however, there is increasing interest in the use of EEG in the intensive care unit with the progress in post-cardiac arrest care. [36,37,38]

While the TTM does not seem to have a major effect on the prognostic ability of EEG, sedative drugs used during thermal treatment can substantially affect the background and reactivity. Several studies suggested that strictly therapeutic dosages of midazolam or propofol do not alter the EEG prognostic accuracy even in the early 24 hours. [39,40]

Despite the absence of a universally accepted classification system, the American Clinical Neurophysiology Society has published standardized guidelines for EEG interpretation that have been validated in the setting of coma prognostication. [41,42]

Due to the discordance in the timing of EEG recordings and the wide range of definitions on EEG patterns, a dichotomization between malignant and benign has often been used for simplicity.

According to the American Clinical Neurophysiology Society (ACNS) recent revision of EEG terminology, a classification of EEG pattern has been proposed as highly malignant, malignant and benign: [43]

- Highly malignant patterns show suppressed background (<10μV), burst suppression (suppression periods > 50%) and continuous discharges on a suppressed background

- Malignant patterns are included in a wide range starting from low voltage patterns, discontinuous or unreactive background and periodic or rhythmic discharge up to seizure activity.

Although cerebral electrical activity would vary over the time, Alvarez and colleagues in a recent study suggested that two traditional EEG recordings provides the same informations as continuous EEG (cEEG).
By contrast, post anoxic status epileptics patterns requires specific considerations and should have monitored carefully on a cEEG.[44]

AAN guidelines EEG findings can be divided in 3 main domains:

1. Background activity

It is a variable representative of global cerebral functioning. Cardiac arrest ischemia leads to neuronal damage. Several studies demonstrated how a decrease in amplitude and slowing of background activity is associated with brain function decline and bad outcome. Several background activity parameters has been correlated with poor prognosis:

- low-voltage (<20 μV) or isoelectric (suppressed) background at 24 h; [37,38]
- burst suppression at any time; [37]
- burst suppression with identical bursts and spontaneously discontinuous background during TTM. [37,45]

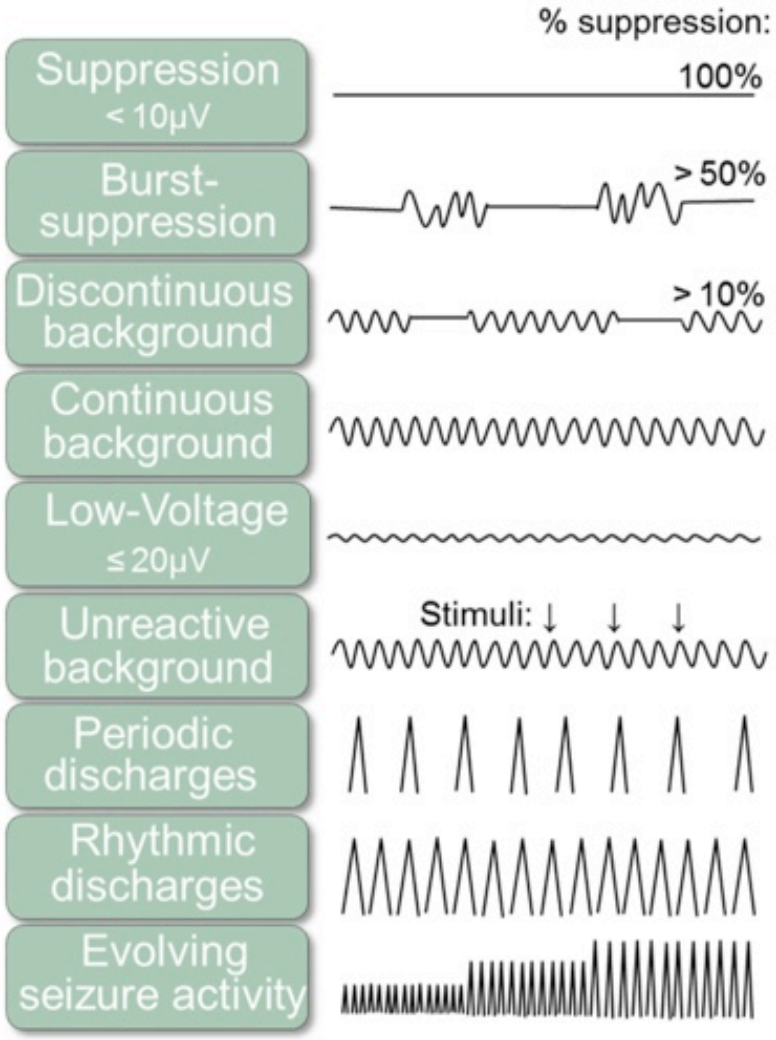


Fig. EEG features after CA according to ACNS EEG terminology

On the contrary, a continuous background has been correlated with favorable outcome. Particular attention should be paid to Alpha coma that seems to be related to a poor prognosis in up to 100% of patients. [46]

2. Background reactivity

Reactivity is a response to an auditory or noxious stimuli that is characterized by an increase or an attenuation in electrical activity on the EEG leads.

The lack of reactivity seems to correlate with poor prognosis during and after the thermal treatment, while the presence of reactivity is related to awakening. [47,48]

Due to the lack of a standardized stimulation protocol, the reactivity could be extremely subjective determinate which is an important limitation.

3. Epileptiform features

The presence of repetitive sharp waves, spikes or poly-spikes, attributable to a epileptiform features registered during the thermal treatment are strongly associated with a poor prognosis, especially if patients are sedated and in therapy with anticonvulsants agents. [36,49]

Nevertheless, the presence of a transient epileptiform features after thermal treatment in patients with preserved brainstem reflexes, reactivity and somatosensory evoked potentials, generally are related to good outcome and maybe be treated with anticonvulsants.

In summary:

- EEG is defined a low voltage when it has an activity <20 μV, while it is defined as flat when the activity is <10 μV
- The "burst suppression" indicates an EEG path in which in more than 50% of the recording an alternation is observed between a track with activity <10 μV and a path with high voltage activity
- An initially flat EEG (<10 μV) is a frequently occurring event of temperature management and therefore of low prognostic value
- In the presence of continuous EEG, the lack of background reactivity to external stimuli (eg tactile, auditory or visual stimulation) after temperature management is associated with an unfavorable prognosis
- A reactive background EEG is strongly predictive of favorable prognosis;

Somatosensory evoked potentials (SSEP)

Somatosensory Evoked Potentials are cortical brain response to a repetitive somatosensory electrical stimulation delivered by an electrode placed at the level of the median nerve at the wrist. Responses are registered with a latency (in ms) at different levels like spinal cord (N13) or subcortical (N18), and test the integrity of the afferent pathways.

The wave appearing at about 20 ms over the scalp, represented as a negative deflection on the recording, is called "N20" . The N20 wave reflects the correct function of the thalamo cortical projections, and can only be reliably interpreted when the peripheral and spinal responses are also present.

Prognosis in Postanoxic Coma (PROPAC I) study evaluated 407 patients for the reliability of SSEP in the prediction of poor outcome after CA. Lack of N20 wave has been recognized as credible marker, even if a few isolated false positive predictions have been reported.[50]

The PROPAC II prospective study has investigated the performance of SSEPs both during TTM and after rewarming. [104] The authors found that three of 43 patients with bilateral absence of N20 on SSEP performed during TTM recovered, and only in a post hoc review, the investigators concluded that these three SSEP recordings were faulty due to noise.

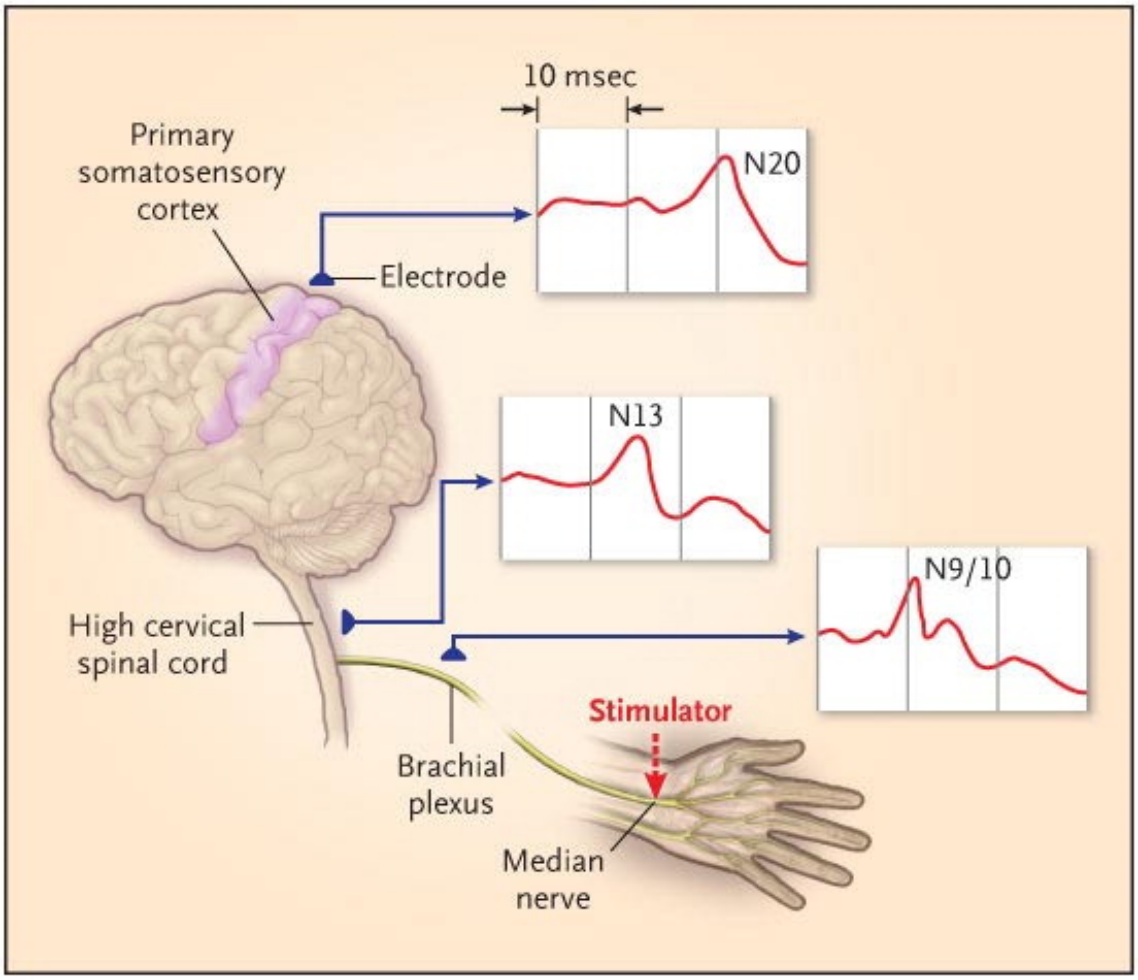


Fig. SSEP waves

Although in post CA patients the bilateral absence of N20 waves is strongly associated with poor outcome during and after TTM, their accuracy in predicting a favourable outcome is disappointing. [51,52,47]

In 2015, Endisch et colleagues, suggested that quantitative assessment of the N20 amplitude may offer more prognostic information about outcome. [53]

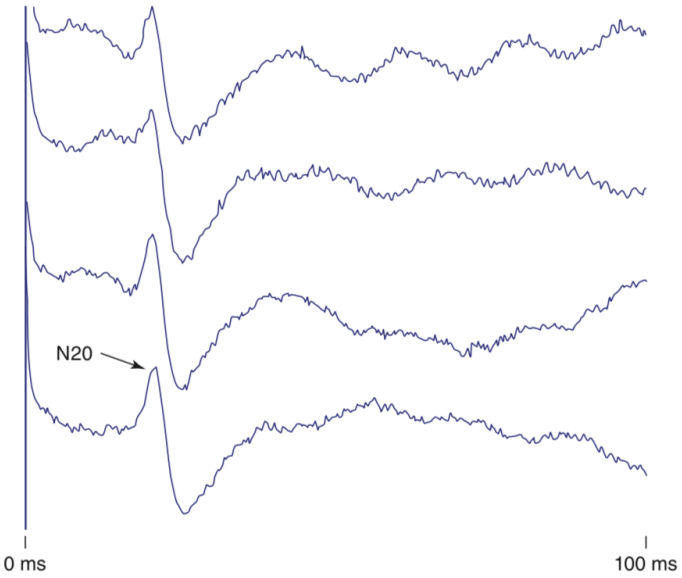
Unlike EEG, SSEP seems not to be affected by sedation and slightly to temperature. The correct execution of the examination can be technically difficult in obese, diabetic or polyneuropatical patients.

The optimal timing of SSEP has been a matter of discussion. Some studies supported that absent N20 is a reliable marker even if performed during TTM.

Some others have suggested postponement of the SSEP due to the improvement or normalisation of N20-peaks that may exist over the first days post arrest.[54]

Recent International guidelines suggest performance of the SSEP at least 72 hours after CA to predict poor outcome in comatose post CA patients.

In summary:



- the bilateral absence of N20 cortical representations after at least 72h post-ROSC predict unfavorable outcome in comatose patients after CA treated with temperature control.
- quantitative assessment of the N20 amplitude may offer more prognostic information
- The limitations of SSEP like the interference effects of noise, inter-observer reliability in interpretation and the low sensitivity to detect a good outcome should be considered by clinicians in predicting outcome after CA.

Biomarkers

The specific neuron enolase (NSE), a structural protein of the central nervous system, is the most commonly biomarkers of CNS tissue damage. [55,56] It is present in tissues of neuro ectodermal origin and, in a small amount, NSE is present in erythrocytes, blood platelets, plasma cells, lymphocytes which explains its physiologically low concentrations in blood. In case of a cellular CNS damage, these proteins are released from cells, and their concentrations increase extracellularly in cerebrospinal fluid (CSF) and blood. Several research studies focuses on monitoring the concentrations of these biomarkers in blood after ischemia and reperfusion injury post CA with a good correlation between NSE levels and brain damage. Unfortunately the reliability to forecast outcome in patients after CA seems to be affected by the uncertainty about cut-off values after temperature management. Furthermore, the same presence of NSE in red blood cells and platelets, could consequently falsify the values in case of hemolysis. However, low values in unconscious patients are indicative of reversible condition. The NSE should always be included with other evaluations in a context of multimodal prognosis.

Neuroimaging

Cerebral edema make a significant contribution for the development of hypoxic ischaemic encephalopathy (HIE) and a decreasing of chance survival in post cardiac arrest patients. Neuroimaging is useful in confirming an early ischemic damage like poor differentiation between white and gray matter, signs of diffuse cerebral edema or tonsillar herniation.

In this context, brain imaging seem to play an important role for prediction of neurological outcome in patients with suspected HIE.

Brain CT Scan 43.54

A loss of contrast between gray and white matter has been shown to be correlated with poor outcome. The measurement obtained calculating the ratio of gray and white matter has resulted in a parameter recently used as an early prognostic indicator of outcome. [57]

The more the cerebral edema is present the lower is the GW ratio value. In case of severe brain edema, the ratio tends to the unity and could become lower, which identifies what is called "reversal sign".

In 2016, Vigneron et colleagues suggested that a certain value of GWR, calculated on the basal ganglia, identifies which patients with HIE are evolving toward brain death (BD).

However, although there is still no general consensus on a cut off value that may predict poor outcome, several studies suggested values lower than 1.2. [58,59,60]

In recent studies cut-off values are very similar. Metter et colleagues in a large court of patients have found a GWR lower than 1.15 with a 100% specificity for poor outcome. Other authors suggested cut-off values lower than 1.18. (Torbay 2000 stroke)

Brain Magnetic resonance imaging (MRI)

Although Magnetic resonance imaging (MRI) is recommended by the ERC algorithm, its reliability has not been sufficiently studied.[26] MRI has shown to be sensitive in detecting acute ischemic lesions if acquired by diffusion-weighted imaging (DWI), especially on the second and fifth day after the CA.

A few small studies have shown that the presence of generalized changes on DWI or fluid-attenuated inversion recovery (FLAIR) can identify cytotoxic edema secondary to ischemia, predicting a poor outcome.[61,62]

CT scan or MRI are not appropriate to allow prognosis as a single parameter, but should be used in combination with other predictors to provide adequate experience in neuroimaging.

Outcome after cardiac arrest

Chance of surviving has grown during the last ten years thanks to the improvement of extra and in hospital management of CA patients, but, even when resuscitation is successful, there is still uncertain prognosis due to the neurological sequelae of the post anoxic brain injury. According to recent studies, survival with severe neurological disability after CA is uncommon, although this data can presumably be affected by "withdrawal of life-supporting treatments" (WLST) in patients in whom it is assumed that prognosis is poor [2].

In recent studies, a large proportion of the survivors has been reported to be affected by mild to moderate cognitive dysfunction at three to six months after cardiac arrest, that may affect daily functioning and quality of life. Depression, anxiety and cognitive impairments have been reported after discharge of CA survivors from the hospital. Moreover, a cardiac arrest can have remarkable impact even on the family and caregivers. (2-4 moulart 2014)

Although the majority of survivors seems to be able to carry out some daily activity, social activity, maintainance of a finance role, work, or family roles can be considerably reduced. [63]

Unfortunately, many of these were limited by small samples size and used inappropriate tests to detect cognitive impairment.

Despite the fact that TTM has been widely recognized to play a substantial role on survival, its effects on cognitive function has been inadequately investigated.

Neurological outcome has often been evaluated with the Pittsburgh Cerebral Performance Cathegory scale (CPC), even though it seems to favorably overestimate outcomes, especially when based on hospital discharge records. [64]

The CPC ranges from 1 to 5. (Table 1) CPC 1 representing intact function and 5 representing brain death. Researchers identify favorable neurological function as CPC 1 or 2 and unfavorable function as 3 or greater (3,5).

Cerebral Performance Category	
1. Good Cerebral Performance (*Normal Life*)	Conscious, alert, able to work and lead a normal life. May have minor psychological or neurologic deficits (mild dysphasia, nonincapacitating hemiparesis, or minor cranial nerve abnormalities).
2. Moderate Cerebral Disability (*Disabled but Independent*)	Conscious. Sufficient cerebral function for part-time work in sheltered environment or independent activities of daily life (dress, travel by public transportation, food preparation). May have hemiplegia, seizures, ataxia, dysarthria, dysphasia, or permanent memory or mental changes.
3. Severe Cerebral Disability (*Conscious but Disabled and Dependent*)	Conscious; dependent on others for daily support (in an institution or at home with exceptional family effort). Has at least limited cognition. This category includes a wide range of cerebral abnormalities, from patients who are ambulatory but have severe memory disturbances or dementia precluding independent existence to those who are paralyzed and can communicate only with their eyes, as in the locked-in syndrome.
4. Coma/Vegetative State (*Unconscious*)	Unconscious, unaware of surroundings, no cognition. No verbal or psychologic interaction with environment.
5. Brain Death (*Certified brain dead or dead by traditional criteria*)	Certified brain dead or dead by traditional criteria.

Table 1. Cerebral performance category scale.

Consequently, in literature "good outcome" is currently used for CPC 1-2 ,or "discharge disposition to home or acute rehabilitation facility", while "bad outcome" for CPC 3-5. This crude classification can sensitively detect between mortality or severe brain injury, but, unfortunately, the scale is unreliable and too subjective to differentiate mild to moderate neurologic impairment.

Aims of the thesis

This thesis is focused on the neurological prognostication in comatose survivors of cardiac arrest at hospital discharge and in follow up after six months. Considering that a single best reliable indicator for predicting outcome does not exist, the aim of the dissertation is to assess the reliability of multiple early indicators as a predictors when combined together for assessing survival at hospital discharge and after six months. Secondary aims are to evaluate the prognostic value of a Somatosensory evoked potential and EEG and radiological Gray to White Matter ratio in predicting functional recovery in survivors at six months from hospital discharge.

The specific aims are:

- To investigate whether the amplitude of SSEP cortical waveforms was independently associated with survival and favorable functional recovery.
- To investigate if the peak to peak N20-P25 absolute amplitude value in both sides collected at different temperatures was independently associated with survival and functional recovery .
- To investigate whether the SSEP provides independent information from EEG and GWR at CT scan.
- To investigate the influence of thermal treatment of 36 °C vs 37 °C and prognostication at release and after six months from hospital discharge.
- To describe the characteristics of patients who were admitted to the study
- To determine whether targeted treatment management at 36°C compared with 37°C affected the prognostic accuracy of somatosensory evoked potentials, EEG reactivity and GWR in comatose patients.
- To investigate the predictability of EEG, GWR and SSEP alone and combined together as prognostic markers at 36 °C and 37 °C

Trieste research protocol

The protocol has been approved by University of Trieste ethics committee and the Friuli Venezia Giulia regional ethics committee (CEUR Egas).

After ROSC, adult patients with sustained coma after OHCA of presumed cardiac cause regardless of presenting rhythm were included, according to inclusion criteria, to the thermal treatment at 36 °C for 24 h followed by controlled rewarming at 37 °C.

Prognostication was protocoled. At 96 h after rewarming and withdrawal of sedation, a physician performed a neurological evaluation.

Survivors were assessed in follow up with GCS and CPC scale at 6 months from the hospital discharge.

Eligibility

The study population is an adult population of 18 years of age or older who experience a cardiac arrest with ROSC.

Inclusion criteria and the exclusion criteria:

Inclusion criteria:

- OHCA of a presumed cardiac or unknown cause
- Unconsciousness (GCS < 9) after sustained ROSC
- Sustained ROSC - defined as 20 minutes with signs of circulation without the need for
  chest compressions

Exclusion criteria:

- Known limitations in care or disease making survival unlikely
- Obvious or suspected pregnancy
- Intracranial bleeding

Plan necessary procedures as soon as possible (angiography/PCI or CT); discuss all patients weather there is an indication for PCI with cardiologist even NSTEMI if the first rhythm was shockable (pVT or VF)

Overview of the ICU period

All patients will be sedated and mechanically ventilated.
Patients will be rapidly cooled with an approved endovascular cooling devices with a target temperature of 36°C. Upon reaching the temperature goal a maintenance phase will commence, which will end 24 hours later. During the maintenance phase the target temperature will be 36°C. This will be followed by rewarming at 0.2 °C/ hour, until reaching the temperature of 37 °C. After the rewarming period, if conservative and pharmacological measures are insufficient and the temperature reaches 37.8°C, cooling with a device will be initiated with a target temperature of 37.5°C.
Sedation will be maintained for the TTM treatment until rewarming using Propofol or Midazolam. Ensure adequate control of shivering.

Diagnostic test and procedures at 36 °C

- Blood test pattern : A complete blood count (CBC); Blood chemistry tests; Blood enzyme tests; Blood clotting tests; NSE, S-100, PCR; Troponin; every 6 hours.
- Blood gas every six hours during the intervention (FiO_2, pCO_2, BE, pH, lactate, glucose)

- Brain CT scan within 6 hours from ROSC.
- EEG and SSEP until reaching 36°C
- Antibiotics are not mandatory. (Use of prophylactic antibiotics for VAP)

Counter warming should be initiated right from the beginning to prevent shivering. Paralyze patient if shivering is present in deep analgesia and sedation and if magnesium iv has been put in therapy.

After 24h start to re-warm at a rate of 0.2°C/hour.
Stop sedation only after return to normothermia (37°C).

In order to prevent rebound fever leave cooling device on the patient for another 24h after return to normothermia (37).

Diagnostic test and procedures at 37 °C

- Blood test pattern : A complete blood count (CBC); Blood chemistry tests; Blood enzyme tests; Blood clotting tests; NSE, S-100, PCR; Troponin; every 6 hours.
- Blood gas every six hours during the intervention (FiO_2, pCO_2, BE, pH, lactate, glucose)
- EEG and SSEP until reaching 37°C

<u>48-72h</u>

Sedation is discontinued or tapered.
Temperature control in normothermic range (36.5-37.5°C) until 72h - unless awake and extubated

<u>From 96h on</u>

- Neurological prognostication at 96 hours
- GCS score at the discharge from ICU/Hospital

At 6 months

- GCS score
- CPC score

Paper

This thesis is supported by both qualitative and quantitative elements. The study design was conceived to factor both the research question and the feasibility of collecting sufficient data to support the conclusions. I was able to collect data throughout the period during which I participated in the doctoral program.
This paper is the culmination of these efforts..

1.Introduction

After cardiac arrest (CA) most resuscitated patients are comatose as a result of hypoxic ischaemic brain injury [1, 2]. Differentiating patients who can awaken from coma from those with irrecoverable injury remains challenging. Bilateral absence of N20 cortical somatosensory evoked potentials (SSEP) at least 72 hours after return of spontaneous circulation (ROSC) is one reliable indicator of poor prognosis. [3] [4]However, presence of cortical responses on SSEPs does not guarantee favorable outcome. [5] Consensus guidelines recommend that clinicians use SSEP as one part of a multimodal approach to prognostication. [6]
There are several gaps in knowledge about SSEP as a prognostic modality after cardiac arrest. First, most studies relate SSEP to short term outcomes like awakening from coma or survival to hospital discharge rather than more important long-term outcomes like function at 3 or 6 months. Second, many studies have used SSEP results in the decision to limit life support for subsets of patients, creating bias that would inflate the SSEP performance. Finally, few studies describe how much incremental information SSEP results provide over other clinical information [7]. To address some of these gaps Scarpino et colleagues investigated the role of a combination of

measures, like SSEP, EEG and GWR, to predict CA patients's cerebral performance after 6 months follow up.

Most studies simplify the complex SSEP waveform into the dichotomous presence or absence of the N20 cortical response. It is not clear whether quantifiable features like latency and amplitude additional also provide prognostic information (Fig.1)

To address some of these gaps, we collected data on the prognostic value of SSEP waveforms performed at regimented times during and after targeted temperature management for predicting outcome after 6 months in a cohort of CA patients with no limitations in life support. We hypothesized that the amplitude of SSEP cortical waveforms is associated with favorable functional recovery, and that SSEP provides independent information from EEG and CT scan.

2. Methods.

2.1 Study design and population.

We performed a retrospective cohort study including consecutive non-traumatic patients resuscitated from out-of-hospital CA who remained comatose (Glasgow Coma Scale score ≤8) on admission to an intensive care unit (ICU) at a single center tertiary university hospital from January 2013 to May 2017. Our local ethics committee approved the study and waived the need for informed consent because of minimal risk.

We excluded patients under 18 years old, with traumatic cardiac arrest, with pregnancy, with previously diagnosed progressive neurodegenerative disease, and those deemed likely to meet the criteria for progress to brain death on admission. (Fig 2a)

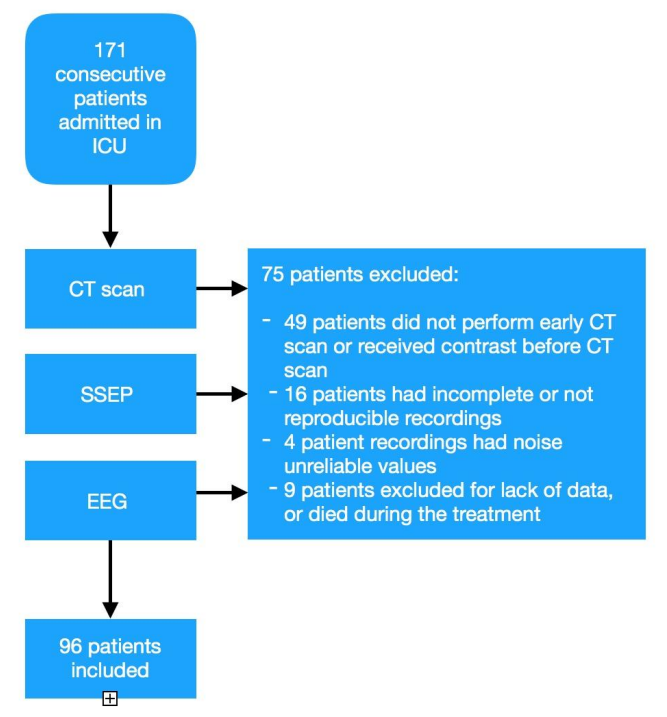


Fig2a. Study design

2.2 Study definition and data collection.

We defined cardiac arrest as the abrupt cessation of cardiac activity that required shocks and/or chest compression for the return of spontaneous circulation (ROSC). We dichotomized initial rhythm as shockable (ventricular fibrillation or pulseless ventricular tachycardia) or non-shockable (pulseless electrical activity or asystole). We estimated the time interval from collapse to ROSC from prehospital reports.

We performed non-contrast enhanced computerized tomography (CT) scan of the brain to exclude neurological causes of arrest or head trauma in unwitnessed collapse. We treated all patients with targeted temperature management (TTM) to 36°C for 24 hours using an intravenous cooling system (CoolGard 3000/Alsius Icy Heat Exchange Catheter, Zoll Medical). We sedated patients with propofol, although we substituted midazolam in cases of severe hypotension. We provide neuromuscular blockade with continuous infusion of cisatracurium to prevent shivering during the induction of TTM. We stopped sedation and paralysis at the beginning of the rewarming period.

We measured survival and functional recovery at discharge from the ICU and at 6 months after the event using medical records and cardiologic reports. Reports characterized functional neurological recovery using the Pittsburgh-Glasgow Cerebral Performance Categories scale (CPC), and we defined good outcome as CPC 1-2.[8][9]

2.2 a EEGs and SSEPs

We acquired SSEPs and EEGs twice, first during the first 12 hours after reaching the target temperature of 36oC (approximately within 12 hours after ROSC) and second after withdrawal of sedation and rewarming to 37 oC (approximately 72 hours after ROSC).

We recorded EEGs for at least 20 minutes using a portable machine (Galileo NT PMS version 3.90/00/17014 - SPD. EBN Neuro) using a 13 electrodes positioned according to the international 10-20 system. [10] A neurophysiologist determined EEG reactivity

as present if there was a clear change in background frequency or amplitude after a pain or voice stimulation.[11] We considered EEGs where electroencephalographic seizures resulted from stimulation to be nonreactive. EEG background was classified as continuous (recognizable clear background activity), discontinuous (burst suppression of almost 10% of the recordings) or flat (isoelectric or suppression less than 10 μV). [12] Epileptiform activity was identified as rhythmic spikes or waves and sharp waves and periodic epileptiform discharges (PEDs). [13]

A certified neurologist evaluated peripheral, spinal and cortical SSEPs in response to the stimulation of the median nerve at the wrist. The cortical N20 amplitude was defined as the highest amplitude of a reproducible potential of CP3/CP4 vs Fz recordings and CP3/CP4 vs contralateral earlobe at least at 4.5 ms longer than the previous N13 peak (cervical spinal cord) and within 50 ms after stimulation.[14] We considered as P25 amplitude the first positive wave that follows N20 wave. (Fig 1) Consequently we examined the peak to peak N20-P25 absolute amplitude value in both sides. N20-P25 complex has been used previously as a prognostic indicator particularly in ischemic stroke patients. [15–17] In patients with background noise levels under 0.25 μV for whom we could not discern any cortical waveform bilaterally, we considered the SSEPs to be absent. Clinical teams in our hospital do not use SSEP recordings as part of any decisions to withdraw or limit life 2 support.

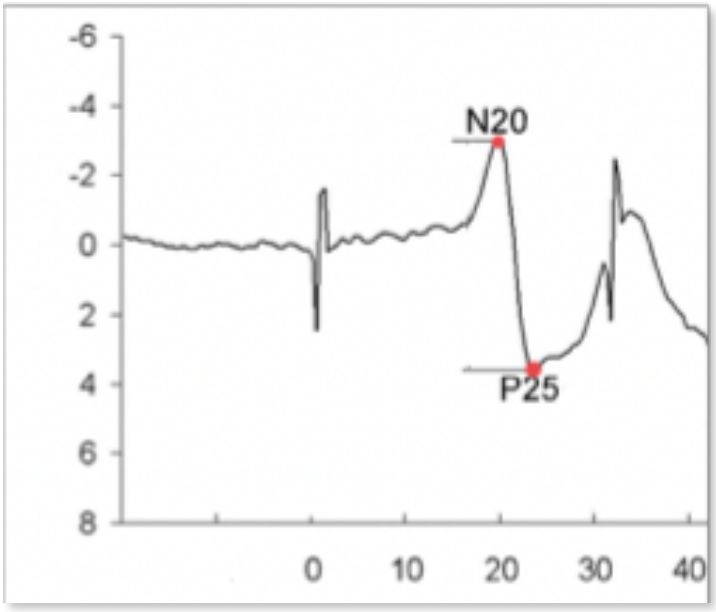


Fig.1 Peak to Peak amplitude of N20-P25 waves.

2.2 b GWR

We acquired non-contrast head CT scans on Aquilion 64 (Toshiba Medical Systems Europe B.V., Zoetermeer, The Netherlands) or Brilliance iCT 256 (Philips Healthcare, Best, The Netherlands) scanners, using 5 mm slices reconstruction in the axial plane. Two investigators blinded to clinical information examined CT scans for each patient using commercial image viewing software (suitEstensa Ris Pacs Software, Esaote Healthcare IT, Genova, Italy) with windowing adjusted to "brain," and identified comparable brain slices at the level of basal ganglia, and at two levels of superior cortex.

Investigators measured average attenuation in Hounsfield Units (HU) of circular regions of measurement (0.1-0.25 cm^2) using the method described by Torbey et al [18], with some

modification according to more recent reports [19]. We recorded HU values bilaterally for gray matter (GM) in the caudate nucleus (CN), putamen (PU), and white matter

(WM) in the corpus callosum (CC), and posterior limb of internal capsule (PIC). In particular we chose the anterior halves of posterior internal capsules in order to minimize the density variation of posterior internal capsules between the anterior and posterior halves due to the presence of focal low-attenuation lesions in the posterior half of the posterior internal capsule in 60% of normal brains, according to Choi et al.[20] We recorded values bilaterally for the medial cortex GM and medial WM at the level of the centrum semiovale (MC1 and MWM1, respectively) and high convexity area (MC2 and MWM2, respectively).

Increasing cerebral edema results in lower attenuation by gray matter and a lower GM to WM ratio (GWR). We calculated GWR basal ganglia =(CN+PU)/(CC+PIC). We calculated GWR cerebrum = (MC1+MC2)/(MWM1+MWM2). We calculated average GWR as the mean of the GWR basal ganglia and GWR cerebrum, and we used average GWR for analysis. We divided GWR results into 3 categories, normal (GWR>1.2), mild edema (GWR 1.1-1.2), or severe edema (GWR <1.1), based on prior studies. [21]

3 Statistical analysis

We describe data with mean (SD) for continuous variables, median (IWR) for non-normally distributed variables, and percentages for categorical variables. We compared variables that differed between patients with good and poor outcome using Chi square or Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables.

We tested a correlation of SSEP N20P25 amplitude measurements between the sides and the inter rater reliability of GWR measurements using Pearson's correlation. We cross- tabulated GWR, EEG reactivity, and SSEP N20P25 amplitude to examine if any particular finding on one test perfectly predicted the results of another test.

We used logistic regression to test associations between average GWR, EEG reactivity, and SSEP N20P25 amplitude at 36oC and 37oC individually and in combination with survival and good outcome at discharge from ICU and after 6 months. Multiple models were created, and the AUC for each compared. With these 3 predictor variables, we created a total of 13 models: 1 model with GWR alone and 6 models at each temperature with SSEP N20P25 amplitude, EEG reactivity, SSEP N20P25+EEG, SSEP N20P25+GWR, EEG+GWR or SSEP N20P25+EEG+GWR.

We use a Hosmer-Lemeshow for goodness of fit for the logistic regression model.

We used a DeLong test to compare the area under the curve (AUC) as each predictor variable was added into subsequent logistic regression models. We used a DeLong comparing AUC both when models included SSEP N20P25 and when the same model was without SSEP N20P25.

Statistical analysis were performed using STATA version 15 (Stata corp, 4905 Lakeway Drive College Station, Texas, USA).

We considered p value≤ 0.05 statistically significant.

4 Results

4.1 Baseline characteristics

Of 171 consecutive patient admitted in our intensive care unit from January 2013 to may 2017, 75 patients were excluded due to missing data, uninterpretable neurophysiology data or because patients died during the treatment. (Fig. 2) Table 1 summarizes baseline and resuscitation characteristics for all subjects and subgroups by ICU survival and outcome. Subjects who died were older. Subjects who died or had poor outcome, received higher total dose of adrenaline and had longer collapse-to-ROSC intervals.

Reliability of SSEPs N20-P25 amplitude measurement between the sides was high with a Pearson's correlation coefficient of 0.94. Inter rater reliability of GWR was similarly high with Pearson's correlation coefficient of 0.93.

4.2 Association between GWR, EEG and SSEP

Table 2 and 3 describes the association of GWR, EEG and SSEP features. Only one subject (1%) had severe edema on CT scan (GWR<1.1). This subject had no detectable N20-P25 waveform and no EEG reactivity both at 36 and 37 °C. Among all other subjects, an unfavorable finding in one of these modalities did not perfectly predict unfavorable findings in the others.

We measured a strong Pearson correlation coefficient between GWR and SSEP (Pwcorr 0.608). The ROC analysis revealed an AUC for GWRav at discharge of 0.682 (IC 95% 0.551-0.811) for survival with a very high sensitivity and a very low specificity. The AUC was 0.674 (IC 95% 0.574-0.769) at 6 months with a decrease of sensitivity and an increase of specificity. The analysis at 6 months for good outcome demonstrated an AUC of 0.727 (IC 95% 0.629-0.815)

Adding SSEP to GWRav to predict survival at discharge, we have seen a rising of the AUC up to 0.838 (IC 95% 0.744-0.932) at 37°C with a slightly decrease in sensitivity (91%) and an increase in specificity (56%). Same results at 36°C [AUC 0.781 (IC 95% 0.681-0.880)]. The combination at different temperatures were both superior than GWR alone. The predictability remains higher also for good outcome. [AUC 0.835 (IC 95% 0.755-0.914) at 37°C; AUC 0.823 (IC 95% 0.735-0.908) at 36°C]. (Table 4)

4.3 GWR and Outcome

GWRav ranged from 1.07 to 1.45. GWR was higher in subjects who survived relative to those who did not, and in subjects who had good outcome relative to those who had poor outcome (Table 3). The lowest GWRav value among subjects with a good outcome was 1.16, and among subjects who survived was 1.15. The median amplitude for cortical complex SSEP N20P25 with GWR≥ 1.2 at 36 °C was 0.63 and 0.66 at 37°C. (Table 2)

4.4 EEG and Outcome

EEG reactivity to stimulus at 37oC after rewarming and withdrawal of sedation was present in 41 patients, of whom 31 (69%) survived and 29 (83%) had good outcome at 6 months. There were 6 patients without EEG reactivity at 37oC who subsequently survived with a good outcome at 6 months. (Tab 3)

4.5 SSEP and Outcome

Amplitude of the N20P25 waveform at 36oC and at 37oC were larger in subjects who survived relative to subjects who did not survive. Amplitudes were also larger in subjects with good outcome relative to subjects with poor outcome (Table 3).

4.6 Prognostic value of combined modality

Table 4 shows the AUC for EEG reactivity, average GWR, and SSEP N20P25 amplitude alone and in combination for predicting good outcome and survival at discharge at 6 months and the survival at discharge. EEG reactivity was the best single predictor of good outcome while N20P25 was the best single predictor for survival at each time point.

Predictive value of each combination of two tests was superior to any test alone. Predictive value of a model including EEG reactivity, average GWR, and SSEP N20P25 amplitude was superior (AUC 0.841 for survival and 0.920 for good outcome) to any combination of two tests or any single test.

5 Discussion

We demonstrate that when SSEP cortical complex N20P25 is added into a model with GWR average and EEG reactivity, the predictivity for good outcome and survival at distance is superior than each single test alone. Furthermore, the predictivity is high also for survival at discharge from ICU. Few studies analysed EEG and SSEP recordings in a same patient before but, to the extent of our knowledge, none of them added GWR in the model to predict good outcome and survival at distance.[22][13] [23–25]

Few isolated cases of N20 false positive prediction have been reported. Only a retrospective analysis of the data confirmed that was due to a noise levels misinterpretation. [26–28] Furthermore, the level of tolerance in noise levels remains still unclear. [6] At the same time the noise misinterpretation could bring to erroneous findings of fact. In order to overcome this issue our findings suggest to considered the total extension of the SSEPs wave from the lowest value of N20 to the highest of P25. As in a recent paper, we considered the relationship between cortical amplitudes and outcome overcoming the presence absence dichotomy.[29]

SSPEs cortical complex has been previously utilized in other clinical situation for predicting outcome but no previous studies specifically considered cortical complex N20P25 amplitude as an indicator for good outcome and survival at distance from CA. [16, 30–32]

Many papers considered the value of SSEPs only after rewarming in patients remained in a comatose state. Despite SSEPs is relatively independent to sedation we found, as in previous studies, a faintest difference between 36 and 37 °C.[14].

Even though, EEG reactivity after withdrawal of sedation at 37 °C was the best solo indicator for good outcome at distance, SSEP complex at 37°C was the best solo predictor for survival at any time.

Normally sedation affect more EEG reactivity than SSEP and, as results showed on

Table 5, the recording of three test combined during the thermal treatment showed a predictivity for outcomes slightly inferior than after normothermia and off sedation, but still significative. These results suggested interesting implications on early prognostic information also in the early stage of treatment.

The minimum amplitude value compatible with a good outcome for the N20-P25 complex was 0.23 μV. Unfortunately there are few patients with amplitudes very close to this values and that bring us to be very careful with the interpretation and prospectively validation is needed with a higher safety margin. A retrospective study has previously investigated the relationship between N20-P25 complex and outcome after CA and the results showed the amplitude reduction of N20-P25 complex were associated with poor outcome. [17]

Although the requisite for amplitude interpretation were well described previously, these data could not consider the difference between cortical and subcortical potentials. Amplitude could be influenced by the intensity and the number of the stimulus, even if we considered a minimum delay after recording. Adding GWR average to SSPEs complex considerably augmented the predictivity for long term outcome [33]. Patients with a hypoxic ischemic encephalopathy manifests a loss of distinction in gray and white matter. Previous studies focused on the presence of cerebral edema in the very early acute period, GWR values are higher when CT scan is performed within the first 6 hours. [33] [34, 35] We found only one patient with a GWR value compatible with severe edema (GWR<1.1), the corresponding N20-P25 complex amplitude value was zero and there was no reactivity at each temperature we tested. The majority of patients were gathered into the no edema group (GWR ≥1.2). Early prognostication could lead to a more rapidly treatment and eventually address to rehabilitation program. Concerning the model for predictivity at 6 months, many factors could influence the survival and the neurological outcome in a so long amount of time. As suggested in other studies a more specific CPC score must be considered for recovery evaluation.[36]

There are several limitations to this study.

First of all, it is a single center retrospective study, with all the implication that this carry with it. Second, studies on prognostication after CA can suffer from fulfilling

prophecy. We usually do not consider SSEP in order to withdrawal therapy. Despite this, we can't exclude that single clinicians could be influenced by neurophysiological results. Third, reactivity was determined as a change in EEG background after a pain or voice stimulation. Nevertheless EEG reactivity is considered a strong predictor of awakening, there is no standardized methods for testing it. This implies that perception to different stimuli could lead different EEG reactivities interpretations. [37]

Conclusions

Our study suggest a strong association between SSEPs N20P25 complex and very early GWR measurement and EEG reactivity to predict good outcome at six months and survival at any time.

The predictability of long terms outcomes could be influenced by several factors. Despite this, the early detection of all these indicators seems to play a significant role in clinical practice.

In detail:

- SSEP cortical complex N20P25 is added into a model with GWR average and EEG reactivity, the predictivity for good outcome and survival at distance is superior than each single test alone.
- the predictivity is high also for survival at discharge from ICU.
- SSEP cortical complex N20P25 can overcome the issue of noise levels and misinterpretation of waves in the perspective of predicting outcome
- EEG reactivity after withdrawal of sedation at 37 °C was the best solo indicator for good outcome at distance
- SSEP cortical complex N20P25at 37°C was the best solo predictor for survival at any time.
- Recording of three test combined (EEG reactivity, SSEP N20P25 complex and GWR) during the thermal treatment showed a predictivity for outcomes slightly inferior than after normothermia and off sedation.
- Adding GWR average to SSPEs complex considerably augmented the predictivity for long term outcome

Future Considerations

The stronger request of early additional prognosticators derives from the increased expectation of family and relatives on the neurological outcome of the patient.

Global brain injury and cognitive dysfunction are well known consequences of a cardiac arrest, even though marginally outlined by crude outcome scales like CPC, which is well suited to identify moderate to severe impairment and less to differentiate in none to mild impairment. [64] [65]

Discharge disposition scarcely correlates with the CPC.

Accordingly, we will focus our attention adding systematic battery of cognitive testing in survivors starting from six months on after hospital discharge to investigate if there is a relationship between early neurophysiological and neuro radiological predictors and the cognitive dysfunctions. The neuro cognitive evaluation of the post cardiac arrest patients is becoming an integral part of post-resuscitation care.

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References

Reference for the dissertation

[1] Britton SW. Extreme hypothermia in various animals and in man: With Notes on the Detection of Life and the Possibility of Recovery in Cases of Apparent Death from Exposure to Cold. Can Med Assoc J 1930;22:257–61.

[2] Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549–56.

[3] Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002;346:557–63.

[4] European Resuscitation Council, Abbas G. Advanced Life Support: ERC Guidelines 2010 Edition. 2011.

[5] Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. In: Cochrane Database of Systematic Reviews 2012;

[6] Atwood C, Eisenberg MS, Herlitz J, Rea TD. Incidence of EMS-treated out-of-hospital cardiac arrest in Europe. Resuscitation 2005;67:75–80.

[7] Berdowski J, Berg RA, Tijssen JGP, Koster RW. Global incidences of out-of-hospital cardiac arrest and survival rates: Systematic review of 67 prospective studies. Resuscitation 2010;81:1479–87.

[8] Hasselqvist-Ax I, Herlitz J, Svensson L. Early CPR in Out-of-Hospital Cardiac Arrest. N Engl J Med 2015;373:1573–4.

[9] Chan PS, McNally B, Tang F, Kellermann A, CARES Surveillance Group. Recent trends in survival from out-of-hospital cardiac arrest in the United States. Circulation 2014;130:1876–82.

[10] Engdahl J, Holmberg M, Karlson BW, Luepker R, Herlitz J. The epidemiology of out-of-hospital "sudden" cardiac arrest. Resuscitation 2002;52:235–45.

[11] Pell JP, Sirel JM, Marsden AK, Ford I, Walker NL, Cobbe SM. Presentation, management, and outcome of out of hospital cardiopulmonary arrest: comparison by underlying aetiology. Heart 2003;89:839–42.

[12] Blom MT, Beesems SG, Homma PCM, Zijlstra JA, Hulleman M, Hoeijen DA van, et al. Improved survival after out-of-hospital cardiac arrest and use of automated external defibrillators. Circulation 2014;130:1868–75.

[13] Farb A, Tang AL, Burke AP, Sessums L, Liang Y, Virmani R. Sudden coronary death. Frequency of active coronary lesions, inactive coronary lesions, and myocardial infarction. Circulation 1995;92:1701–9.

[14] Nolan J. European Resuscitation Council Guidelines for Resuscitation 2005. Resuscitation 2005;67:S3–6.

[15] Oddo M, Ribordy V, Feihl F, Rossetti AO, Schaller M-D, Chioléro R, et al. Early predictors of outcome in comatose survivors of ventricular fibrillation and non-ventricular fibrillation cardiac arrest treated with hypothermia: a prospective study. Crit Care Med 2008;36:2296–301.

[16] Nielsen N, Hovdenes J, Nilsson F, Rubertsson S, Stammet P, Sunde K, et al. Outcome, timing and adverse events in therapeutic hypothermia after out-of-hospital cardiac arrest. Acta Anaesthesiol Scand 2009;53:926–34.

[17] Kern KB, Mostafizi K. A hands-on approach. What compression-only CPR means for EMS. JEMS 2009;Suppl:suppl 8–11.

[18] Ewy GA. Cardiocerebral resuscitation: the new cardiopulmonary resuscitation. Circulation 2005;111:2134–42.

[19] Neumar RW, Nolan JP, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A consensus statement from the International Liaison Committee on

Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; and the Stroke Council. Circulation 2008;118:2452–83.

[20] Laver S, Farrow C, Turner D, Nolan J. Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 2004;30:2126–8.

[21] Dragancea I, Rundgren M, Englund E, Friberg H, Cronberg T. The influence of induced hypothermia and delayed prognostication on the mode of death after cardiac arrest. Resuscitation 2013;84:337–42.

[22] Laurent I, Monchi M, Chiche J-D, Joly L-M, Spaulding C, Bourgeois B, et al. Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 2002;40:2110–6.

[23] Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, et al. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication. A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. Resuscitation 2008;79:350–79.

[24] Safar P. COMMUNITY-WIDE CARDIOPULMONARY RESUSCITATION. J Iowa Med Soc 1964;54:629–35.

[25] Walters JH, Morley PT, Nolan JP. The role of hypothermia in post-cardiac arrest patients with return of spontaneous circulation: a systematic review. Resuscitation 2011;82:508–16.

[26] Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted temperature management at 33°C versus 36°C after cardiac arrest. N Engl J Med 2013;369:2197–206.

[27] Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, et al. Part 8: Post-Cardiac Arrest Care: 2015 American Heart Association Guidelines Update for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015;132:S465–82.

[28] Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. Lancet 2008;371:1955–69.

[29] Sandroni C, Cariou A, Cavallaro F, Cronberg T, Friberg H, Hoedemaekers C, 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.

[30] Sandroni C, Cavallaro F, Callaway CW, D'Arrigo S, Sanna T, Kuiper MA, et al. Predictors of poor neurological outcome in adult comatose survivors of cardiac arrest: a systematic review and meta-analysis. Part 2: Patients treated with therapeutic hypothermia. Resuscitation 2013;84:1324–38.

[31] Samaniego EA, Persoon S, Wijman CAC. Prognosis after cardiac arrest and hypothermia: a new paradigm. Curr Neurol Neurosci Rep 2011;11:111–9.

[32] Oddo M, Rossetti AO. Predicting neurological outcome after cardiac arrest. Curr Opin Crit Care 2011;17:254–9.

[33] Cronberg T, Brizzi M, Liedholm LJ, Rosén I, Rubertsson S, Rylander C, et al. Neurological prognostication after cardiac arrest—Recommendations from the Swedish Resuscitation Council. Resuscitation 2013;84:867–72.

[34] Wijdicks EFM, Wijdicks CA. The portrayal of coma in contemporary motion pictures. Neurology 2006;66:1300–3.

[35] Samaniego EA, Mlynash M, Caulfield AF, Eyngorn I, Wijman CAC. Sedation confounds outcome prediction in cardiac arrest survivors treated with hypothermia. Neurocrit Care 2011;15:113–9.

[36] Rossetti AO, Carrera E, Oddo M. Early EEG correlates of neuronal injury after brain anoxia. Neurology 2012;78:796–802.

[37] Rossetti AO, Rabinstein AA, Oddo M. Neurological prognostication of outcome in patients in coma after cardiac arrest. Lancet Neurol 2016;15:597–609.

[38] Synek VM. Value of a revised EEG coma scale for prognosis after cerebral anoxia and diffuse head injury. Clin Electroencephalogr 1990;21:25–30.

[39] Hofmeijer J, Beernink TMJ, Bosch FH, Beishuizen A, Tjepkema-Cloostermans MC, Putten MJAM van. Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology 2015;85:137–43.

[40] Sivaraju A, Gilmore EJ, Wira CR, Stevens A, Rampal N, Moeller JJ, et al. Prognostication of post-cardiac arrest coma: early clinical and electroencephalographic predictors of outcome. Intensive Care Med 2015;41:1264–72.

[41] Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 2013;30:1–27.

[42] Westhall E, Rosén I, Rossetti AO, Rootselaar A-F van, Wesenberg Kjaer T, Friberg H, et al. Interrater variability of EEG interpretation in comatose cardiac arrest patients. Clin Neurophysiol 2015;126:2397–404.

[43] Westhall E, Rossetti AO, Rootselaar A-F van, Wesenberg Kjaer T, Horn J, Ullén S, et al. Standardized EEG interpretation accurately predicts prognosis after cardiac arrest. Neurology 2016;86:1482–90.

[44] Alvarez V, Sierra-Marcos A, Oddo M, Rossetti AO. Yield of intermittent versus continuous EEG in comatose survivors of cardiac arrest treated with hypothermia. Crit Care 2013;17:R190.

[45] Rossetti AO. Clinical neurophysiology for neurological prognostication of comatose patients after cardiac arrest. Clin Neurophysiol Pract 2017;2:76–80.

[46] Berkhoff M, Donati F, Bassetti C. Postanoxic alpha (theta) coma: a reappraisal of its prognostic significance. Clin Neurophysiol 2000;111:297–304.

[47] Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med 2014;42:1340–7.

[48] Juan E, Novy J, Suys T, Oddo M, Rossetti AO. Clinical evolution after a non-reactive hypothermic EEG following cardiac arrest. Neurocrit Care 2015;22:403–8.

[49] Sadaka F, O'Brien J, Prakash S. Red Cell Distribution Width and Outcome in Patients With Septic Shock. J Intensive Care Med 2012;28:307–13.

[50] Zandbergen EGJ, Koelman JHTM, Haan RJ de, Hijdra A, PROPAC-Study Group. SSEPs and prognosis in postanoxic coma: only short or also long latency responses? Neurology 2006;67:583–6.

[51] Bouwes A, Binnekade JM, Kuiper MA, Bosch FH, Zandstra DF, Toornvliet AC, et al. Prognosis of coma after therapeutic hypothermia: a prospective cohort study. Ann Neurol 2012;71:206–12.

[52] Leithner C, Ploner CJ, Hasper D, Storm C. Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? Neurology 2010;74:965–9.

[53] Endisch C, Storm C, Ploner CJ, Leithner C. Amplitudes of SSEP and outcome in cardiac arrest survivors: A prospective cohort study. Neurology 2015;85:1752–60.

[54] Gendo A, Kramer L, Häfner M, Funk GC, Zauner C, Sterz F, et al. Time-dependency of sensory evoked potentials in comatose cardiac arrest survivors. Intensive Care Med 2001;27:1305–11.

[55] Steffen IG, Hasper D, Ploner CJ, Schefold JC, Dietz E, Martens F, et al. Mild therapeutic hypothermia alters neuron specific enolase as an outcome predictor after resuscitation: 97 prospective hypothermia patients compared to 133 historical non-hypothermia patients. Crit Care 2010;14:R69.

[56] Cronberg T, Rundgren M, Westhall E, Englund E, Siemund R, Rosén I, et al. Neuron-specific enolase correlates with other prognostic markers after cardiac arrest. Neurology 2011;77:623–30.

[57] Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009;37:S186–202.

[58] Metter RB, Rittenberger JC, Guyette FX, Callaway CW. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation 2011;82:1180–5.

[59] Choi SP, Park HK, Park KN, Kim YM, Ahn KJ, Choi KH, et al. The density ratio of grey to white matter on computed tomography as an early predictor of vegetative state or death after cardiac arrest. Emerg Med J 2008;25:666–9.

[60] Scheel M, Storm C, Gentsch A, Nee J, Luckenbach F, Ploner CJ, et al. The prognostic value of gray-white-matter ratio in cardiac arrest patients treated with hypothermia. Scand J Trauma Resusc Emerg Med 2013;21:23.

[61] Wu O, Sorensen AG, Benner T, Singhal AB, Furie KL, Greer DM. Comatose patients with cardiac arrest: predicting clinical outcome with diffusion-weighted MR imaging. Radiology 2009;252:173–81.

[62] Järnum H, Knutsson L, Rundgren M, Siemund R, Englund E, Friberg H, et al. Diffusion and perfusion MRI of the brain in comatose patients treated with mild hypothermia after cardiac arrest: a prospective observational study. Resuscitation 2009;80:425–30.

[63] Moulaert VRM, Haastregt JCM van, Wade DT, Heugten CM van, Verbunt JA. "Stand still …, and move on" , an early neurologically-focused follow-up for cardiac arrest survivors and their caregivers: a process evaluation. BMC Health Serv Res 2014;14:34.

[64] Moulaert VR, Verbunt JA, van Heugten CM, Wade DT. Cognitive impairments in survivors of out-of-hospital cardiac arrest: a systematic review. Resuscitation. 2009 Mar;80(3):297-305. doi: 10.1016/j.resuscitation.2008.10.034. Epub 2008 Dec 30.

[65] Raina KD, Callaway C, Rittenberger JC, Holm MB. Neurological and functional status following cardiac arrest: method and tool utility.Neurological and functional status following cardiac arrest: method and tool utility.

References for the paper

[1].Coppler PJ, Elmer J, Calderon L, et al. Validation of the Pittsburgh Cardiac Arrest Category illness severity score. Resuscitation 2015;89(April):86–92.

[2].Rittenberger JC, Raina K, Holm MB, Kim YJ, Callaway CW. Association between Cerebral Performance Category, Modified Rankin Scale, and discharge disposition after cardiac arrest. Resuscitation 2011;82(August (8)):1036–40.

[3].Oddo M, Rossetti AO. Early multimodal outcome prediction after cardiac arrest in patients treated with hypothermia. Crit Care Med 2014;42(June (6)):1340–7.

[4].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(December (12)):1779–89.

[5].Hofmeijer J, Beernink TMJ, Bosch FH, et al. Early EEG contributes to multimodal outcome prediction of postanoxic coma. Neurology 2015;85(July (2)):137–43.

[6].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(December (12)):1779–89.

[7].Zandbergen EGJ, Hijdra A, H.T.M. Koelman J, et al. Prediction of poor outcome within the first 3 days of postanoxic coma. Neurology 2006;66((1)):62–8.

[8].Edgren E, Hedstrand U, Kelsey S, Sutton-Tyrrell K, Safar P. Assessment of neurological prognosis in comatose survivors of cardiac arrest. BRCT I Study Group. Lancet 1994;343(April (8905)):1055–9.

[9].Booth CM, Boone RH, Tomlinson G, Detsky AS. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. JAMA 2004;291(February (7)):870–9.

[10].Guideline thirteen: guidelines for standard electrode position nomenclature. American Electroencephalographic Society. J Clin Neurophysiol 1994;11(January (1)): 111–3.

[11].EEG reactivity to pain in comatose patients: Importance of the stimulus type. Resuscitation Elsevier2015;97(December):34–7.

[12].Hirsch LJ, LaRoche SM, Gaspard N, et al. American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2012 version. J Clin Neurophysiol 2013;30(February (1)):1–27.

[13].Rossetti AO, Oddo M, Logroscino G, Kaplan PW. Prognostication after cardiac arrest and hypothermia: a prospective study. Ann Neurol 2010;67(March (3)):301–7.

[14].Horn J, Tjepkema-Cloostermans MC. Somatosensory Evoked Potentials in Patients with Hypoxic-Ischemic Brain Injury. Semin Neurol Thieme Medical Publishers2017;37(February (01)):060–5.

[15].Tzvetanov P, Rousseff RT, Atanassova P. Prognostic value of median and tibial somatosensory evoked potentials in acute stroke. Neurosci Lett 2005;380((1-2)):99–104.

[16].Manninen PH, Tan TK, Sarjeant RM. Somatosensory Evoked Potential Monitoring During Carotid Endarterectomy in Patients with a Stroke. Anesth Analg 2001;39–44.

[17].Carrai R, Grippo A, Spalletti M, et al. P328 Not only the absence but also amplitude reduction of cortical SEPs predict ominous outcome in comatose patients after cardiac arrest. Clin Neurophysiol 2017;128(September (9)):e284.

[18].Torbey MT, Selim M, Knorr J, Bigelow C, Recht L. Quantitative analysis of the loss of distinction between gray and white matter in comatose patients after cardiac arrest. Stroke 2000;31(September (9)):2163–7.

[19].Metter RB, Rittenberger JC, Guyette FX, Callaway CW. Association between a quantitative CT scan measure of brain edema and outcome after cardiac arrest. Resuscitation 2011;82(September (9)):1180–5.

[20].Choi SP, Park HK, Park KN, et al. The density ratio of grey to white matter on computed tomography as an early predictor of vegetative state or death after cardiac arrest. Emerg Med J 2008;25(October (10)):666–9.

[21].Combination of initial neurologic examination, quantitative brain imaging and electroencephalography to predict outcome after cardiac arrest. Resuscitation Elsevier2017;110(January):120–5.

[22].Grippo A, Carrai R, Scarpino M, et al. Neurophysiological prediction of neurological good and poor outcome in post-anoxic coma. Acta Neurol Scand 2017;135(June (6)):641–8.

[23].Fugate JE, Wijdicks EFM, Mandrekar J, et al. Predictors of neurologic outcome in hypothermia after cardiac arrest. Ann Neurol 2010;68(December (6)):907–14.

[24].Bisschops LLA, Alfen N van, Bons S, Hoeven JG van der, Hoedemaekers CWE. Predictors of poor neurologic outcome in patients after cardiac arrest treated with hypothermia: a retrospective study. Resuscitation 2011;82(June (6)):696–701.

[25].Cloostermans MC, Meulen FB van, Eertman CJ, Hom HW, Putten MJAM van. Continuous electroencephalography monitoring for early prediction of neurological outcome in postanoxic patients after cardiac arrest: a prospective cohort study. Crit Care Med 2012;40(October (10)):2867–75.

[26].Bouwes A, Poppelen D van, Koelman JHTM, et al. Acute posthypoxic myoclonus after cardiopulmonary resuscitation. BMC Neurol 2012;12(August):63.

[27].Leithner C, Ploner CJ, Hasper D, Storm C. Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? Neurology 2010;74((12)): 965–9.

[28].Klein A-M, Howell K, Straube A, Pfefferkorn T, Bender A. Rehabilitation outcome of patients with severe and prolonged disorders of consciousness after aneurysmal subarachnoid hemorrhage (aSAH). Clin Neurol Neurosurg 2013;115(October (10)):2136–41.

[29].Endisch C, Storm C, Ploner CJ, Leithner C. Amplitudes of SSEP and outcome in cardiac arrest survivors: A prospective cohort study. Neurology 2015;85(November (20)):1752–60.

[30].Coppola G, Iacovelli E, Bracaglia M, et al. Electrophysiological correlates of episodic migraine chronification: evidence for thalamic involvement. J Headache Pain 2013;14(September):76.

[31].Amantini A, Grippo A, Fossi S, et al. Prediction of "awakening" and outcome in 10

prolonged acute coma from severe traumatic brain injury: evidence for validity of short latency SEPs. Clin Neurophysiol 2005;116((1)):229–35.

[32].Monitoring of subcortical and cortical somatosensory evoked potentials during carotid endarterectomy: comparison with stump pressure levels. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section Elsevier1987;68(November (6)):424–32.

[33].Scheel M, Storm C, Gentsch A, et al. The prognostic value of gray-white-matter ratio in cardiac arrest patients treated with hypothermia. Scand J Trauma Resusc Emerg Med 2013;21(April):23.

[34].Inamasu J, Miyatake S, Suzuki M, et al. Early CT signs in out-of-hospital cardiac arrest survivors: Temporal profile and prognostic significance. Resuscitation 2010;81(May (5)): 534–8.

[35].Inamasu J, Miyatake S, Nakatsukasa M, Koh H, Yagami T. Loss of gray-white matter discrimination as an early CT sign of brain ischemia/hypoxia in victims of asphyxial cardiac arrest. Emerg Radiol 2011;18(August (4)):295–8.

[36].Howell K, Grill E, Klein A-M, Straube A, Bender A. Rehabilitation outcome of anoxic- ischaemic encephalopathy survivors with prolonged disorders of consciousness. Resuscitation 2013;84(October (10)):1409–15.

[37].Fantaneanu TA, Tolchin B, Alvarez V, et al. Effect of stimulus type and temperature on EEG reactivity in cardiac arrest. Clin Neurophysiol 2016;127(November (11)):3412–7.

Tables

		at discharge			at 6 months					
	tot	survival	non survival	p	survival	non survival	p	good outcome	bad outcome	p
number (n, %)	96 (100)	69 (72)	27 (28)		50 (52)	46 (48)		40 (42)	56 (58)	
age (median, IQR)	62 (53-71)	61 (50-67)	72 (60-76)	<0.001	60 (48-66)	67 (60-74)	<0.001	61 (50-67)	72 (60-76)	0,01
Baseline characteristics (n, %)										
Male (%)	69 (72)	49 (71)	20 (74)	0.8	37 (74)	32 (70)	0,6	28 (70)	41 (73)	0,7
Hypertension	23 (25)	14 (22)	9 (33)	0.2	10 (21)	13 (29)	0,4	7 (19)	16 (30)	0,2
Coronary artery disease	13 (14)	7 (11)	6 (22)	0.2	5 (11)	8 (18)	0,3	3 (8)	10 (18)	0,2
Chronic heart failure	8 (9)	5 (8)	3 (11)	0.6	4 (8)	4 (9)	0,9	2 (5)	6 (11)	0,3
Diabetes	21 (23)	12 (19)	9 (33)	0.1	9 (19)	12 (27)	0,4	5 (13)	16 (30)	0,07
Chronic kidney injury	7 (8)	5 (8)	2 (7)	0.2	5 (11)	2 (4)	0,3	4 (11)	3 (6)	0,3
Smoke history	21 (23)	13 (20)	8 (30)	0.3	10 (21)	11 (25)	0,7	8 (22)	13 (24)	0,8
COPD	9 (10)	5 (8)	4 (15)	0.3	3 (6)	6 (14)	0,2	3 (8)	6 (11)	0,6
Resuscitation details										
Adrenaline mg (mean, IQR)	3 (1-5)	2 (0-4)	4 (2-6)	<0.001	2 (0-3)	4 (2-6)	<0.001	1 (0-3)	4 (2-6)	<0.0001
Shockable rhythm (n, %)	58 (68)	46 (74)	12 (52)	0.05	34 (74)	24 (54)	0,2	28 (76)	30 (62)	0,2
Time to Rosc minutes (mean, IQR)	17 (12-26)	15 (10-24)	23 (16-29)	0.01	14 (10-20)	23 (16-30)	0,001	14 (10-17)	22 (16-30)	0,0001
n° of Shocks during CPR (mean, IQR)	2 (0-5)	2 (1-5)	1 (0-5)	0.1	2 (1-5)	2 (0-5)	0,3	2 (1-4)	2 (0-5)	0,8

Table 1 baseline characteristics and resuscitation details

	GWR average		
	Severe Edema <1.1	**Mild Edema 1.1-1.2**	**No Edema ≥1.2**
n (%)	1(1)	17 (18)	78 (81)
EEG Reactivity at 36°C	0(0)	4 (27)	23 (31)
EEG Reactivity at 37°C	0(0)	4 (25)	37 (51)
N20-P25 amplitude at 36°C, (median, IQR)	0 (0-0)	0 (0-1.13)	0.63 (0-1.73)
If N20-P25 ampl ≠ 0 (median, IQR)	-	1.1 (0.4-1.9)	1.4 (0.7-2.8)
N20-P25 amplitude at 37°C (median, IQR)	0 (0-0)	0 (0-1.98)	0.66 (0-1.88)
If N20-P25 ampl ≠ 0 (median, IQR)	-	2.3 (0.6-2.7)	1.5 (0.7-2.3)

Table 2 Association between GW ratio and SSEP amplitudes and EEG reactivity at different temperature. ∅: no data, -: no observation, GWR average : Gray to white matter ratio average

n (%)		at discharge			at 6 months				
EEG 36°C (< 12 h)	**tot**	**survival**	**non survival**	**p**	**survival**	**non survival**	**p**	**good outcome**	**bad outcome**	**p**
Reactivity	27/90 (30)	25 (38)	2 (8)	*<0.01*	*20 (42)*	7 (16)	*<0.01*	18 (49)	9 (17)	0.001
Background										
flat	10 (11)	3 (4)	7 (29)	*0.001*	*2 (4)*	8 (19)	<0.05	1 (3)	9 (17)	<0.05
discontinuous	15 (17)	10 (15)	5 (21)	*0.5*	*5 (11)*	10 (23)	0.1	2(5)	13 (24)	<0.05
continuous	65 (72)	53 (80)	12 (50)	*0.005*	*40 (85)*	25 (58)	<0.005	34 (92)	31 (58)	<0.001
Ictal										
no discharge	67 (74)	54 (82)	13 (54)	*<0.01*	*41 (87)*	26 (60)	<0.005	35 (95)	32 (60)	<0.001
periodic discharge	11 (12)	5 (8)	6 (25)	*<0.05*	*4 (8)*	7 (16)	<0.5	2(5)	9 (17)	0.1
seizures	12 (13)	7 (11)	5 (21)	*0.2*	*2 (4)*	10 (23)	<0.01	0 (0)	12 (23)	<0.005
EEG 37°C (> 72h)										
Reactivity	41 (46)	39 (61)	2 (8)	*< 0.001*	*31 (69)*	10 (23)	<0.001	29 (83)	12 (23)	<0.001
Background										
flat	12 (13)	3 (5)	9 (36)	*<0.001*	*2 (4)*	10 (23)	0.01	0 (0)	12 (23)	<0.005
discontinuous	11 (12)	7 (11)	4 (16)	*0.5*	*5 (11)*	6 (14)	0.7	3 (9)	8 (15)	<0.5
continuous	66 (74)	54 (84)	12 (48)	*<0.001*	*38 (84)*	28 (64)	<0.05	32 (91)	34 (63)	<0.005
Ictal										
no discharge	62 (70)	48 (75)	14 (56)	*<0.1*	*40 (89)*	22 (50)	<0.001	32 (91)	30 (56)	<0.001
periodic discharge	11 (12)	9 (14)	2 (8)	*<0.5*	*3 (7)*	8 (18)	<0.1	2 (6)	9 (17)	0.1
seizure	16 (18)	7 (11)	9 (36)	*<0.01*	*2 (4)*	14 (32)	1	1 (3)	15 (28)	<0.005
GWR (median, IQR)										
Basal Ganglia	1.25 (1.2-1.3)	1.27 (1.23-1.3)	1.22 (1.17-1.29)	*0.03*	*1.27 (1.23-1.31)*	1.24 (1.19-1.27)	<0.005	1.28 (1.25-1.34)	1.23 (1.19-1.27)	<0.001
Average	1.25 (1.2-1.31)	1.26 (1.22-1.3)	1.21 (1.17-1.29)	*<0.01*	*1.27 (1.22-1.32)*	1-23 (1.19-1.29)	<0.005	1.29 (1.23-1.33)	1.23 (1.19-1.27)	<0.001
SSPEs (median, IQR)										
n20p25 amplitude at 36°C	0.48 (0-1.47)	0.83 (0-2.16)	0 (0.0.43)	*<0.0005*	*1.17 (0-2.59)*	0 (0-0.73)	<0.0005	1.41 (0.12-2.83)	0.04 (0-0.94)	0.0001
if n20p25 ampl ≠ 0	1.38 (0.7-2.2)	1.47 (0.8-2.8)	0.6 (0.4-1.4)	*<0.01*	*1.9 (0.8-3.5)*	0.93 (0.4-1.39)	0.001	2.2 (1.2-3.9)	0.94 (0.4-1.4)	<0.0005
n20p25 amplitude at 37°C	0.52 (0-1.88)	1.06 (0-2.18)	0 (0-0.16)	*< 0.0001*	*1.49 (0.23-2.33)*	0 (0-0.62)	<0.0001	1.66 (0.6-2.36)	0 (0-0.68)	<0.0001
if n20p25 ampl ≠ 0	1.62 (0.7-2.3)	1.8 (0.9-2.4)	0.48 (0.2-0.7)	*<0.005*	*1.93 (1.1-2.6)*	0.7 (0.35-1.9)	<0.005	1.98 (1.3-2.6)	0.73 (0.5-1.89)	<0.005

Table 3. EEG, SSEP N20P25 complex and GWR at 36°C and 37°C

	Background			Ictal		
median (IQR)	**Flat (10)**	**Discontinuous (15)**	**Continuous (65)**	**No Discharge (67)**	**'eriodic Discharge (11)**	**Seizures (12)**
EEG Reactivity at 36°C	1 (10)	3 (20)	23 (35)	25 (37)	2 (18)	0 (0)
I20-P25 amplitude at 36°	0.59 (0.08-1.39)	0.45 (0-0.73)	0.83 (0-2.2)	0.88 (0-2.2)	0 (0-0.55)	0 (0-0.58)
If N20-P25 ampl ≠ 0	1.05 (0.41-1.4)	0.66 (0.46-0.82)	1.67 (1.13-2.84)	1.41 (0.73-2.76)	0.93 (0.47-1.52)	0.86 (0.58-1.21)
	Flat (12)	**Discontinuous (11)**	**Continuous (66)**	**No Discharge (62)**	**'eriodic Discharge (11)**	**Seizure (16)**
EEG Reactivity at 37°C	0 (0)	3 (27)	38 (58)	36 (58)	4 (36)	1 (6)
I20-P25 amplitude at 37°	*0 (0-0)	0.35 (0-1.88)	0.78 (0-2.0)	0.83 (0-2.33)	0.3 (0-0.55)	0 (0-0.79)
If N20-P25 ampl ≠ 0	0.18 (0.16-0.2)	1.5 (0.6-2.8)	1.7 (0.7-2.4)	1.98 (0.88-2.69)	0.53 (0.51-0.62)	0.82 (0.67-1.09)

Table 4 Association between SSEPs amplitudes and EEGs features at different temperature. (): number of patients for each cathegory.

* there are 12 patients with flat EEG at 37 degrees. 10 patients have amplitude 0 and 2 patients have amplitude > 0. If I calculate the IQR on these measurements the result is 0(0-0) instead if I remove all the patients with zero SSPEs the IQR is 0.18 (0.16-0.2)

	Discharge from ICU		At 6 months			
	survival		survival		good outcome	
	AUC	(IC 95%)	AUC	(IC 95%)	AUC	(IC 95%)
EEG Reactivity 36°C	0.647	(0.566-0.729)	0.631	(0.540-0.722)	0.658	(0.562-0.754)
EEG Reactivity 37°C	0.764	(0.683-0.845)	0.731	(0.626-0.819)	0.803	(0.699-0.875)
GWRav	0.682	(0.551-0.811)	0.674	(0.574-0.769)	0.727	(0.629-0.815)
N20p25 amplitude 36°C	0.731	(0.629-0.815)	0.707	(0.607-0.797)	0.730	(0.629-0.815)
N20p25 amplitude 37°C	0.775	(0.674-0.850)	0.747	(0.651-0.833)	0.759	(0.662-0.842)
EEG reactivity 36°C GWRav	0.783	(0.674-0.893)	0.745	(0.642-0.848)	0.804	(0.709-0.899)
EEG reactivity 37°C GWRav	0.819	(0.721-0.917)	0.790	(0.697-0.882)	0.872	(0.797-0.947)
EEG reactivity 36°C N20p25 amplitude 36°C	0.821	(0.730-0.913)	0.781	(0.687-0.874)	0.831	(0.746-0.917)
EEG reactivity 37 °C N20p25 amplitude 37°C	0.859	(0.778-0.940)	0.812	(0.722-0.902)	0.887	(0.816-0.958)
GWRav N20p25 amplitude 36°C	0.781	(0.681-0.880)	0.733	(0.680-0.865)	0.823	(0.735-0.908)
GWRav N20p25 amplitude 37°C	0.838	(0.744-0.932)	0.798	(0.706-0.890)	0.835	(0.755-0.914)
EEG reactivity 36°C GWRav N20p25 amplitude 36°C	0.845	(0.755-0.936)	0.818	(0.731-0.906)	0.882	(0.812-0.953)
EEG reactivity 37°C GWRav N20p25 amplitude 37°C	0.882	(0.801-0.963)	0.841	(0.760-0.922)	0.920	(0.864-0.977)

table 5

Table 5. Area under the curve between EEG reactivity, SSPS N20P25 complex and GWR at 36°C and 37°C as single parameter and combined for predicting survival and good outcome.