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Summary

Etiologies of coma are various and prognosis is tightly linked to the underlying pathology. In this inhomogeneous patient group no simple prognostic parameter has a universal value. The largest subgroup of comatose patients consists of patients after outpatient circulatory arrest. For this group of patients, there is some empirical data, which can predict an unfavorable outcome. However, these data were validated before the therapy concept of therapeutic hypothermia and now new therapeutic temperature management were introduced. In this article, the current state of prognosis estimation using clinical and electrophysiological parameters is resumed for this group of patients. The significance of modern imaging techniques in this condition is discussed.

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Key words: Out of hospital cardiac arrest, prognosis, coma

Prognostische Parameter für Koma und Bewusstseinsstörungen

Die zugrunde liegenden Ursachen eines Komats sind mannigfaltig, die Prognose bezüglich Verlauf und Erwachen aus dem Koma ist sehr mit der ursächlichen Pathologie verknüpft. Aus diesem Grunde gibt es keine einfachen prognostischen Parameter, welche allgemein gültig sind. Die grösste Untergruppe der komatösen Patienten sind Erkrankte nach einem ausserhalb des Spitals erlittenen Herz-Kreislauf-Stillstand. Für diese Patientengruppe gibt es einige empirische Daten, welche ein ungünstiges Outcome vorhersagen können. Problematisch ist jedoch, dass diese Daten validiert wurden, bevor das Therapiekonzept der therapeutischen Hypothermie und nun neu des therapeutischen Temperaturmanagements eingeführt wurden. In diesem Artikel

wird der aktuelle Stand des Abschätzens des Verlaufs für klinische und elektrophysiologische Parameter in dieser Patientengruppe dargestellt und weiterhin der Stellenwert moderner bildgebender Verfahren beschrieben.

Schlüsselwörter: Herz-Kreislauf-Stillstand ausserklinisch, Prognose, Koma

Les signes pronostiques du coma et des troubles de la conscience

Les étiologies de coma sont diverses et le pronostic est étroitement lié à la pathologie sous-jacente. Dans ce groupe de patients non homogène, aucun paramètre pronostique simple n'a une valeur universelle. La plus importante sous-groupe de patients dans le coma se compose des patients après un arrêt circulatoire en ambulatoire. Pour ce groupe de patients, il y a certaines données empiriques, qui peuvent prédire une évaluation clinique défavorable. Cependant, ces données ont été validées avant l'introduction du concept de traitement de l'hypothermie thérapeutique et, plus récente, de la gestion de la température thérapeutique. Dans cet article, l'état actuel de l'estimation de pronostic à l'aide des paramètres cliniques et électrophysiologiques est repris pour ce groupe de patients. L'importance des techniques d'imagerie modernes dans cette condition est discutée.

Mots clés : Arrêt cardiocirculatoire extrahospitalière, pronostic, coma

Introduction

Coma is a state of unarousable unconsciousness and is characterized by a failure of the arousal and alerting system of the brain (the ascending reticular activating system ARAS) [1]. Disorders interfering with

the ARAS may produce at least transient coma. Causative disorders can be grouped into i) structural brain lesions (other than traumatic brain injury), ii) metabolic and nutritional disorders, iii) exogenous toxins, iv) central nervous system infections and septic illness, v) seizures and status epilepticus, vi) hypo- and hyperthermia and vii) head trauma. Whereas coma per se puts the patient's life at risk independent of the underlying disease, chance of recovery from a comatose state is determined largely on cause of coma and on age of the patient. Because of these numerous variations, this manuscript further aims to focus on comatose adult patients suffering from hypoxic ischemic encephalopathy after cardiac arrest.

Patients suffering from sudden unexpected out-of-hospital cardiac arrest (OHCA) have a dismal prognosis if no efforts to restore circulation are immediately undertaken. The London Ambulance Service (LAS) is the largest single provider of emergency medical service of the world and serves Greater London's population of about 8.2 million people. In the Cardiac Arrest Annual Report 2012/13, which covers the period from 1st April 2012 to 31st March 2013, LAS attended a total of 10,111 patients who presumably had suffered an OHCA [2]. In 55.8% (n=5645) of these cases no attempts to resuscitate the patient were made. Of those patients in whom resuscitation was attempted, the great majority had a presumed cardiac origin of the cardiac arrest (n= 3848). Although 63.7% of these patients were transported to hospital, only 9.3% (n=355) were discharged alive. The proportion of surviving patients suffering from cardiac arrest from trauma was 5.1% (n=12), and survival of cardiac arrest from "other" causes (mainly respiratory, terminal illness and overdose) was 6.1% (n=23). No data of outcome other than dead or alive were reported, so quality of life after discharge of hospital remains obscure. These data undermine that most patients suffering an OHCA do not survive until hospital admission, thus introducing a large bias in literature reporting predictors of good outcome, which range up to 50% [3]. Another problem in the literature of prognostication of outcome in critically ill patients (not limited to comatose survivors of OHCA) arises because of the phenomena of "self-fulfilling prophecy". This term was coined by Merton, who characterized the self-fulfilling prophecy as, in the beginning, a false definition of the situation evoking a new behavior, which makes the original false conception come 'true'. This specious validity of the self-fulfilling prophecy perpetuates a reign of error [4]. Translated into clinical practice this means that the initial belief in bad outcome will later lead to withdrawal of support, mostly ventilation and circulatory support, and the patient inevitably dies. The clinician, who has to put a decision on further treatment – and to provide his best advice to the family – in order to continue or to withdraw life-sustaining treatment is stuck in the dilemma on which side to weight his information: in case of a "low" probability of good outcome, the prob-

ability is not zero, and some patients will survive with a good outcome. Unfortunately, most patients in this particular situation will receive treatment for an unwanted outcome, either death or with a substantial risk survival with disabling neuropsychological deficits [5]. This "risk/benefit ratio" has to be explained to the next of kin, and individual decisions have to be made. The base of this decision have to be made first on clinical grounds, supported by electrophysiological methods and, in selected cases, by neuroimaging or laboratory testing, the latter being reviewed later in this issue.

Clinical and paraclinical prognostic factors

Determination of possible outcomes relying on clinical examination and medical history is dependent on timing: in an ideal world, patients with terminal illness or elderly patients have already discussed with their family and family physician what can be expected in quality of life in case of an unexpected event and therefore have put an advanced medical directive with or without a DNR (do not resuscitate) order in place. In case of an OHCA, survival is dependent on whether or not the arrest is witnessed, the initial cardiac rhythm (asystolic arrest and pulseless electrical activity versus ventricular fibrillation and ventricular tachycardia without pulse, the latter is also considered as shockable rhythm), bystander cardio-pulmonary resuscitation (CPR), and time to defibrillation in case of an initial shockable rhythm [6]. Rules for termination of resuscitation efforts have been developed, but validation is difficult to achieve. In the Japanese population (in which a larger proportion of patients with OHCA suffer from central nervous bleeding), the combination of no prehospital return of spontaneous circulation, an unshockable initial rhythm, and unwitnessed onset by bystanders was shown to predict a very poor outcome in > 99% of the patients [7]. Another easily available parameter to predict outcome during resuscitation is the end-tidal CO₂ value, which is a parameter of circulation under cardiopulmonary resuscitation (CPR). After 20 minutes of CPR, an end-tidal CO₂ < 1.9 kPa (14.3 mmHg) predict unfavorable outcome with accuracy [8].

There exists no proven clinical prognostic factor for poor outcome immediately after return of spontaneous circulation, and after hospital admission. Absence of pupillary reflexes are seen frequently, but have no association with outcome. Even absence of all brainstem reflexes is not sufficient for formal brain death testing within the first hours after OHCA. Only, ancillary tests such as computed tomographic angiography, cerebral angiography transcranial doppler or duplexsonography demonstrating absence of cerebral blood flow are valuable at this time interval.

In the era preceding therapeutic hypothermia (TH), a large body of evidence existed to predict unfavorable outcome in patients after cardiac arrest [9]. The indi-

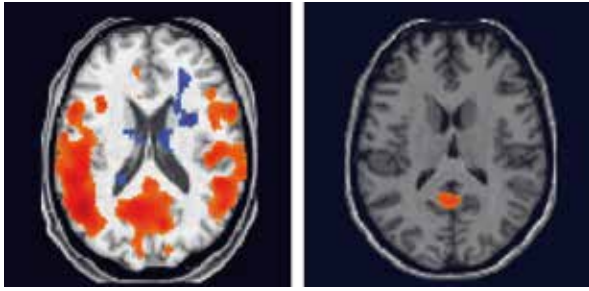


Figure 1: Resting state fMRI: Seed-based functional connectivity map of the Default mode network in a) a healthy wake subject and b) a patient with OHCA. Note the disrupted connectivity between the precuneus and the frontal/parietal association cortices following loss of consciousness.

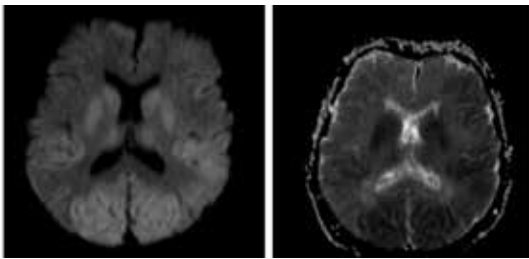


Figure 2: Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) of a patient with OHCA. Note the widespread DWI restrictions in the precuneus, basal ganglia and thalamus (ADC < 480 mm²/s²) indicating a poor prognosis.

cators of poor outcome after CPR are absent pupillary light response or corneal reflexes at least 24 hours after arrest, and extensor or no motor response to pain after 3 days of observation, and myoclonus status epilepticus after day 1. Bilateral absent cortical responses on somatosensory evoked potential studies recorded 3 days after CPR also predicted poor outcome, the same is true for serum neuron-specific enolase (NSE) higher than 33 microg/L. Burst suppression or generalized epileptiform discharges on EEG predicted poor outcomes but with insufficient prognostic accuracy [9].

Therapeutic hypothermia – changing prognostic factors

In 2002, 2 studies demonstrated a superior outcome in patients after OHCA treated with therapeutic hypothermia [10, 11], and meantime induced hypothermia replaced standard therapy in these patients in many centers. With this treatment, prediction had become more difficult, because the “old” guidelines had no validity anymore. It has been shown that hypothermia delays recovery of motor responses and renders clinical examination unreliable [12]. The reason for the delayed

recovery is because induced hypothermia regularly requires deep sedation for 12 - 24 hours (depending on the protocol used), and the pharmacokinetic and -dynamic change with body temperature. So weaning off the sedative medication can be delayed, and timing of prognostication becomes more difficult.

Meanwhile solid data for prognostication of outcome of OHCA patients treated with therapeutic hypothermia have been published [12, 13]. The most recent publication by Rossetti and Oddo describes the performance of the so called early multimodal outcome prediction approach, derived from a cohort of 134 patients treated with TH [14]. Clinical examination comprised of brainstem reflexes (pupillary, oculocephalic and corneal reflex, either all present versus at least one absent after rewarming, but before 72 hours after CA) and occurrence of myoclonus (appearing within 24 h after sedation stop). EEG was categorized as “presence of background reactivity”, “spontaneous discontinuous pattern” and “epileptic activity” during TH and at normothermia. NSE was collected at different time points within the first 72 hours, and a cut-off higher than 33 microg/L was used. SSEP were performed at early normothermia. The combination of clinical examination, EEG (background reactivity) and high NSE-levels had a 1.00 (CI 0.89 – 1.00) positive predictive value (PPV) for predicting mortality at 3 months, and a 1.00 (CI 0.90 – 1.00) PPV for prediction of a poor outcome (defined as death or dependency on daily activities) at 3 months. Addition of SSEP did not improve the performance of the prediction model, and, albeit not reported in detail, the addition of NSE into the model seemed to have added only little value. Unfortunately, the accuracy of predicting good outcome of this model was poor. By now, this is the largest cohort of patients, and although it comes from a single center, these results seem to be generalizable.

Criticism about TH arose because albeit both big studies in 2002 claimed to compare therapeutic hypothermia versus normothermia, in reality therapeutic hypothermia was compared to standard care. Because cardiac arrest evokes a global ischemia-reperfusion syndrome, the consequence is reperfusion injury with associated cytokine release and fever. In the European HACA-trial, the temperature of one quarter of the patients in the normothermia group exceeded 38.0°C [10]. So discussion arose whether TH improves outcome because of hypothermia, or simply because of the absence of fever. In 2013, a multicenter trial was published in which 939 patients suffering from OHCA were randomized into either a TH group (33°C) or a targeted temperature of 36°C [3]. The primary outcome was all-cause mortality through the end of the trial. Secondary outcomes included a composite of poor neurologic function or death at 180 days, as evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale. The study did not demonstrate any difference between both groups, patients survived

in > 50%. One of the greatest innovations in this trial was the adoption of a protocol for withdrawal of life-sustaining treatment to avoid the above discussed problems. The earliest time point for prognostication was 108 hours after study inclusion, until then, therapy could be withdrawn only either in case of brain death due to cerebral herniation, or myoclonus status (defined as generalized myoclonic convulsions in face and extremities and continuous for a minimum of 30 min) within the first 24 hours after admission and a bilateral absence of N20-peak on median nerve somatosensory evoked potentials (SSEP), or for ethical reasons (for instance: previously unknown information about disseminated end-stage cancer or refractory shock with end-stage multiorgan failure). The neurological evaluation was based on clinical neurological examination (including Glasgow Coma Scale (GCS), pupillary and corneal reflexes), SSEP and EEG. Biomarkers for brain damage were not used for operational prognostication. Findings allowing for discontinuation of active intensive care after 108 hours were brain death due to cerebral herniation, severe myoclonus status within the first 24 hours after admission and a bilateral absence of N20-peak on median nerve SSEP (if not already therapy withdrawn), persisting coma with a Glasgow Motor Score 1-2 and bilateral absence of N20-peak on median nerve SSEP, or persisting coma with a Glasgow Motor Score 1-2 and a treatment refractory status epilepticus (defined by EEG as sequences (>10 sec) of repetitive epileptiform discharges with an amplitude >50 μ V and a medium frequency \geq 1Hz, constituting >50% of a 30 minute period in a patient with or without clinical manifestations; treatment refractory defined as unresponsive to treatment with propofol, midazolam or pentothal to a slow suppression burst pattern for 24 hours in combination with at least one intravenous antiepileptic substance (including valproate and/or fos-Phenytoin) in adequate dose for at least 24 hours; free use of further antiepileptic substances and combinations at the discretion of the attending physician). This protocol of withdrawal of therapy was based on consensus. The analysis of the data of this trial is ongoing, and in the future results of accuracy of this withdrawal protocol to predict outcome will arise. We believe that the retrospective analysis of these data will allow accurate prediction of poor outcome only, and that we will still lack good and reliable prognostic markers of a good outcome.

Neuroimaging in coma

The ongoing search for novel biomarkers has led to a novel field of promise for prognostication – the use of advanced neuroimaging, since it is less prone to biases due to sedation and metabolic distress, the unravelling of structural abnormalities underlying coma and the information about regional and/or global hypoxic damage in brain areas crucial for maintenance of conscious-

ness. MRI is hampered by the requirement of trained personnel, MR-compatible material and larger examination slots to carry out MR studies in ventilated and sedated patients. The principal advantage of MRI is the application of diffusion-weighted imaging, a MRI technique used to image the movement of molecules. Molecular diffusion is limited by boundaries such as membranes and interaction between molecules in the extracellular space and can be used as a measure of hypoxic damage in case of restricted extracellular movement of water protons. The apparent diffusion quotient (ADC) can be calculated from two or more DWI images with different b-values and is displayed as an ADC map. A low diffusion value appears dark on the ADC and indicates restricted diffusion in that area. In the largest study used to investigate comatose cardiac arrest survivors (n=80) ADC values lower than $665 \times 10^{-6} \text{ mm}^2/\text{s}$ correlated with poor outcome *regardless* of the time to MRI with a specificity of 100%, but low sensitivity of 21% [15]. Diffusion-tensor imaging has been used as a prognostic tool in traumatic brain injury, where damage of specific brain areas (the internal capsule, corpus callosum, cerebral peduncle and white matter tracts) correlated with unfavorable outcome [16, 17]. MR-Spectroscopy of the brain stem has been successfully applied to disentangle patients who did not recover from those who regained consciousness [18]. Very recently, resting-state fMRI examinations have been applied to investigate disruptions of coherent fluctuations among functionally defined neuroanatomical networks encompassing the precuneus, posterior parietal lobe and medial prefrontal cortex. Fluorodeoxyglucose positron emission tomography studies confirmed these findings of widespread thalamocortical network disruptions (encompassing the thalamus, precuneus and mesiofrontal, prefrontal, and posteroparietal cortex) and showed impaired metabolism in unresponsive wakefulness syndrome patients [19]. Functional connectivity in the thalamocortical network correlated with the level of consciousness up to complete disruption in brain-dead patients [20]. However, up to now, no prospective studies for any of these modalities are available to validate the use of neuroimaging for coma and disorders of consciousness. In daily practice, intensive care physicians will continue to talk to families who are filled with fear and hope. The certainty of poor outcome is helpful for discontinuation of futile care, but as long as a good outcome cannot be predicted, the decision to continue or to withdraw life-sustaining therapy must be practiced with the art of medicine: a shared decision between the family and the physician, based on honest discussion, presumed wishes of the patient and best evidence, if available.

Conclusion

Clinical markers that indicate favorable outcome are lacking, especially due to the heterogeneity of underlying pathologies. Clinical criteria that aid to identify OHCA patients with poor prognosis encompass the absence of pupillary or corneal reflexes, whereas motor responses are not considered as reliable indicators, especially in patients treated with hypothermia. Exact definitions of time frames to estimate the outcome by clinical and neurophysiological examinations are still lacking. Novel imaging biomarkers, especially DWI, PET and recently, BOLD-fMRI appear to be promising but are difficult to perform in ICU patients and have an uncertain predictive value. Further research is needed to better define the prognostically meaningful patterns of brain damage and their sensitivity with respect to fair vs. poor outcome.

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