Post-anoxic vegetative state: imaging and prognostic perspectives

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Summary

Prognostic determination of patients in coma after resuscitation from cardiac arrest is a common and difficult requirement with significant ethical, social and legal implications.
We set out to seek markers that can be used for the early detection of patients with a poor prognosis, so as to reduce uncertainty over treatment and non-treatment decisions, and to improve relationships with families.
We reviewed the medical literature from 1991 to 2010, using key words such as post-anoxic coma, post-anoxic vegetative state, vegetative state prognosis, recovery after cardiac arrest.
Neurological examination, electrophysiology, imaging, and biochemical markers are all useful tools for estimating patients' chances of recovery from cardiac arrest.
It seems unlikely that any single test will prove to have 100% predictive value for outcome; but the combination of various prognostic markers, as shown in some articles, could increase the reliability of outcome prediction. However, further research is needed.

KEY WORDS: anoxic brain injury, prognostic factors, vegetative state

Introduction

Anoxia is the third most frequent cause of coma, after trauma and vascular lesions. The most common causes of post-anoxic coma in adults are: cardiopulmonary arrest, stroke, respiratory arrest and carbon monoxide poisoning (1). In children, the causes include asphyxia, congenital malformations, and perinatal injuries (2). 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 about 450000 Americans per year (3). Almost eighty per cent of patients who initially survive a cardiac arrest remain comatose for varying lengths of time, and approximately forty per cent of these progress to vegetative state (4). Early identification of patients with a poor prognosis is desirable in order to reduce uncertainty over treatment and non-treatment decisions, and to improve relationships with families. Various clinical parameters, neurological examination models, biochemical tests, neuroimaging and electrophysiological techniques have been proposed for the prognostic evaluation of brain function in comatose cardiac arrest survivors.

Clinical-prognostic factors

Some factors, such as age, duration of arrest and duration of coma, have been investigated as predictors of functional outcome in post-anoxic patients. To consider age a negative prognostic factor is still controversial. Schultz et al. showed a significant difference in survival between patients under 60 and those over 80 years (15% vs 4%, respectively) (5) and Roest et al. observed that prognosis is twice as good in younger patients not only at 30 days but also at 180 days after coma onset (6). Conversely, Berger and Kelley in a prospective analysis of 255 inhospital cardiopulmonary arrests in non-critical patients demonstrated that age was not an independent predictor of survival (7). In addition, Rogove et al., in a prospective study of 774 patients, found that old age did not negate good cerebral outcome after cardiorespiratory arrest (8). In reality, to make an overall assessment, we should also take into account patients' comorbidities and complications of cardiac arrest. Since the duration of cardiac arrest correlates with the extent of brain damage, one can expect to observe a direct proportional relationship between the duration of the arrest and the outcome (8,9). Several studies have indeed shown a close relationship: the survival rate has been found to be 48% for a period of less than 10 minutes and 2% for longer than 10 minutes (5). Saklayen et al. confirmed that a shorter duration of anoxia correlates with a better prognosis (10), but in practice it is difficult to determine the duration of arrest when evaluating a patient. As noted before, up to 80% of patients are comatose after an arrest. Of those patients destined to awaken, over 90% will do so within the first 72 hours (10). Thereafter, the probability of awakening decreases progressively. In fact, in post-anoxic coma, the probability of recovery after three months of vegetative state becomes statistically close to zero, and at this point the condition is defined permanent vegetative state (11). The most widely studied and reliable predictors of neurological outcome continue to be provided

by the bedside neurological examination (12,13). An absent pupillary reaction to light after 72 hours carries a prognosis of coma until death with 100% specificity (14,15). Another parameter widely discussed is the motor response to painful stimuli. Absence of this response after three days of coma is related to a poor outcome with a specificity of 100%, although not all patients with poor outcomes were identified only by this parameter (16). Moreover, in the Brain Resuscitation Clinical Trials I, lack of the motor response after 72 hours was the only independent predictor of poor outcome (17). The corneal reflex is tested by touching the cornea with a gauze or cotton swab and looking for contraction of the orbicularis oculi on either side. In two prospective studies, absence of the corneal reflex at 72 hours was associated with no false positives for a poor outcome (18,19). The post-resuscitation clinical course has also been found to influence the outcome of these patients. The occurrence of status epilepticus in cardiac arrest survivors has been strongly associated with mortality (20). Many studies have also considered myoclonic status epilepticus (bilaterally synchronous twitches of limb, trunk, or facial muscles) as a predictor of poor outcome in patients with severe injury (19,21). In a prospective study involving 407 patients, myoclonic status epilepticus at 24 hours after cardiac arrest was associated with no false positives (19). The Glasgow Coma Scale (GCS) score has been extensively investigated as a predictor of individual outcome following cardiac arrest with cardiopulmonary resuscitation. In particular, the Cerebral Resuscitation Study Group of the Belgian Society for Intensive Care found GCS scores of <5 and >9 to predict poor and good outcome respectively. For patients with GCS scores of 5 to 9, a repeated score >8 during the first six days was shown to be a cut-off for good prognosis (22). Others claimed that a GCS value of <4 after three days of coma was the best indicator of poor outcome with a specificity of 100% (17). Zandbergen et al., in a systematic review, showed that a GCS score of 5 or less in the first 24 hours was not helpful in predicting outcome (14). Results of a recent study, conducted in patients treated with hypothermia, showed that at day 3 after cardiac arrest a GCS score >6 had a specificity of 87% and a sensitivity of 73% for predicting a good outcome (23). In view of these (to date) conflicting data, the GCS cannot be considered a sufficiently sensitive measure compared with other tests of central nervous system function (24). Fugate et al. conducted a study to determine whether the FOUR score is an accurate predictor of outcome in patients after cardiac arrest. They showed that most patients with a FOUR score >8 at days 3-5 after cardiac arrest survived to hospital discharge, while no patient with a FOUR score <4 survived (25). In the future, this simple score could be used as a prognostic tool, but further studies are needed to confirm its validity.

Neurophysiological prognostic factors

The electroencephalogram (EEG) during cardiac arrest is isoelectric. Half of all patients, immediately after resuscitation, do not show cortical activity on EEG (15). This finding does not reliably predict poor outcome (15) and it is usual for clinicians to wait at least 24 hours before ordering an EEG in order to avoid falsely disappointing results. Several unequivocal patterns have prognostic value after this time. In particular, a generalized suppression $\leq$ 20 μV, burst suppression with generalized epileptiform activity, and generalized periodic complexes on a flat background are related to poor outcome (6). In combining data from different trials, Zandbergen et al. found that an EEG with an isoelectric or burst suppression pattern during the first week after resuscitation had a 100% positive predictive value for coma until death or persistent vegetative state (14). Recently, some authors have remarked on the prognostic significance of reactivity in alpha-theta coma (ATC), either at the first observation or during the evolution of the electroencephalographic pattern, suggesting that there exist two forms of ATC having different prognostic value. They identified a complete ATC with a-reactive, monotonous, continuous and frontally distributed alpha activity, typically associated with abnormal or absent cortical somatosensory evoked potentials (SEPs). This variant is associated with little improvement in the first 48 hours after cardiac arrest and poor outcome (26). The other form is incomplete ATC, characterized by less monotonous, posteriorly accentuated and partially reactive EEG activity typically associated with normal SEPs. It is associated with a better prognosis and with the possibility of recovery of consciousness (26,27). Sensory evoked potentials, especially SEPs, have been investigated for their potential to predict long term outcome from coma (over 20 years) (28). SEPs are non-invasive, reproducible, and simple to perform and to interpret. In addition, compared with the EEG, they are less susceptible to electrical interference and less affected by metabolic disturbances or medications, although it is recommended to wait 24 hours before measuring them (29). They test the integrity of the neuronal pathways from the peripheral nerve, spinal cord, brainstem and cerebral cortex. The N20 component, which is the first cortical response of the SEP, is the evoked potential waveform best studied as a prognostic indicator. Absence of N20, after stimulation of the median nerve, has been shown to be a reliable predictor of poor outcome in several studies of patients in coma after cardiac arrest (19,29-34). Recently, a systematic review of 18 studies analyzed the predictive ability of SEPs acquired early after onset of coma in 1136 adult patients with hypoxic-ischemic encephalopathy. It was found that all 336 patients with bilaterally absent cortical N20 SEP peaks did not awake from coma (35). Two other clinical trials also showed that absence of cortical SEP peaks was associated with poor prognosis, with a specificity of 100% (36,37). However, the presence of cortical N20 SEP responses is not a guarantee for awakening from coma (36). To improve the accuracy of SEPs in predicting good outcomes in comatose cardiac arrest survivors, Madl and coworkers evaluated long-latency N70 peaks in 66 patients. In this series, N70 latency was less than 118 milliseconds in all patients who had a good recovery and was absent or greater than 118 milliseconds in patients who had a poor outcome (38). In recent years, it has been suggested that routine clinical tests should also include the assessment of higher-order cortical activity via endogenous evoked potentials (EPs). The presence of a P300 component in comatose patients proved to be effective in predicting awakening in small patient series,

while its absence does not necessarily predict a good prognosis (39,40). However, since the P300, which is agreed to be associated with attention or expectancy, is dependent on the level of vigilance, it is preferable to record mismatch negativity (MMN), which does not require awareness. Furthermore, several studies have shown that the presence of MMN in a comatose patient is associated with a high percentage of evolution toward awakening (41-43). In summary, it can be concluded that absent exogenous EPs are well established prognosticators of poor outcome, whereas the presence of endogenous components, notably the MMN and P300, appears to predict a favorable outcome (44).

Biochemical prognostic markers

In recent years it has been shown that increased serum levels of neuron-specific enolase (NSE) and of the astroglial protein S100 are associated with hypoxic-ischemic brain injury and unfavorable neurological outcome (45). S100 is a calcium-binding protein present in high concentrations in glial and Schwann cells. Serum levels of S100 increase transiently, reaching a peak within 24 hours of the anoxic episode, and continuing to show high, but declining, values on the following two days. This initial rise may reflect reversible brain edema combined with a disturbance of astroglial cell membrane integrity and blood-brain barrier function. The low weight and high solubility of the molecule probably facilitate this process. In cases with a short period of anoxia, the pathological S100 levels rapidly return to normal within 24 hours, which is compatible with the fast turnover of S100 in serum. Values remaining high or increasing on days 2 and 3 may indicate permanent brain damage, which is of importance for the prognosis (46,47). Moreover, levels elevated above 0.217 µg/l on day 2 after return of spontaneous circulation indicate severe neurological injury and predict poor outcome with a 100% positive predictive value (47). Another study demonstrated that at 48 hours after cardiac arrest, an S100 serum level >1.10 µg/l has a specificity of 100% for the diagnosis of brain damage (48). However, both studies, despite the different cut-off, claim that S100 represents an early marker of short-term outcome after cardiac arrest. NSE is the neuronal form of the intracytoplasmic glycolytic enzyme enolase. As opposed to the transient increase in S100, levels of NSE have been found to increase continuously after cardiac arrest and to peak on the third day. This is in line with the fact that NSE has shown promising results, in terms of prognosis, at later stages after cardiac arrest (48-51). Although cerebrospinal fluid (CSF) levels of NSE are more sensitive for neuronal damage, a serum level above 23.2 µg/l has a 100% positive predictive value for coma, vegetative state, or death (41). In one prospective multicenter study involving 231 patients, an NSE level of more than 33 µg/l, sampled between 1 and 3 days after cardiac arrest, was strongly predictive of a poor outcome with no false positives (19,51). Instead, elevated levels of S100, as indeed the BB fraction of creatine kinase in CSF or serum and the neurofilament protein, did not show high specificity for a poor outcome (51). It is worth noting that the widespread use of biochemical markers is limited due to widely varying cut-off levels for identifying specific outcomes, inconsistency in sampling times, and lack of uniformity in patient populations.

Neuroimaging prognostic factors

Computed tomographic (CT) images are usually normal immediately after a cardiac arrest, but by day 3 they often show brain swelling and reversal of the gray/white matter densities (with the use of quantitative measures) in patients with a poor outcome (35). Further study is needed to assess the clinical use of these findings in establishing prognosis. Magnetic resonance imaging (MRI) has also been proposed as a means of assessing prognosis after cardiac arrest, but limited data call its use into question. Among four case series, each with no more than 12 patients assessed with MRI at variable time points (52,53), two studies showed that diffusely abnormal findings on diffusion weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) correlated with a poor outcome (54,55). DWI detects cytotoxic edema by measuring the random motion of water protons, a process that is reduced by failure of the energy-requiring active water transport mechanism. DWI studies in animal models have demonstrated a decline in brain apparent diffusion coefficient (ADC) values during cardiac arrest, which then reverse after successful resuscitation (56,57). Despite successful reperfusion, however, secondary energy failure and ADC decrease appear after several hours (58). It has been shown in preliminary studies that quantitative MRI brain changes are correlated with functional outcome in comatose cardiac arrest survivors (59,60). The percentage of brain tissue below a threshold of $650x10^{-6}$ mm^2/s to $700x10^{-6}$ mm^2/s was found to be correlated with functional outcome at three months after the arrest (59). Based on whole-brain quantitative DWI analyses, the ideal time window for prognostication appears to be between 49 and 108 hours after the arrest, when the ADC reductions are most apparent. None of the patients with >10% of brain tissue with an ADC value <650 $x10^{-6}$ mm^2/s to $700x10^{-6}$ mm^2/s during this time window regained consciousness. In a prospective study, Mlynash et al. analyzed in detail which brain structures at which time point were the most severely affected by ADC reductions by comparing good- and poor-outcome patients with normal controls and with each other (61). In agreement with the results of another retrospective study (60), they found that ADC changes, in post-cardiac arrest patients, are both time- and region-dependent during the first week. In addition, both the qualitative and the quantitative MRI changes in poor-outcome patients were most severe in the cortical regions and most apparent between three and five days after the arrest. Indeed, in these conditions, although ADC changes occur globally, they most profoundly affect the cortical gray matter structures. By contrast, patients who are able to wake up from their coma exhibit increased diffusion involving the temporal and occipital lobes, corona radiata, and hippocampus; in addition, qualitative changes in the deep gray nuclei alone are common in these patients. MR spectroscopy (e.g., for pH and N-acetyl aspartate, a neuronal marker) has been reported to correlate with a poor outcome in small studies (60,62), but more data are needed. Functional brain imaging in comatose sur-

vivors of cardiac arrest could provide important diagnostic and prognostic information beyond that available from bedside examination alone (63,64). Di et al. reviewed 15 positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies involving 48 published cases which were classified as 'absent cortical activation', 'typical activation' (involving low-level primary sensory cortices), and 'atypical activation' (corresponding to higher-level associative cortices). The results show that atypical patterns of activity appear to predict recovery from the vegetative state with 93% specificity and 69% sensitivity. That is to say, nine of 11 (3 post-anoxic) patients exhibiting atypical patterns of activity recovered consciousness, whereas 21 of 25 (18 post-anoxic) patients with typical primary cortical activity patterns, and four out of four (3 post-anoxic) patients with absent activity failed to recover (65). In another recent study of 41 patients with disorders of consciousness, Coleman et al. found direct evidence of prognostically important information within neuroimaging data that was at odds with the behavioral assessment performed at the time of scanning. Thus, contrary to the clinical impression of a specialist team using behavioral assessment tools, two patients (one with brainstem stroke) who had been referred to the study with a diagnosis of vegetative state did in fact demonstrate clear signs of speech comprehension when assessed using fMRI. More importantly, however, across the whole group of patients, the fMRI data were found to have no association with the behavioral presentation at the time of the investigation, but correlated significantly with subsequent behavioral recovery, six months after the scan. In this case, the fMRI data predicted subsequent recovery in a way that a specialist behavioral assessment could not (66). Another interesting study is the one proposed by Gofton et al. in which, using fMRI, the authors measured cerebral activation in response to somatosensory stimulation of the palm of the hand in 19 comatose survivors of cardiac arrest and in 10 healthy control subjects and compared it to SEP testing of the median nerve. They demonstrated that patients with a favorable outcome and with SEP responses had a greater blood oxygenation-level dependent (BOLD) signal in the primary somatosensory cortex (S1) controlateral to the stimulated hand, when compared with patients with an unfavorable outcome and without SEP responses. Furthermore, there also emerged positive correlations between BOLD in S1 and both levels of consciousness and clinical measures of outcome at three months (67). However, further studies should be done before fMRI can be deemed a useful tool for predicting outcome of patients in post-anoxic coma. Most of the studies on prognostic markers in cardiac arrest have used single variables. However, several studies (68,69) have looked at combining the values of the above tests to increase the reliability of outcome predictions. One example is the study by Bassetti and colleagues that assessed the value of combining clinical examination, EEG, SEPs, and two serum biochemical markers (ionized calcium and NSE). Individually, clinical examination correctly predicted outcome in 58%, SEPs in 59%, EEG in 41%, while combining the three factors (clinical examination, SEPs, and EEG) increased the rate of correct predictions to 82%. No false pessimistic prediction was observed using the combination (69).

Concluding remarks

From this review of the literature, there emerges a series of key points in relation to the prognosis of patients in post-anoxic coma. First of all, **age** is not a significant factor in outcome, especially when considered alone; conversely, **cardiac arrest lasting** more than 10 minutes and **coma lasting** more than 24 hours are good individual predictors of poor outcome. Absence of a **pupillary reaction** to light, absence of the **corneal reflex** and absence of a **motor response** to painful stimuli at 72 hours are each suggestive of a poor outcome. Also indicative of a poor outcome is an **EEG** with an isoelectric or burst suppression pattern during the first week after resuscitation and/or a complete ATC.

Somatosensory evoked potentials have shown some usefulness and are unaffected by confounding factors. Abnormalities are 100% specific for a poor outcome, although only after at least 24 hours of coma. The absence of abnormalities, on the other hand, does not necessarily predict a good outcome.

The predictive value of **neurobiochemical markers** is variable; these markers are unhelpful before 48 hours have elapsed.

Neuroimaging after return of spontaneous circulation has not been studied extensively but recent data indicate that a diffuse cortical hypersignal on DWI may predict a poor outcome. It is possible that fMRI, in the near future, will become very helpful in predicting outcome in comatose patients.

Finally, **combining** various prognostic markers could increase outcome prediction reliability.

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