Chapter 1

General introduction
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Postanoxic coma

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.

Survival and outcome after cardiac arrest

The survival rate of out-of-hospital and in-hospital cardiac arrest (OHCA and IHCA) is dependent on several different steps from immediate treatment at the site of the collapse, up to, and including treatment at the Intensive Care Unit (ICU). For OHCA, the Amsterdam Resuscitation Study (ARREST), which prospectively collected data in Noord-Holland, showed a stable incidence rate of about 35 per 100,000 inhabitants per year and a substantial improvement of survival during a thirteen-year observation period. In the period 1995-1997, the total survival rate was 9%, in 2005-2006 17% and in 2008 21%. This improvement was attributed to a change of the compression/ventilation ratio, implementation of the Automatic External Defibrillator (AED), on field administration of amiodarone, and treatment with hypothermia in the ICU. Of the patients who were discharged alive, almost 90% had a good outcome, defined as good recovery or moderate disability (see below).

The international literature shows conflicting results about improvement of survival. A recent meta-analysis of studies published between 1984 and 2008, involving more than 140,000 patients from all over the world with OHCA showed no significant improvement of survival in three decades: survival to hospital discharge remained stable at about 8%. More recent studies, however, do report improved survival.

Fewer reports are available for IHCA. A recently published report of a large registry in North America showed a survival rate of 18% to hospital discharge; 75% had a good outcome. A retrospective study from Austria showed a survival rate of 36% with a good outcome. Patients who received CPR in a hospital ward with monitoring (e.g. coronary care unit) had a better outcome than patients on regular wards or other locations, such as the radiology department.
Introduction

Early prediction of outcome

Patients who are successfully resuscitated after cardiac arrest are generally admitted to the ICU. During admission, 50-60% of these patients will die, mostly related to severe brain damage\textsuperscript{9,10}. About 4% will survive with severe disability and 0.4% will remain in a vegetative state\textsuperscript{9}. Therefore, it is important in daily clinical care to have prognostic variables available in the first few days 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.

Prognostic variables

Several variables are associated with outcome, such as age, gender, initial rhythm, performance of bystander CPR, and duration of CPR. Data on these variables were collected in large groups and give only information on the prognosis on a group level, e.g. “older patients generally have a worse prognosis”. However, these variables fail to provide information about the prognosis in the individual patient.

In 1965 already, Hockaday et al. reported about the prognostic value of electroencephalogram changes in individual patients after cardiac or respiratory arrest\textsuperscript{11}. From the 1970s onwards, the prognostic value of neurologic examination was described in patient cohorts. A large prospective cohort study on prognostication in patients with postanoxic coma was published by Levy et al. in 1985\textsuperscript{12}. This study provided algorithms using neurologic assessment at different time points after the event and was widely used in daily clinical practice. An important multicenter prospective cohort study was the PROPAC study (prognosis in postanoxic coma), which was performed in the Netherlands from 2000–2003\textsuperscript{13}. This study included adult patients who were still in a coma 24 hours after CPR. The results of these and several other studies were used in the American Academy of Neurology Practice Parameter for the prediction of outcome in comatose survivors after CPR\textsuperscript{14}. In this guideline a number of variables were identified as reliable predictors of a poor outcome (see algorithm in Figure 1), defined as death or vegetative state after 1 month; or death, vegetative state or severe disability after 6 months. A major drawback of the 2006 AAN Practice Parameter is that all data analyzed for the guideline were derived from studies in which patients were not treated with mild hypothermia after CPR.

Induced hypothermia

Treatment with hypothermia after CPR has been reported as early as 1959 by Benson et al.\textsuperscript{15}. However, serious complications of moderate to deep hypothermia led to
abandonment of this therapy. In 2002, this treatment was reintroduced after two randomized controlled trials which showed a positive effect of treatment with mild hypothermia (32-34°C) on mortality and neurologic outcome in adult comatose survivors of OHCA\textsuperscript{16,17}. Patients with ventricular fibrillation or ventricular tachycardia as initial rhythm and persistent coma after return of spontaneous circulation were included in these studies. Soon thereafter, this therapy was also applied to patients with asystole or pulseless electric activity as initial rhythm and to patients with IHCA. Nowadays, this treatment has become standard care in many countries and is part of all guidelines concerning post-cardiac arrest care\textsuperscript{18,19}. The predictive value of prognostic variables might well be different in these patients because of the modified natural history of the brain injury after CPR or the use of sedative drugs administered during cooling\textsuperscript{20-22}. Therefore, new data are needed to predict the outcome in patients who remain unconscious after hypothermia treatment.

![Algorithm for prognostication of comatose patients after cardiopulmonary resuscitation\textsuperscript{14}.

FPR = false-positive rate with 95% confidence intervals.](image-url)
Some problems of outcome research in postanoxic coma

Important problems in outcome research are the definition and validity of outcome measurements and the restriction of treatment in selected patients, i.e. patients with characteristics presumed to be predictive of poor outcome.

Which outcome?
Because reliable prediction of good outcome is less successful than that of poor outcome, most studies use poor outcome in analysis. In older studies, outcome after CPR has often simply been classified as “mortality”, “alive at ICU discharge” or “alive at hospital discharge”. In daily practice, these classifications are unhelpful, as the condition of patients who are discharged may vary from “recovered to previous level of functioning” to “permanent vegetative state”. Outcome measures should be chosen that are clinically meaningful, i.e. do not only answer the question of survival, but also that of remaining disability. “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.

It is important to realize that the patients who are assessed to have made a “good recovery” are not always completely recovered. Prospective studies about the long-term prognosis in patients after CPR report cognitive problems in about 50% of the patients. Memory problems and problems with attention and executive functioning are the most common. Quality of life after CPR is related to cognitive problems, fatigue, emotional problems, post-traumatic stress and difficulties in daily activities, which can be targeted in rehabilitation programs.

Self-fulfilling prophecy
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 poor outcome may lead to the false conclusion that such characteristics are indeed good predictors of poor outcome. Symptoms and signs “known” to be related to a poor outcome will lead to treatment restrictions and therefore will prove to be good predictors, as the treatment restriction in itself will at least contribute to the poor outcome. This is important to realize when interpreting literature. In the ideal study, treatment should not be limited or
withdrawn in any patient included in the study, but for ethical, practical and financial reasons such a study is impossible to conduct in daily clinical practice. A ‘second best’ type of study is one in which treatment restrictions are carefully recorded and reported for the interpretation of its results.

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, however, results of neurologic examination and results of somatosensory evoked potentials (SEP) after rewarming are often disclosed to the treating physicians.

**Background and outline of this thesis**

Since 1998, research concerning prediction of outcome in patients with postanoxic coma has been conducted in the Academic Medical Center in collaboration with many other Dutch hospitals. The last years, the main focus 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. These themes are the main topics of this thesis.

Two studies are focused on the hypothermia treatment itself: its implementation and methods used in the Netherlands (Chapter 2) and the effect of rewarming after hypothermia treatment and the development of fever on outcome (Chapter 3). In two studies the prediction of poor outcome in patients treated with hypothermia was evaluated: using SEPs already during hypothermia (a pilot study reported in Chapter 4); and using clinical variables, the biomarker neuron-specific enolase and SEPs (a larger national study, Chapter 5). Since SEPs play an important role in the prediction of poor outcome, some aspects of this technique were studied: the influence of hypothermia on characteristics of SEPs (Chapter 6) and the association between clinical variables and the absence or presence of SEPs in patients not treated with hypothermia (Chapter 7). Finally, two clinical variables of which the prognostic value is controversial were studied: myoclonus (Chapter 8) en status epilepticus (Chapter 9). A general discussion and summaries in English and Dutch are provided in Chapters 10-12.
References


