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Anoxic-ischemic encephalopathy: association of predictors with the vital and functional prognosis of patients

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INDEX:

INTRODUCTION AND JUSTIFICATION:

Anoxia is the third most frequent cause of coma, and the most common cause of post-anoxic coma in adults is the cardiac arrest. The incidence of hypoxic-ischemic brain injury is not well known, but it is certain that cardiac arrest, the most common cause of post-anoxic coma, affects approximately 24000 to 50000 Spanish people every year, most of them occuring out of the hospital [1].

A cardiac arrest is the abrupt cessation of normal circulation of the blood due to failure of the heart to contract effectively during systole. It is different from, but may be caused by, a heart attack or myocardial infarction, where blood flow to the still-beating heart is interrupted. Arrested blood circulation prevents delivery of oxygen to all parts of the body. Cerebral hypoxia, or lack of oxygen supply to the brain, causes victims to lose consciousness and to stop normal breathing, although agonal breathing may still occur. Brain injury is likely if cardiac arrest is untreated for more than five minutes.

About 80% of arrests occur at home, for which the rate of death is at least 90% [2]. But survivors of out-of-hospital cardiac arrests are increasing, mostly because there are more community programs about the implementation of automated external defibrillators in the streets, and also there is the creation of mobile intensive care units, which provide a fastest action and often succeed in resuscitating patients, but severe cerebral damage cannot be avoided [3]. On the other hand, in-hospital cardiac arrests have slightly better outcomes.

Despite these improvements, the survival rate without brain damage ranges from 10 to 20%. More than half the survivors have permanent brain damage or varying degrees of brain injuries, which affect their lifes [2]. Almost 80% of patients who inicially survive a cardiac arrest remain comatose for varying lengths of time, approximately 40% of these progress to vegetative state [4], and the 1-year mortality exceeds 80% [5].

After a cardiac arrest, ischemic anoxia develops, meaning that the cerebral blood flow is insufficient to supply cerebral tissues. Ischemia is generally more dangerous than hypoxia alone because potentially toxic products of cerebral metabolism such as lactic acid are not removed. Cerebral damage is caused by specific biochemical disturbances both due to ischemia and to reperfusion injury. Ischemia consists of inadequate oxygen delivery and disruption of the blood-brain barrier.

Certain neurons seem to be more vulnerable to the secondary consequences of ischemia, those that occur after restoration of cerebral circulation [3].

Hypoxic-ischemic encephalopathy is a condition in which the entire brain does not receive enough oxygen, and there is a decreased amount of blood perfussion, resulting in the supression of electrical activity and cortical depression. Incomplete or delayed restoration of blood flow creates anoxic injury, and clinical recovery may be slow, incomplete, or absent. Metabolic failure occurs due to brain anoxia immediately. It's not completely deprived and affects the whole brain, rather than only a part of it. If cardiorespiratory function is restored within 5 minutes, the recovery may be complete. If anoxia is prolonged, permanent brain injuries occur in susceptible regions, such as the globus pallidus, cerebellum or hippocampus [6], causing multifocal or diffuse laminar cortical necrosis in these areas. Oedema may occur and produce vascular compression as the brain shifts, thus causing successive damage to arterial border zones. The result could be widespread subcortical damage [7]. And it can also cause long-term damage.

Following an hypoxic-ischemic insult, neuronal death can occur in two ways. A primary neuronal death, which is the immediate death if the insult is severe, related to cellular hypoxia leading to primary energy failure and cellular depolarisation.
And a secondary phase, in which after a latent period, between 6 and 100 hours, neuronal death may be iniciated by a cascade of pathological processes, associated with a marked encephalopathy, and involves cytotoxic oedema, accumulation of excitotoxins, active brain death and cytotoxic action of the activated microglia. Seizure activity is increased in this phase.

Hypoxic coma is associated with the highest mortality rate among the different causes of coma, with only around 30% of patients ever regaining awareness [8]. Coma is defined as a state of pathologic unconsciousness. Patients are unaware of their environment, they are unresponsive, and also they are unarousable, meaning they are not awaken by any stimulation, including pain. It is caused by either dysfunction of the reticular activating system above the level of the mid-pons, or dysfunction of both cerebral hemispheres.

The main factor still limiting recovery after an initially successful resuscitation is the brain's vulnerability to hypoxia [9]. Neurologic complications can lead to long stays in hospital, and to a poor vital and functional prognosis [1]. The damage must be determined early, in order to plan and administer appropiate postresuscitation therapy and to support the counseling of relatives. But the

prognostic determination of patients in coma after resuscitation from a cardiac arrest is both common and difficult [10]. Clinical scales often fail to adequately reflect the actual prognosis, because many resuscitated patients are still under analgesia and sedation and thus not fully assessable by clinical tests [9].

Intensivists are often confronted with the question of whether it is justified to continue expensive treatments in comatose survivors of cardiac arrests [5]. Many patients require ongoing life support after resuscitation, and the decision to continue treatment is heavily influenced by the likely prognosis [8]. Early identification of patients with a poor prognosis is desirable in order to reduce uncertainty over treatment and non-treatment decisions [4]. Current trends in ethical decision making have increased the need for accurate and early predict the outcome of these patients [11].

Some progress has been made in the prediction of outcomes for initially comatose patients, mainly in the prediction of poor outcomes [2]. A poor prognosis usually leads to the consideration of withdrawal of life support. To avoid withdrawal of support in patients which have a plausible chance at recovery, tests should have a near zero rate of false positives for determining poor prognosis. The difficulty of an early prognostication leads to the "self-fulfilling prophecy", in which support is withdrawn because of an unfavorable result of that test being evaluated. So, an early prediction of poor outcomes would be valuable. But except for unfavorable somatosensory evoked potentials (SSEP) results, predictors of unfavorable outcome with 100% specificity and high sensitivity are lacking [12].

The duration of the cardiac arrest or anoxic period correlates with the extent of brain damage. It's difficult to determine the duration of arrest when evaluating a patient because up to 80% of patients are still comatose [4]. The duration of anoxia is defined as the period between cardiac arrest and initiation of reanimation. An anoxic period under 5 minutes is related to electroencephalographic (EEG) patterns of good prognosis (grades I and II of the Hockaday scale) resulting in no neurological disorders. If it's longer, the EEG patterns are those of poor outcome [13]. Improved techniques in resuscitation have successfully increased the survival rate of patients after cardiac arrest, but the most important factor is the promptness with which the resuscitation procedure is started, since the brain is highly vulnerable in an anoxic condition. The time it takes from the arrest to the return of spontaneous circulation (ROSC) is the resuscitation period. It's correlated with the outcome, contributing to a poor vital and functional prognosis when it lasts more than 15 minutes. But the length of post-anoxic coma is not always a reliable prognostic criteria [13].

There is clinical evidence that therapeutic hypothermia is the only treatment, during the post cardiac arrest period, that can improve vital and functional prognosis of patients [7, 14]. It protects the brain against ischemia and anoxia, and increases it's recovery. In the initial hours after cardiac arrest, it improves the neurologic outcome of resuscitated patients. But it impacts the utility of clinical examination findings and ancillary testing such as SSEP and biochemical markers (neuron-specific enolase NSE) [4]. Because the effect of hypothermia on the predictive value of various test results remains uncertain, for example it's suggested that reduces the predictive value of motor response early after a cardiac arrest and that a small number of patients may have a good outcome despite the bilaterally absence of N20, there has to wait at least 24 hours after rewarming from hypothermia to believe in the test results for the outcome prediction and the decision-making [2, 15].

The post-resuscitation clinical course infuences in the outcome [4]. The most predicitve variable at the initial examination is the pupillary light reflex. An absent pupillary reaction to light 72h after the arrest, carries a prognosis of coma until death with 100% specificity. Also, the absence of the corneal reflex 72h after the cardiac arrest is associated with no false positives for a poor outcome. Although the absence of various cranial nerve reflexes beyond day 1 is strongly supportive of a lack of neurological recovery, such reflexes are often regained, even in those who fare badly. The use of such reflexes to assess outcome is based on the inference that the cerebral cortex is usually more vulnerable to anoxic-ischemic insults than the brainstem nucli. But they don't provide a direct assessement of thalamo-cortical function [10].

The motor response is the variabe having the greatest predictive power. Absence of motor response to painful stimuli after 3 days of coma is related to poor outcome with specificity of 100%. Status epilepticus and myoclonus status epilepticus are predictors of poor outcome in patients with severe injury [4]. The poor prognosis of patients whose brainstem reflexes are still absent at day 3 is explained by the fact that brainstem failure in this condition necessarily implies severe cortical damage [16]. A Glasgow Coma Scale < 4 after 3 days of coma is the best indicator of poor outcome with 100% specificity. But it can't be considered a sufficiently sensitive measure compared with other tests of the Central Nervous System (CNS) function. The best predictors of good outcome are presence of motor response to pain and GCS > 4, with a sensitivity of 100% [17].

Hypothermia and sedation, used as standard care of this comatose patients, interferes the clinical examination, particularly the motor response, decreasing their utility in determining the prognosis of these patients [18].

The EEG has emerged as a routine screening tool in comatose patients. It's non-invasive and useful for prognosis. It provides information about the brain electrical activity, even when the brain function is depressed and it can't be explored by other means, such as in coma. It improves the prognostication of this patients when added to a neurological examination [18]. With the EEG we obtain information about the global cortical function, the reactivity to external stimuli and the presence of paroxysmal activities, but with a low specificity and an even lower sensitivity for identifying patients who will not recover. And it is sensitive to major central nervous system sedative drugs. In the initial stages following resuscitation, there may be electrical silence, but dystinct rhythms may gradually evolve after 24 hours in non-hypothermia and free of toxic ingestion or pharmacological sedation, which guide prognosis [19].

The EEG patterns are classified using the Hockaday Scale, with modifications of Synek. They are based on the background activity (continuous or discontinuous pattern), and reactivity to painful and auditory stimulation (reactive or not). It has been concluded that the reactivity to external stimuli and the presence of spontaneous fluctuations is associated with a favourable outcome. And that EEG findings with a poor prognosis are the spontaneous burst supression or the generalized periodic discharges [18]. It also allows the detection of seizures, which bring a poorer prognosis to the 10-30% patients suffering from them.

The EEG is a good indicator of patient prognosis after cardiopulmonary resuscitation (CPR), however, the clinical significance of morphological differences of various periodic patterns that can occur during and EEG remains to be established. The evolution in EEG picture in the first hours of resuscitation after CPR provides a powerful tool for prognostication [3], since half of the patients don't show cortical activity on EEG immediately after resuscitation. There has to wait 24 hours before an EEG to avoid falsely disappointing results [4]. It's susceptible to the effects of sedative drugs, metabolic disturbances, and sepsis.

The EEG is a sensitive indicator of cerebral ischemia. The clinical value of EEG is unclear because different classification systems have been used, so there's the need of correlation between EEG and clinical parameters, on the purpose to establish more valid markers to assist clinical decision [19]. Also, certain subcategories of findings have not been examined, and the clinical significance of periodic patterns in EEG and their differences have not been clarified [13]. Thus, their prognostic relevance has not been established and more attention is needed to improve the prediction of a positive outcome [2].

Sometimes, there is a discrepancy between SSEP and EEG in prognosis results. We can finish with no correlation between the registered EEG rhythms and the N20 component of the somatosensory evoked potentials. The N20 is generated in the somatosensory cortex, and not in subcortical structures, and thus SSEP reflects thalamocortical synaptic function [receiving mode]. On the other hand, the EEG provides the resulting signals of the interaction between the pyramidal cells (cortical function, or intra-cortical synaptic connections) [sending mode] [15].

EEG reflects the synchrony of pyramidal cell function, so a minimum number of functional cells are needed, and also of functional synapses. The synaptic function needs more metabolic demand, and it's more vulnerable, so in long periods of hypoxia, only the synapses could be affected. The EEG or sending mode depends on the intact synaptic transmission between pyramidal cells, and they are highly dependent on the oxygen and glucose supply, being more sensitive to hypoxic insults. On the other hand, the cortical response to median nerve stimulation (N20) depends on the receiving mode of the deep pyramidal cells (extracellular current, generated by postsynaptic potentials) in the tahalmocortical cells (presence of generation of intracellular currents due to synaptic input from thalamocortical cells), and can't become affected in presence of intra-cortical synpasis blockage. In conclusion, thalamocortical synapses are less vulnerable to hypoxia [15].
So, we can find preserved SSEP and EEG patterns of cortical dysfunction, because only the sending mode can be affected. The preservation of the N20 response can't lead to high sensitivity, and in consequence, preservation of N20 is necessary but not sufficient to return to consciousness [20].

The recording of SSEPs is a noninvasive and reproducible bedside technique, which is useful in assessing the integrity of the transmission within the CNS, including the brainstem somatosensory pathways, thalamo-cortical projections, and the primary somatosensory cortical function, by showing the integrity of the neuroaxis [20]. The cerebral cortex is always the most severely damaged structure, whereas brainstem structures remain intact in all but the most afflicted patients [16]. Global insults producing random multifocal laminar cortical and subcortical injury may preserve the neurons that generate the N20 [7]. They are more promising in the evaluation of comatose patients since they are less affected than EEG by sedative drugs like barbiturics, or metabolic disturbances. They are less global than EEG, and thus they allow the avaluation of the topography of dysfunctions [21]. And because early cortical responses after median nerve stimulation of SSEPs are generated in the somatosensory cortex, it will identify more patients with severe brain damage than testing brainstem reflexes alone.

Depending on the extent of cerebral anoxia, SSEP peaks are delayed or absent. The bilateral absence of N20 is highly correlated with nonsurvival and invariably associated with a poor outcome with no false positives, and it preceeds the development of electrocerebral silence [3, 20]. But the preservation of the N20 doesn't indicate a good prognosis, it's still poor, and it's not a guarantee for awakening from coma. There is a limited specificity of the presence of the N20 response regarding good outcome, and its preservation is combined with a lot of different EEG patterns [20]. Following a cardiac arrest, SSEPs have a better capacity to identify patients with a poor outcome than to predict good outcomes, since absent SSEP were associated with no patients awakening from coma, particularly when combiend with absent EEG reactivity [22]. A meta-analysis identified SSEP as the method with the highest prognostic reliability. It's the most valuable and best validated test in the prognosis of these patients [5, 20].

Many post-ischemic metabolic and circulatory disorders occur immediately and delayed after a successful CPR, including post-ischemic hypoperfusion and dysregulation of blood flow, permeability changes in the blood-brain barrier, and even secondary depression of previously recovered metabolic activities. All this changes affect the results of the tests, including SSEP, which are time-dependent, and they are also affected by therapeutic hypothermia. So, when N20 is present after 24 hours from the arrest, it has to be repeated in the first 2-3 days. When it's lost after 72 hours from the arrest, it won't be regained, and thus it's a reliable result [5].

In a recent study, it has been concluded that the measurement of the response amplitudes in the SSEPs is informative. They found a significant association between amplitude reduction of SSEPs and a poor outcome. In anoxic-ischemic coma patients, not only the absence but also the amplitude reduction of SSEPs are associated with no recovery [21]. It has also been found that the latency of the N20 is significantly longer in nonsurvivors [5]. The N20 is the cortical response and is considered to be an activation of the primary somatosensory cortex following input from the thalamus, and delay or loss of N20 peak implies an interruption of the connecting pathways between cervicomedullary junction and the sensory cortex.

The neuron-specific enolase (NSE) is the neuronal form of the intracytoplasmatic glycolytic enzyme enolase, and is a biomarker of hypoxic brain damage. It can be easily measured and can be reproduced with minor invasiveness in patients. Its levels increase continuously after a cardiac arrest and they peak on the third day. A serum level above 33 ng/ml between days 1 and 3 after a cardiac arrest, is strongly predictive of poor outcome with no false positives. The predictive value

of neurobiochemical markers is variable, and they are unhelpful before 48 hours have elapsed, due to the metabolical changes occuring immediately after an arrest [4]. The present predictive value of biochemical markers is insufficient when compared with SSEPs, but they may provide additional information about the patient's course of disease [9]. Currently, no established algorithms exist to combine serum NSE concentrations and the various other predictors into a composite score that gives clear predictive outcome information.

Ancillary testing is often useful at arriving at an earlier prognostic determination than would be possible with clinical testing alone. While very specific, these signs aren't very sensitive for poor neurological outcomes [10]. Except for unfavorable SSEP results, predictors of unfavourable outcome with a 100% specificity and high sensitivity are lacking [12]. The outcome of these patients is often poor, so it's important to establish an accurate prognosis as soon as possible to guide mangement [19], and also many patients who don't have unfavorable clinical features still have poor outcomes. The combination of SSEP and EEG produce a greater predictive value [10], but there are 20% of patients that can't be classified into the EEG scales right now [6], so there's the need to revise and redefinite them.

There is a relationship between the different tests, for example a combination of clinical and EEG findings can predict the absence of cortical response in the SSEP. SSEP is superior to clinical or EEG tests in terms of low false positive rates, and the results of SSEP are less affected by metabolic changes and sedative drugs, than are clinical and EEG tests. In patients with a favorable result in SSEP, clinical signs and EEG could help to identify a subgroup of patients with poor outcome (but with lower sensitivity than an unfavorable result in SSEP) [12]. So there is a value of EEG and SSEP tests in addition to clinical evaluation when stabilshing prognosis. This, combined with biochemical data, can produce a greater predictive power [10].

It seems unlikely that any single test will prove to have 100% predictive value for outcome, but the combination of various prognostic markers could increase the reliability of outcome prediction [4]. Studies combining clinical, EEG, SSEP and biochemical testings are needed.

It is desirable to have reliable predictors of both favorable and unfavorable outcomes for resources allocation, management, and counseling of family members. We can make an early selection of patients with a defined poor prognosis, but there isn't the certainty to predict good outcomes. In many studies, clinical, EEG, SSEP and biochemical test results have been correlated with the

outcome of patients after a cardiac arrest, but few have examined these variables prospectively in the same patients and ensuring that patients survived for at least several days to prevent premature "self-fulfilling prophesies". It remains uncertain whether patients with more than one poor test result have a larger probability of poor outcome than patients with a single poor test result [17].
And until today, studies to assess the prognostic value of early neurological and neurophysiological findings in patients with anoxic-ischemic coma have not led to precise, generally accepted, prognostic rules [17].

There still remains a considerable degree of uncertainty [3].

OBJECTIVE:

Improve the prediction of the vital and functional prognosis of comatose patients suffering from anoxic-ischemic encephalopathy after successful resuscitation from a cardiac arrest, addmitted to the Intensive Care and Coronary Units of the Dr. Josep Trueta Hospital, based on clinical, neurophysiological and biochemical results.

HYPOTHESIS:

The results of these different tests, revised and combined all together, will improve the prediction of the patients' prognosis, leading to an accurate vital and functional outcome, as they only have been studied separately so far.

METHODOLOGY:

Study design:

It's a retrospective and observational study.

Population definition:

The sample consists of patients registered from January 2010 to October 2013, admitted to, and hospitalised in the Intensive Care and Coronary Units of the J. Trueta Hospital, who were comatose due to an anoxic-ischemic encephalopathy following successful resuscitation from a cardiac arrest.

Inclusion criteria:

Patients who suffered either in-hospital or out-of-hospital succesfully resuscitated cardiac arrests.
Patients who underwent successful resuscitation, but remained unconscious after 6 hours from the resuscitation, when sedation was withdrawn.
Patients who did not awake after undergoing therapeutic hypothermia, performed after the resuscitated cardiac arrest, or those who awaken but with clinical myoclonies.
Comatose patients with anoxic-ischemic encephalopathy secondary to a cardiac arrest.

Exclusion criteria:

Prior brain disease or brain death.
Patients under 18 years old.
Confounders such as coincident head injury, or the continuous infusion of anesthetic drugs, that could not be discontinued to allow assessement, which alteres the neurophysiological results, such as the electroencephalography (EEG).
Coma from other medical conditions or trauma, secondary to: stroke, drowning, hanging, metabolic dysfunction, traumatic head injury, hypotensive shock, or respiratory failure.

Sampling:

Consecutive non-probabilistic sampling.
We will introduce into the study all patients who meet the inclusion and exclusion criteria, without obtaining any sample of this population afterwards.

Definition of the Variables in the study:

Independent variables:

- ROSC time.

  It's defined as the time it takes from the arrest to the return of spontaneous circulation (ROSC), which is the resuscitation period. Is the resumption of sustained perfusing cardiac activity associated with significant respiratory effort after cardiac arrest. Signs of ROSC include breathing, coughing or movement, with a palpable pulse or a measurable blood pressure.
  Based on clinical evidence, ROSC influences and is correlated with the outcome of this patients, contributing to a poor vital and functional prognosis when it lasts for more than 15 minutes. Moreover, cardiopulmonary resuscitation and defibrillation have increased the chances of returning to spontaneous circulation.

  Considering the most recent studies [13], we treat this variable as dichotomus. So we divided the data obtained into two groups: those who had a ROSC less than 15 minutes, and those who had a ROSC greater or equal to 15 minutes.

- Neurological status.

  We recorded several data from the neurological examination:
  - Presence or absence of spontaneous movements.
  - Response to voice, light, touch, and painful stimuli.
  - Pupillary size and its response to light.
  - Corneal and oculovestibular reflexes (brainstem reflexes).

  Based on the most recent studies [11, 4], we treat these variables as dichotomus. So we divided the data obtained from the neurological examination into these groups:

  For the spontaneous movements, we divided patients who had spontaneous movements, of those who hadn't.

  For the motor response to voice, light, touch and painful stimuli, we divided those patients who had no movements, or extension (decerebrate response), or abnormal flexion response (decorticate response); from those who had other motor responses, such as localization.

  For the pupillary reflex, we divided in patients who had it, from those who hadn't.

  For the corneal and oculovestibular reflexes, we also divided those who presented it, from the others who didn't.

- Somatosensory Evoked Potentials (SSEP).

  SSEPs are a useful and noninvasive technique in assessing the function of the somatosensory system. They are the averaged electrical signals generated by the nervous system in response to somatosensory stimuli, and thus they evaluate time-locked responses of the nervous system to an external stimulus.

By combining SSEP recordings at different levels of the somatosensory pathways, they represent the function of the ascending sensory pathways by using an afferent potential, which travels from the peripheral nerve to the plexus, root, spinal cord (or posterior column), contralateral medial lemniscus, thalamus, and finally to the somatosensory cortex.

They can be obtained in response to a brief mechanical stimulation, but in clinical studies they are commonly elicited by bipolar transcutaneous electrical stimulation applied on the skin over the trajectory of peripheral nerves. It is initiated by a repetitive submaximal stimulation of a sensory nerve, mixed nerve or dermatome, and it's recorded from the scalp.

The obtained results consist of a series of positive and negative waves that reflect sequential activation of neural structures along the somatosensory pathways.

Based on clinical evidence [11, 9] and in the Guidelines of the International Federation of Clinical Neurophysiology, we treat this variable as an ordinal and categorical variable. We made three groups based on the results of the SSEPs obtained:

Grade 1a: normal SSEPs. Patients with uni- or bilateral presence of early cortical responses. Clearly recognizable contralateral N20 wave, giving rise to a normal amplitude ratio N20/P25 of at least 0,8, and a normal latency of N20 (<23 msec).

Grade 1b: bilateral amplitude reduction (N20-P25 amplitude < 0,8 microvolts) or N20 latency longer than 23 msec (at least at one side).

Grade 2: bilateral absence of early cortical response (N20).

- Electroencephalography (EEG).

  It is the recording of electrical activity along the scalp. EEG measures voltage fluctuations resulting from ionic current flows within the neurons of the brain. In clinical contexts, EEG refers to the recording of the brain's spontaneous electrical activity, recorded from multiple electrodes placed on the scalp.

  The brain's electrical charge is maintained by billions of neurons, which are electrically charged or polarized by membrane transport proteins that pump ions across their membranes. Neurons are constantly exchanging ions with the extracellular liquids. Ions of similar charge repel each other, and when many ions are pushed out of many neurons, they create a wave, known as volume conduction. When the wave of ions reaches the electrodes on the scalp, they can push or pull electrons on the metal of the electrodes. Since metal conducts electrons easily, the differences in voltages between any two electrodes can be measured by a voltemeter. Recording these voltages over time gives the EEG.

  The EEG activity reflects the summation of the synchronous activity of millions of neurons that have similar spatial orientation. It shows oscillations at a variety of frequencies, meaning different and characteristic spatial distributions, or different states of the brain function, such as awakening or sleeping states.

  Because voltage fields fall off with the square of distance, activity from deep sources is more difficult to detect than currents near the skull.
  Based on the recent evidence, we treat this variable as a categorical and nominal variable.

  We used an EEG grading which was performed using a modification of the original and validated Hockaday scale (HS) [18, 13, 6].

  EEGs are classified attending to the predominating basal activity, its presence or absence of reactivity to external stimuli, and the presence or absence of paroxysms.

Grade I: normal and reactive alpha rhythm.

Defined as the presence of dominant normal alpha activity (50 - 100 microvolts), with little topographic differentiation, with or without theta (with an amplitude similar to alpha) or delta (low voltage) activity. Positive reactivity to stimuli. It entails an excellent vital and functional prognosis.

Grade II: midly abnormal layout. Theta activity.

Defined as a predominant theta activity with rare alpha or delta activities.

- Grade IIa: reactive theta activity.

Defined as a predominant theta activity (50-100 microvolts), bilaterally distributed and with an increased expression in central areas, with attenuation response to acoustic stimulation and nociceptive deal (reactivity).

The persistence over time of this pattern indicates good prognosis, both survival and functional recovery.

- Grade IIb: non-reactive theta activity.

Defined as a predominant theta activity of small amplitude (<50 microvolts), with little or non reactivity. It can also show some discontinuous high voltage delta waves. There are not fast pace rhythms. Functional prognosis remains uncertain.

Grade III: moderately abnormal layout. Reactive delta activity.

Defined as a diffuse delta acitivity (100-200 microvolts), predominant or mixed with theta or rare alpha activities. Attenuation with external stimuli (reactivity). This pattern is associated with an uncertain vital prognosis, and a poor functional prognosis.

- Grade IIIa: synchronized and reactive delta activity.

Defined as high voltage (150 microvolts) delta waves, and with an increased expression in the frontal areas. Theta waves are scarce and of low-voltage, with alpha activity in posterior areas. Preserved reactivity to external stimuli.

The persistence of this pattern suggests a greater chance of survival.

- Grade IIIb: non-reactive and irregular delta activity.

Defined as low amplitude (<50 microvolts) delta waves, with wide distribution. This delta activity can be interrupted occasionally by brief periods of attenuation (less than 1 second). The pattern doesn't change with external stimuli (non-reactive).

This pattern is associated with a very poor prognosis, most of the times evolving to an isoelectric layout (Grade V).

- Grade IIIc: spindle coma pattern.

Defined as a bilateral slowing brain activity with K complexes and sleep spindles.

It's an unusual pattern, due to subcortical and brainstem damage. It is associated with an uncertain vital prognosis.

-Grade IIId: paroxysmal activity with slow background base.

Defined as a periodic paroxysmal activity, consisting in a generalised slowed brain activity, with delta and theta frequencies (100-150 microvolts). Waves can addopt the morphology of a biphasic or triphasic acute-phase, or those of high voltage spikes (200microvolts). Myoclonus can be associated.

It is usually a reactive pattern, and the prognosis is more favorable than those in group IV.

A paroxysmal pattern can occure, including the morphology of PLEDs (periodic lateralized discharges epileptiforms) and BIPLEDs (bilateral PLEDs, affecting an entire hemisphere).

Grade IV: severely abnormal and non reactive patterns. They are associated with an extremely poor vital and functional prognosis.

- Grade IVa: Burst supression.

Defined as a combination of isoelectric periods of variable duration, generally of more than a second, interrupted by paroxysmal activities at different frequencies.

This pattern doesn't change with external stimuli (non reactive).

- Grade IVb: Paroxysmal activity with sharp waves and generalized poly-tips.

They are totally asynchronous between hemispheres, and with a widespread expression. They repeat in a frequency of 1 to 5 seconds. This pattern is frequently associated with clinical myoclonus.

- Grade IVc: Low output activity.

Defined as a non-reactive cerebral activity, with delta waves at low amplitude frequencies (<20 microvolts). It evolves to an isoelectric layout, and it may be preceded by a Grade IIIb.

- Grade IVd: Alpha coma.

Defined as an alpha frequency of brain activity (8Hz), with amplitudes over 50 microvolts, in a diffuse distribution, predominating in the anterior regions (frontal lobes). Sometimes delta activity is present. It is always non-reactive, and it's typical of brainstem injuries.
It is associated with a poor vital and functional prognosis.

- Grade IVe: Theta coma.

Defined as an intermittent theta activity, predominant in the frontal areas. It's non-reactive, but sometimes some kind of a non-specified response can be obtained. In all studies, it implies a poor vital and functional prognosis.

Grade V: extremely abnormal pattern.

Defined as a flat to isoeletric pattern, with voltages below the 20 microvolts. It is always a non-reactive pattern. And it is associated with an extremely poor vital and functional prognosis. It equals brain death activity.

- Serum neuron-specific enolase (NSE) concentration.

Enolase is a glycolytic enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate. Enolase exists in the form of several tissue-specific isoenzymes, consisting of homo or heterodimers of 3 different monomer-isoforms (alpha, beta, and gamma). Neuron specific enolase (NSE) is a 78 kD gamma-homodimer and represents the dominant enolase-isoenzyme found in neuronal and neuroendocrine tissues. Its levels in other tissues, except erythrocytes, are negligible. The biological half-life of NSE in body fluids is approximately 24 hours.

Due to this organ-specificity, concentrations of NSE in serum or cerebrospinal fluid, are often elevated in diseases which result in relative rapid (hours/days to weeks, rather than months to years) neuronal destruction. Several biochemicals, such as NSE, are released from the brain into the blood and cerebrospinal fluid after a cardiac arrest.

Based on clinical evidence, a NSE > 33 mcg/l is indicative of poor outcome with a false-positive rate of 0. Also, based on the current protocols in the J.Trueta Hospital [14], a NSE level of more than 33 mycrograms/l, sampled between 1-3 days after cardiac arrest, is strongly predictive of poor outcome with no false positives.

We treat this variable as dichotomus, defining two groups, one with NSE levels below 33 mcg/l, and the other with patients having NSE levels over 33 mcg/l.

Dependent variable or Outcome:

- Neurological and vital status.

It is defined by the Glasgow-Pittsburg scale, or in other words, the cerebral performance categories (CPC).

This outcome scale has become the most widely used approach to evaluate quality of life after successful resuscitation from a cardiac arrest, because of its established validity and low interobserver variability.

The scale is divided into five categories, as follows:

CPC 1: no sequelae and good recovery of the patients. They remain conscious, alert and oriented. They have normal cognitive functions, or only a slight disability.

CPC 2: mild disability of patients. They are independent and no institutionalization is required. Able to participate in activities of the daily living, but work and social life are compromised because of mental or physical disability. They remain conscious and alert.

CPC 3: severe disability. They are dependent and institutionalization is required. They are able to follow commands but cannot live independently. They require support for activities of the daily living. They remain conscious.

CPC 4: persistent vegetative state. They are awake but not aware, and they don't interact in any cognitive way with the environment. They don't fixate or follow with the eyes, and vegetative functions are preserved.

The persistent vegetative state is, like coma, characterised by unawareness, but these patients have normal sleep-wake cycles and are arousable. Moving from coma to a CPC 4 doesn't mean it's associated with an improvement in the overall functional outcome.

This patients suffer severe anoxic brain injury and they progress to a state of wakefulness without awareness. It is defined as:

- No evidence of awareness of themself or environment and an ability to interact with others.
- No evidence of sustained, reproducible, purposeful, or voluntary behavioral responses to visual, auditory, tacticle, or noxious stimuli.
- No evidence of language comprehension or expression.
- Intermittent wakefulness displayed by the presence of sleep-wake cycles.
- Sufficiently preserved hypothalamic and brainstem autonomic function to allow survival with medical and nursing care.
- Bowel and bladder incontinence.
- Variably preserved cranial nerve reflexes and spinal reflexes.

It is judged to be permanent after 3 months if induced nontraumatically. Related to hypoxic-ischemic encephalopathy, recovery is rare after this period of time, and is associated with moderate to sever disability at best.

CPC 5: death.

Based on recent evidence and previous studies, we treat this variable as dichotomus.
CPC1 and CPC2 are considered good neurologic and vital outcomes, and the othrt three remaining (CPC3, CPC4 and CPC5), of poor neurologic and vital outcome or death.

Covariates or Confusion-variables:

- Acute metabolic derangements, such as acute renal or liver failure.

Acute renal failure is defined as a rapid loss of kidney function. For its diagnosis are required both a rapid time course (less than 48 hours) and a reduction of kidney function. The reduction of its function is determined by the rise in serum creatinine, either an absolute increase in serum creatinine of ≥ 0.3 mg/dl (or $\geq 50\%$) or a reduction in urine output, defined as < 0.5 ml/kg/h for more than 6 hours.

The diagnosis of acute liver failure requires the finding of liver test abnormalities indicative of acute liver injury, accompanied by signs or symptoms of hepatic encephalopathy in a patient with no known previous liver injury. Typical features of acute liver failure include: acute elevations in serum enzyme elevations with serum aminotransferase levels greater than 10 times the upper limit of the normal range, early in the course of illness; mild to moderate elevations in serum alkaline phosphatase levels (early in the injury); latency of a few days to 6 months after starting the medication; increased prothrombin time (>3 seconds prolonged) or international normalized ratio (INR >1.5); and symptoms or signs of hepatic encephalopathy.

- Administration of sedatives and neuromuscular agents. Sedation was standardized with midazolam and fentanyl.

- Age over 70 years old.

- Medications such as anticholinergics or sedatives, and paralytic agens used in resuscitation or after the cardiac arrest.

- Medical history: cardiovascular, neurologic, respiratory, or metabolic diseases.

Measuring instruments and data collection:

- ROSC time.

  The time it takes from the arrest to the return of spontaneous circulation (ROSC) is collected from the emergency medical services, at the moment of the resuscitation.

- Neurological status.

  The neurological examination is performed three days after the cardiac arrest and its succesful resuscitation, with the patients in coma, after the withdrawal of sedation.
  Though, consideration regarding neurological outcome are postponed until 72h after the onset of coma.
  The prognostic value of several clinical variables is then more accurate, because there is a shock- phase early after the insult from which the brain can partly recover.

  The presence or absence of spontaneous movements, was assessed by observing the patient. The response to voice, light, touch, and painful stimuli, was assessed by shouting his name, or producing a painful reaction in some parts of the body, and observing the patient's immediately reaction after the stimuli.

The motor activity test provides useful data on the level of impairment of consciousness, and on the evolution of the process.

The presence of spontaneous movements of all four limbs indicates moderate involvement of the cerebral hemispheres, especially if this is due to simple commands. A degree of involvement is one in which the patient is still not responding to commands but it is able to locate the painful stimulus by contracting the muscles underlying the stimulated point, and by even removing the member.
Stimulus points used are the supraorbital pressure, impingement mammillary area or any part of the sternum and the compression of members. Asymmetric responses are possible.

In the next step, the patient spontaneously adopts stiffness decortication posture characterized by hyperextension of the lower limbs with flexion of the upper and which is exacerbated by painful stimuli. It is indicative of diencephalic involvement.

Finally, when the patient takes spontaneously decerebrate rigidity position, involvement level reaches the midbrain, indicating severe impairment and warning sign. Its serious expression is the position of opisthotonos: a muscle spasm that causes curvature of the back and a head retraction with high rigidity of the muscles of the neck and back.

The pupillary size and its response to light, or the pupillary reflex, was assessed by stimulating the eye with an intense light stimulus, showing a bilateral contraction of the pupils.
They note the size, equality and reactivity. It must be performed in a low light environment preventing a spotlight in another part of the body, leading a powerful flashlight or spotlight from the outer corner of the eye inwards, and then alternately keeping both open and directing the light to the medium size checking equality.
Its integrity implies normal eye's optic nerve and III stimulated bilateral pair. This way we evalueated the direct and consensual pupillary reflex.

The corneal reflex is triggered by a light touch on the cornea with a sterile gauze. Then, flicker occurs and also an eye deviation upwards, and it demonstrates that the brainstem is intact. We didn't abuse this reflex to avoid complications like corneal ulcers, especially if

was suspected the possibility of brain death and the possible donation of the corneas.

The oculovestibular reflex (brainstem reflex) is triggered with opened eyes and by turning the patient's head quickly from one side to the other. The comatose patient whose brainstem is intact, the eyes are directed in the opposite direction to that the head is turned, as if facing forward to the starting position. Patients with midbrain or pontine injuries have random eye movements.

- Somatosensory Evoked Potentials (SSEP).

SSEPs were assessed after rewarming if hypothermia was induced, at least 24 hours after the cardiac arrest and the subsequent induced hypothermia [16].

SSEPs from right and left bilateral median nerves were recorded at the patients bedside in the ICU, using II channels: Erb's point, C3' or C4' contralateral to the stimulated hand, and Fz.

SSEPs were performed with median nerve stimulation at the wrist. Square-wave electrical pulses were delivered for 0.2 millisecond at 0.5 Hz with sufficient intensity to produce a moderate twitch of the tenar muscles. SSEP were recorded with a 2-channel montage. Stainless steel needle electrodes were placed at C3', C4' and Fz positions of the 10-10 System.

For the second channel, an electrode was placed at the ipsilateral Erb's point and referred to the contralateral Erb's point. Amplifier bandpass were 1 to 1500 Hz, and signals were digitized with a sampling rate of 512 points every epoch and averaged for 200 msec after the stimulus. At least two averages of 600 responses were acquired from each arm to check for reproducibility.

Absence of early cortical responses to somatosensory evoked potentials (N20) were asserted only if the 2 following conditions were present:

- Correct peripheral (N9) component.
- No deflexion higher than 0,5 mycrovolts on C3' – Fz or C4' – Fz.

The N20 is the response from the primary sensory area of the cerebral cortex, and is the signal of interest. It results from a wide area, as represented in the Penfield's homunculus. When the N20 is absent, there is no upward deflection at 20 ± 2 msec from the time of the stimulus.

We measured the peak-to-peak amplitude of the N20-P25 deflection, taken even very small values (>0,1 microvolts) into account. In case of asymmetry, the better response was chosen for analysis.

Recordings were performed when the contribution of evoked potentials to prognosis was expected to be useful. Consequently, patients with an early evolution towards awakening and a complete recovery were not recorded and not included in the present study.
All patients had been administered sedative drugs on admission to the ICU. At the time of the recording, no sedatives were being administered, but some patients received small doses of midazolam in the previous hours prior to the recording.

All patients were normothermic at the time of the SSEP measurement.

- Electroencephalography (EEG).

EEG were recorded after off sedation and after 24 hours after the resuscitation. Before reaching this time period, there's an improving of the brain's function, which can interfere in the results, and thus can missmatch the prognosis decision.

EEGs were performed with commercial digital EEG machines, with 18 channels, using both bipolar and referential montages, the 10-20 System of electrode placement, and at least 20 minutes of recording.
As part of the recording, repeated noxious, tactile, verbal and auditory stimuli were systematically delivered, and the reaction of the patient was registered.

Whenever applicable, administration of anaesthetic agents was discontinued shortly after the beginning of the recording to assess their effect on the EEG.

EEG findings and further classification are based on the dominant background frequency, the waves' amplitude and their topographic distribution, the presence of other activities such as regular or paroxysmal activities, its reactivity to external stimuli, or the ability of the pattern to produce sleep cycles.

Prognostic criteria should not be applied in situations where drugs with Central Nervous System depressant action are being administered, as well as under hypothermia conditions, due to its effects in the results obtained.

- Serum neuron-specific enolase (NSE) concentration.

Blood samples were collected between 24h and 72h after the time of the cardiac arrest.

All samples with visible hemolysis were discarded from analysis to avoid any falsely elevated values for serum NSE. Blood was centrifuged at 3000 rpm for 10 min. The isolated serum was immediately frozen at -80ºC and stored until time of assay.
The serum NSE level was measured using a solid-phase immunoassay with double monoclonal antibodies directed against NSE.
The limit of detection was 0,05 ng/ml and the institutional normal value was < 33 ng/ml. When the NSE level reached 50 ng/ml, the serum was diluted to avoid a hook effect.

For each patient, the highest measurement of NSE was tested for outcome prediction.

All neuron-specific enolase (NSE) test results must be considered in the clinical context, and interferences or artifactual elevations should be suspected if the clinical NSE test results are at odds with the clinical picture or other tests.

Hemolysis can lead to significant artifactual NSE elevations, since erythrocytes contain NSE. Hemoglobin concentrations as low as 20 mg/dL were found to have an adverse effect on NSE testing.

Proton pump inhibitor treatment, hemolytic anemia, hepatic failure, and end stage renal failure can also result in artifactual NSE elevations.

- Neurological and vital status: Assessement of outcome.

Neurological status was recorded using the five grades of the Glasgow-Pittsburgh Cerebral Performance Category (GP-CPC) scale.

Neurological outcome was classified as favorable (CPC1 and CPC2) and unfavorable (CPC3, CPC4 and CPC5).
Group CPC 1 – 2 contained patients who regained consciousness, defined as the ability to follow commands, and to use comprehensible speech or both.

Recovery of cerebral functions and patient's outcome were established at the time of the discharge from hospital of the patients, according to the G-P outcome Categories of the Utstein recommendations CPCs, defined in the variables definition section of this protocol.

- Treatments.

  All patients received standard intensive care management and monitoring, including induced hypothermia as recommended.

  Hypothermia was induced using an endovascular cooling catheter, inserted in the inferior cava vein via the femoral vein and connected to a cooling device, and was maintained during 24 hours in a body temperature of 32-34ºC.
  For patients who underwent cooling after resuscitation, clinical variables and neurophysiological tests were performed after rewarming.

  Propofol, midazolan and other sedatives where used as standard, and were stopped shortly before clinical examination and EEG recording when it was possible.

STATISTICAL ANALYSIS:

We describe the characteristics and frequency of this health problem, by describing the association between these variables with the outcome, without assuming any causal relationship between them. The results obtained from this study, will generate reasonable hypothesis that should be tested further by analytical studies.

We describe the categorical and qualitative variables using percentages.

The characteristics of patients with good and poor prognoses were compared using the Chi Square test or Fisher's exact test for categorical variables.

To assess the independent effect of various predictors collected at admission on the incidence of good neurologic prognosis at discharge, a logistic regression model was constructed including the variables that showed $P<0,05$ in the univariate analysis, as well as those previously reported to provide prognostic information and the covariates or confusion-variables. The variables were entered in the model as a block.

All EEGs were reviewed, but for subjects who had more than one EEG performed, only data from the first test and obtained in the best conditions (without sedatives), were used for analysis. The association between selected EEG characteristics and the clinical outcome was assessed by Fisher's exact test with $P=0,05$ as the significance level.
For the statistical analysis, the EEG grades obtained using the modified HS scale were merged into 2 categories, one including Grades I and II; and the other Grades III, IV and V.

We will also calculate the power of the sample, based on the consecutive and non-probabilistic inclusion of patients.

ETHICAL ASPECTS:

We had a good medical practice following the Declaration of Helsinki, of the ethical principles for medical research involving human subjects, according to the 64ª General Assembly, Fortaleza, Brasil, October 2013.

We have respected the confidentiality of the data based on the procedures according to the Law on Data Protection. We guaranteed the anonymity of all patients' data, in order to protect the confidentiality and privacy of patients. We have also requested informed consent of patients and/or relatives prior to the patients' inclusion.

We have respected the confidentiality of data according to the Organic Law 15/1999 of 13 December on Protection of Personal Data (LOPD), the Royal Decree 994/1999 on Security Measures for automated files containing personal data of June 11, 1999 (RMS), and the Royal Decree 1720/2007, of December 21 of the Development of the Organic Law on Data Protection.

We will submit the present protocol for an Ethics Review conducted by the Clinical Research Ethics Committee (CEIC) of the J. Trueta Hospital for its approval.

LIMITATIONS OF THE STUDY:

- There is the influence of the self-fulfilling prophecy whereby the treatment of patients with unfavorable findings is withheld prematurely. This could limit the applicability of this data. So the results can't be extrapolated to the general population.

- The difficulties in the follow-up of patients and the use of the CPC classification at the time of the discharge from hospital did not allow a precise analysis of the neurologic status, even though is the methodology currently used.

- Our data doesn't represent the natural history of the anoxic-ischemic encephalopathy. The duration of unconsciousness of patients can be prolonged by the use of sedatives. Patients' outcome may be unknown because of the implementation of treatment limitations, potencially leading to earlier death of selected patients.

- Because it's an observational and retrospective study, some data may not be collected, and we can't control the tests to be carried out. So what we do is the best interpretation of the results as possible, and its further classification of the data obtained following the variables detailed in our study.

RESEARCH TEAM AND RESOURCES:

All members and investigators involved in this study, have participated in many other studies of the same research field, and they also attend annual meetings regularly and have been speakers repeatedly.

All researchers and associates are competent in this field of the medical research, and have a long working experience.

To conduct the study, we need an accurate data collection from the medical records in the hospital, and a proper interpretation of the data obtained is needed. It will be successfully achieved due to the neurophysiology service professionals, experts in all the tests described in this protocol.

SCHEDULE AND EXECUTION PLAN:

Phase 1: Data management

At least six months will be required to collect all the information from the medical records, considering they will have to be collected from different sources. Also, a following validation will be required, thus defining and classifiying the information obtained using the guidelines described in the variables section of this protocol.

Weekly meetings will be held with the membership of the neurophysiology service and the technician or technicians responsibles for the collection of information, in order to debate those doubtful cases that may arise, being able to correctly classify the different test results obtained.

Phase 2: Statistical analysis

A minimum of three months will be required to perform the statistical analysis exposed.

Phase 3: Interpretation of results

Two or three months will be required to interpret the statistical analysis performance, and to write the results and conclusions.

Phase 4: Article publication

Two months will be needed to write the article. And then, we will send it to a Neurophysiological magazine for its official publication.

Phase 5: Scientific difussion

From here, we will present the results of our work at annual conferences both in the state and also international.

Schedule:

TASK	Nov-Dec 2013	Jan-Mar 2014	Apr-Jun 2014	Jul-Sept 2014	Oct-Dec 2014	Jan-Feb 2015	From Mar 2015
Phase 1: Data collection							
Phase 1: Weekly meetings							
Phase 2: Statistical analysis							
Phase 3: Results							
Phase 4: Article publication							
Phase 5: Scientific diffusion							

BUDGET:

Material resources:

No extra money will be needed for the clinical techniques necessary for the study, since all of them were made in the ordinary way, following the current protocol of the hospital.
The required tests will not involve additional expenditure.

Human resources:

It is required a minimum of one technical person who will do all the research in the computer database program of the hospital, searching those patients who meet the inclusion and exclusion criteria required and specified in this protocol.

From there, they should read all the information in the medical records, collecting only the information necessary for the study, in an accurate way, respecting the principles of confidentiality of patients.

One or several neurophysiologists from the neurophysiology service of the hospital, will make, in their free time, a thorough reading of the EEG and SSEPs, correctly defining the characteristics of these tests, in order to divide the patients in different groups, according to the definition of variables mentioned earlier in this protocol.
When reading and interpreting these tests, the neurophysiologist will not know what is the dependent variable or prognosis of that patient, thus being the most objective possible, in order to obtain a reliable description and classification of the information into the different groups detailed.

An statistics group of people is required for the analysis of all the data, according to the statistical analysis section in this protocol.

Article publication and difussion:

We will need a technician to write the final work, money for its publication in magazines, and money for the conferences in which we will explain the results widely.

		Subtotal		Total
Material Resources			0.00 €	0.00 €
Human Resources	Technician Neurophysiologist Statistics Analysis Typist	Half-day Overtime Full day Half-day	1.200,00 € 600,00 € 1.800,00 € 950,00 €	9.600,00 € 8.400,00 € 5.400,00 € 1.900,00 €
Article Publication			5,500.00 €	5,500.00 €
Scientific Diffusion	3 State travels 2 International travels	3 members 2 members	1.200,00 € 2.100,00 €	10.800,00 € 8.400,00 €
Weekly Meetings			200.00 €	3,600.00 €
Total Sum				53,600.00 €

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