Postanoxic coma: prognosis after therapeutic hypothermia
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Summary
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Introduction

Postanoxic coma, also known as anoxic-ischemic coma, is a state of unconsciousness caused by global anoxia of the brain. The most common cause is primary cardiac arrest followed by successful cardiopulmonary resuscitation (CPR). Other causes include primary respiratory arrest, near-drowning, strangulation, and prolonged severe hypotension. Patients may recover consciousness after variable periods of time, or remain unconscious indefinitely. The main focus of this thesis is on prediction of outcome in patients with postanoxic coma who are treated with hypothermia after CPR. Furthermore, less investigated clinical variables such as myoclonus and status epilepticus after CPR were subject of research.

Thesis

Chapter 1 provides an introduction about survival and outcome after cardiac arrest, early prediction of outcome, and discusses some problems of outcome research in postanoxic coma.

It is important in daily clinical care to have prognostic variables available in the first few days of admission, which can indicate the outcome. This can reduce uncertainty in family members and treating physicians about prognosis and may prevent unjustified discontinuation or prolongation of treatment. A frequently used international guideline for the prediction of outcome in comatose survivors after CPR is the American Academy of Neurology Practice Parameter. A major drawback of this guideline is that all data were derived from studies in which patients were not treated with mild hypothermia. This treatment nowadays has become standard care in many countries and is part of all guidelines concerning post-cardiac arrest care.

To determine outcome, measures should be chosen that are clinically meaningful. “Severe disability” should only be regarded as “poor outcome” (combined with “death” and “vegetative state”) in studies with follow-up periods of at least six months. After such an interval, no further improvement in severely disabled patients can be expected. In studies with shorter follow-up periods, poor outcome can only be defined as “death or vegetative state”. It is therefore imperative that studies use follow-up periods of at least six months to be clinically useful.

A well-known problem with studies investigating the reliability of diagnostic methods to predict a poor prognosis is the so-called self-fulfilling prophecy. The tendency to restrict
treatment selectively in patients with characteristics presumed to predict a poor outcome may lead to the false conclusion that such characteristics are indeed good predictors of poor outcome. A problem related to that of self-fulfilling prophecy is blinding of physicians for the results of tests that are evaluated for their prognostic predictive value. Ideally, results of the diagnostic tests are not available for the treating physicians so that the results will not influence their decisions about treatment restrictions. During data collection for research, results of neurologic examination and additional tests are often disclosed to the treating physicians.

We performed two studies that focused on hypothermia treatment itself. **Chapter 2** shows the results of our web-based survey, performed in 2008. In this survey one physician of each Intensive Care Unit (ICU) in the Netherlands was invited to participate. A response rate of 76% was achieved. Treatment with hypothermia after CPR was implemented in 92% of the ICUs, which, compared to previous reports, was an exceedingly high percentage. Neurologic outcome was predominantly predicted by clinical neurologic examination (92%) and cortical N20 responses of somatosensory evoked potentials (SEP) (94%). Also performance of an electroencephalogram (EEG) (56%) and determination of serum levels of neuron-specific proteins (5%) were used for outcome prediction. The method used varied substantially between ICUs.

**Chapter 3** reports the results of our retrospective study about the effect of active rewarming, rate of rewarming or development of fever after treatment with hypothermia after cardiac arrest. Actively rewarmed patients had a higher risk for poor outcome, however, this effect disappeared after adjustment for the confounders age and initial rhythm. In addition, our results suggested that neither speed of rewarming, nor development of fever had an effect on outcome.

In the next two chapters, the results of two studies concerning prediction of poor outcome in patients treated with hypothermia are reported. In **Chapter 4** the results of the pilot study (2006 until 2008) are presented. This study was performed at the Onze Lieve Vrouwe Gasthuis and the Academic Medical Center (Amsterdam, the Netherlands). We investigated whether an absent SEP during hypothermia can reliably predict an absent SEP during normothermia, as well as a poor outcome. The results show that bilaterally absent cortical N20 responses of median nerve SEP performed during hypothermia can predict similar results in SEP recorded during normothermia. All patients with an absent SEP during hypothermia had a poor outcome.
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In Chapter 5 we described the results of the PROgnosis after PostAnoxic Coma II (PROPACII)-study, a multicenter prospective cohort study which was performed in 10 Dutch ICUs (2007 until 2009). We investigated the role of neurologic examination, the biomarker neuron-specific enolase (NSE) and SEPs in prognostication after CPR and hypothermia. In total 391 adult comatose patients admitted to the ICU after CPR and treated with hypothermia were included. About half of the patients had a poor outcome after 6 months, of whom a small minority were severely disabled (4%). Our results showed that use of motor scores 72 hours after CPR or serum NSE levels, as recommended in current guidelines, are too unreliable for outcome prediction in patients with persisting coma after CPR and treatment with hypothermia. This could possibly lead to inappropriate withdrawal of treatment. We also showed that poor outcome can reliably be predicted with: (1) absent pupillary light responses or absent corneal reflexes 72 hours after CPR, or (2) bilateral absence of cortical N20 responses of the median nerve SEP. An important limitation of this study was that based on the results of the SEP after rewarming, decisions about treatment limitations were made, which potentially have led to a self-fulfilling prophecy. Furthermore, physicians assessing SEP results should be aware of the major consequences of inaccurate decisions when recordings are hampered by ICU noise.

Since SEPs play an important role in the prediction of poor outcome, some aspects of this technique were studied. We investigated the influence of hypothermia on conduction times and amplitudes of SEP components in patients after CPR and these results are presented in Chapter 6. Latencies and amplitudes of N9 (peripheral conduction time, PCT), N13 and N20 were measured. The central conduction time (CCT) was defined as peak-peak latency N13-N20. Mean latencies of N9, N13 and N20 and mean CCT were significantly longer during hypothermia compared with recordings after rewarming in the same patient. Furthermore, we found that N20 latencies after rewarming remained longer in this patient group compared to the normal population. This is an important pitfall in assessing median nerve SEP in patients after CPR. There were no consistent differences in amplitudes.

Also the association between clinical variables and the absence or presence of SEPs in patients not treated with hypothermia was explored. These results are described in Chapter 7. We used data from the multicenter prospective cohort study “PROPAC” (PROgnosis in PostAnoxic Coma, 2000–2003). Neurologic examination, consisting of Glasgow Coma Score and brain stem reflexes, and SEP were performed 24, 48, and 72 hours after CPR. The results of this study showed that neurologic examination cannot reliably predict absent or present cortical N20 responses in median nerve SEPs in patients after CPR.
Finally, two clinical variables of which the prognostic value is controversial were studied. **Chapter 8** presents the results of our study, which investigated whether acute posthypoxic myoclonus (PHM) originates from cortical or subcortical structures, using SEP and EEG. Patients with acute PHM (focal myoclonus or status myoclonus) within 72 hours after CPR were retrospectively selected from the PROPACII study. Criteria for cortical origin of the myoclonus were: giant SEP potentials; or epileptic activity, status epilepticus, or generalized periodic discharges on the EEG (no back-averaging was used). The results of this study show that acute PHM originates from subcortical, as well as cortical structures. Outcome of patients admitted after CPR who develop acute PHM in this cohort was better than previously reported in literature. The broad variety of drugs used for treatment shows the existing uncertainty about optimal treatment.

Clinical features and outcome of patients with postanoxic status epilepticus (PSE), treated according to a prolonged intensive protocol were studied in **Chapter 9**. This study was performed two centers, St. Antonius Hospital (Nieuwegein, the Netherlands) and Academic Medical Center (Amsterdam, the Netherlands). Thirty-six patients after CPR with an electroencephalographic or a clinical PSE were included. Good outcome was found in 2 patient (6%). Treatment consisted of the stepwise administration of benzodiazepines and anti-epileptic drugs (AEDs), and the induction of burst-suppression EEG with propofol (and midazolam) and barbiturates. The majority received more than one AED. In <50% of the patients a BS-EEG was induced. Patient characteristics which implicate a higher chance for good outcome could not be identified. Our results were comparable to other case series, about 6% of patients recover. Future studies should investigate which patient characteristics and additional diagnostics can help to identify the patients which will benefit most from such an extensive therapy.

**Conclusion**

The studies described in this thesis show that a reliable prognosis of a poor outcome is possible in patients with postanoxic coma who have been treated with hypothermia after cardiopulmonary resuscitation (CPR), but current international guidelines need to be revised. Use of those guidelines could lead to incorrect treatment withdrawal. It is also clear that there are some important pitfalls of which clinicians involved in making a prognosis should be aware. In **Chapter 10**, the general discussion, current knowledge and future challenges about prognostication in postanoxic coma after hypothermia concerning neurologic examination, SEP, EEG, biomarkers, and imaging are described. Furthermore, different aspects of target temperature management and other potential neuroprotective strategies are pointed out. New treatments may not only modify the clinical course of the
condition, but may also change the predictive values of prognostic variables, as we have demonstrated for poor motor responses in patients treated with hypothermia. Future research should ideally consist of large prospective clinical trials, which could investigate both potentially effective treatments and prognostic variables in the same group. In such studies, to avoid self-fulfilling prophecy, limited use of treatment restrictions would be preferable. A related problem is that of the continuing update of prognostic guidelines. Methods currently recommended are based on studies performed before the implementation of hypothermia. Some of these recommended methods are no longer reliable and could lead to incorrect treatment withdrawal. In 2011 a new Dutch national guideline “Prognosis of postanoxic coma” was presented. This guideline discusses prognostic variables of a poor outcome for patients after CPR with and without subsequent hypothermia treatment. In daily clinical practice, decisions about prognostication in the individual patient should not be based on one single test but rather on a multi-modality approach. In patients with an uncertain outcome after neurologic and neurophysiologic testing, other clinical variables such as age, comorbidity, pre-existing clinical condition, multiple organ failure, etc. should be taken into account when decisions on treatment limitations are considered. The ongoing search for “a perfect test” to predict outcome in patients after CPR seems a utopia. Every test has its own limitations due to the technique, artifacts, influences of drugs, or interobserver agreement and withdrawal of therapy in patients with a poor prognosis.