Postanoxic coma: prognosis after therapeutic hypothermia
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Chapter 10

General discussion and future perspectives
Prediction of outcome

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 this general discussion, current knowledge about prognostication in postanoxic coma after hypothermia and potential neuroprotective strategies will be described. Also future challenges will be addressed.

Several important issues should be kept in mind when reading this discussion. First, most patients described in literature about prognostication after CPR are patients with a primary cardiac cause for the cerebral anoxia-ischemia. This limits conclusions about prognostication in patients with postanoxic coma from other causes. Second, the patient population admitted to the intensive care unit (ICU) after CPR has changed over the last decades and the mortality rate has decreased dramatically. Previously, patients who woke up shortly after CPR were directly admitted to the coronary care unit and were therefore not included in cohort studies on ICU patients. Nowadays, almost all patients are treated with hypothermia on the ICU, which leads to different case mix in ICU cohort studies and partly explains the improved survival in ICU populations.

Neurologic examination

Neurologic examination is always done as a first test in ICU patients who are expected to wake up after CPR. Although the false-positive rates (FPRs) of “absent pupillary light responses together with absent corneal reflexes” suggest a robust reliability in patients treated with hypothermia, physicians should realize that the confidence intervals (CIs) are wide, which leads to uncertainty. Future studies should provide more information about the “exact” reliability.

The most remarkable finding in patients treated with hypothermia is the unreliability of an absent or extensor motor response (M1 or M2) at 72 hours. In the PROgnosis in PostAnoxic Coma II study (PROPACII), 14% of the patients with a M1 or M2 three days after CPR had a good outcome after 6 months. A possible explanation for this decrease in reliability of the motor score is the use of sedative drugs and neuromuscular blocking agents during hypothermia. Hypothermia decreases metabolism and, therefore, reduces clearance of sedative drugs and neuromuscular blocking agents. Physicians on the ICU should preferably use sedative drugs and neuromuscular blocking agents with a short half-
life during hypothermia in the lowest possible dosage. But even then, one should realize that after discontinuation metabolites of these drugs still might influence neurological examination. The motor score should therefore not be used anymore as a predictor of poor outcome in this patient group.

Information about the value of motor scores examined later than 72 hours after CPR is sparse. Most studies evaluated the prognostic value of motor score until 72 hours after CPR. A retrospective study of Bisschops et al. reported the predictive value of motor scores up to 7 days after CPR. In this study, 13% (1/8) with a M1 or M2 at day 7 awoke and had a favorable outcome. Future large prospective cohort studies should investigate the predictive value of neurologic examination, especially motor scores, at longer time intervals, e.g. at 5, 7, 10, and 14 days in patients with uncertain outcome at 72 hours after CPR.

The Glasgow Coma Scale (GCS) is the most widely used coma score. It consists of an eye, motor and verbal score. It was initially designed to assess level of consciousness after traumatic brain injury. The verbal score cannot be defined in intubated and mechanically ventilated patients. The interobserver agreement for the GCS has been reported variable. The accurate use of the scale has been shown to increase with the user’s experience. Inexperienced users have been shown to make consistent errors. A recently developed coma scale is the Full Outline of UnResponsiveness (FOUR) score. It incorporates eye opening and eye movements, brainstem reflexes, respiration patterns, motor responses, and specific ways to assess comprehension to a command. This scale gives more specific information about the clinical condition of the patient in coma at the ICU and interobserver agreement has been found to be good to excellent. The FOUR score seems useful to predict outcome after CPR, but further prospective (multicenter) studies are necessary to confirm these preliminary results.

In 9-35% of the patients after CPR, a postanoxic status epilepticus (PSE) may contribute to the comatose state. In most patients, this condition is a sign of extensive brain damage and 90-100% of the patients with a PSE had a poor outcome. However, some patients show a good recovery, often after prolonged intensive treatment. No evidence is available to guide (non)treatment decisions and clinicians are uncertain about what to do with this condition in patients after CPR. Future research should focus on patient characteristics and electroencephalography (EEG) patterns which may identify patients who will benefit from prolonged intensive treatment. Furthermore, as continuous EEG monitoring during hypothermia and rewarming increasingly will be implemented in daily practice, effectiveness of (early) treatment should be investigated (see below).
Clinical neurophysiology

Somatosensory evoked potentials

Bilateral absence of median nerve somatosensory evoked potentials (SEPs) after rewarming was shown to have a good prognostic reliability in the PROPACII and other studies. This could easily lead to the impression that SEP after rewarming is a perfect test. However, there are two points that should be addressed. The results of SEP after rewarming were disclosed to treating physicians, which limits robust conclusions due to the possibility of a self-fulfilling prophecy (see Chapter 1). Furthermore, sporadic cases have been published with good outcome despite absent cortical N20 responses, one after treatment with hypothermia and subsequent rewarming and one without hypothermia treatment\textsuperscript{17,18}. In my opinion, until more cases with detailed documentation are reported, SEP after rewarming remains a reliable prognosticator.

An important advantage of SEP is the low susceptibility to metabolic changes or sedative drugs compared to other prognosticators, such as neurologic examination or electroencephalography. However, there are some well-known pitfalls. Muscle activity and interference of electric devices are known to increase the noise levels of SEP recording, with a concomitant increase in the possibility of misinterpretation. Administration of muscle relaxants and turning electric equipment off in order to reduce noise levels to $< 0.25 \mu V$ will improve the interobserver reliability from “fair” to “substantial agreement”\textsuperscript{19}. Another possible pitfall is the effect of hypothermia on the SEP responses. Most literature available describes the influence of deep hypothermia (11.4-30.1\degree C) on median nerve SEP when performed during hypothermic cardiopulmonary bypass\textsuperscript{20-25}. The cortical N20 response disappears with temperatures between 14.5 and 29.6\degree C and latencies of peripheral and central components are prolonged\textsuperscript{20-26}. These changes, however, may be less prominent with the mild hypothermia (32-34\degree C), as used in patients after CPR. We demonstrated an increase of both peripheral and central conduction times during treatment with mild hypothermia compared with the recordings in the same patient after rewarming. We also found that amplitudes did not differ consistently between hypothermia SEP and SEP after rewarming. Furthermore, we demonstrated that absent SEP responses during hypothermia predict the absence of SEP responses after rewarming.

The clinician interpreting the SEP registration in patients after CPR should be aware of all these problems. The results of the SEP strongly contribute to the decision of the treating team to limit or withdraw treatment. In case of uncertainty about the recordings, the clinician should assess the results as “undeterminable”. 
Electroencephalogram

Electroencephalographic studies include routine EEG and continuous EEG (cEEG). An important limitation of EEG is the substantial interobserver variability in determining EEG patterns in intensive care patients. One study showed only a moderate agreement for the presence of rhythmic or periodic patterns and a slight to fair agreement for other patterns. Hypothermia itself can influence EEG patterns with appearance of unilateral or bilateral periodic complexes and burst suppression. Studies with routine EEG have shown that an isoelectric EEG or a low-voltage EEG (< 20 µV) is a reliable predictor for a poor outcome. Any confounders, such as hypothermia, (ongoing) effects of sedative drugs, intoxication, hypotension, or metabolic disturbances have to be excluded.

A rather new development is cEEG monitoring in post-CPR patients. There are two goals of applying cEEG: identification of cEEG patterns in relation with good or poor outcome; and early identification of (non-)convulsive seizures/status epilepticus to start treatment. Rundgren et al. showed that more than half of the patients after CPR with a flat cEEG during hypothermia treatment had a continuous pattern on the cEEG at rewarming. A continuous pattern on the cEEG was strongly associated with regaining consciousness.

Studies evaluating cEEG monitoring showed that electrographic seizures or epileptiform activity are common during hypothermia and/or rewarming. There are currently no studies available comparing results of routine EEG (at specific times) with cEEG and subsequently, the influence on outcome. Future research should focus on which cEEG patterns during hypothermia and rewarming warrant treatment and its effectiveness; and which patterns are correlated with good or poor outcome.

Neuron-specific enolase and other biomarkers

Serum neuron-specific enolase (NSE) is the most extensively investigated biomarker in patients after CPR and hypothermia. Data on the prognostic reliability of NSE are conflicting and NSE does not seem to be as “neuron-specific” as suggested. Reported NSE levels above which a poor outcome could be predicted reliably, range from 28-85 µg/liter. Other important technical restrictions of use of NSE in daily clinical practice are different reference levels among laboratory methods and increased NSE levels due to blood hemolysis.

Other reported biomarkers are S100beta, glial fibrillary acid protein, brain derived neurotrophic factor, blood ammonia and serum procalcitonin. A relatively new biomarker is neurofilament heavy chain. A recently published study showed a correlation of neurofilament levels with outcome at 2 and 36 hours after cardiac arrest, but elevated
plasma levels were also found in patients with a good outcome\textsuperscript{39}. Furthermore, a substantial part of the cohort had neurologic comorbidities, which might already lead to an elevated plasma neurofilament level. In conclusion, there are far too few data to draw firm conclusions, but due to the limitations of each biomarker, it seems unlikely that one of these will be reliable enough to use for prognostication in the individual patient.

**Imaging**

Imaging in ICU-patients, especially when they are hemodynamically unstable, encounters practical problems of transportation. Furthermore, interpretation from literature is made difficult by the small numbers of patients studied, and differences in timing of imaging.

A computed tomography (CT)-scan is often performed on admission to exclude other causes for the collapse, such as subarachnoid hemorrhage which occurs in 4-16\% of the patients with CPR\textsuperscript{40,41}. Furthermore, it can reveal information about traumatic brain injury caused by the fall. In patients with postanoxic coma the CT-scan can show brain edema with diffuse swelling and loss of differentiation between grey and white matter. In my opinion, the role of standard CT, except for exclusion of other causes of the comatose state, is limited.

Magnetic resonance imaging (MRI) techniques may be a more promising method. Practical problems, such as duration of scanning and availability of MRI-compatible ventilators, are more prominent when compared with performance of a standard CT. MRI can show abnormalities in different time frames after CPR. DWI/ADC imaging can show acute ischemia within the first 24 hours, as abnormalities on T2/FLAIR sequences often appear thereafter\textsuperscript{42}. Greer et al. recently showed a high sensitivity for DWI abnormalities and prediction of poor outcome, but a low specificity of only 46\%\textsuperscript{43}. Another problem is the inter-observer reliability, which is only moderate\textsuperscript{43}.

Literature on this subject is limited and imaging alone should not be used for prognostication. Future research should prospectively investigate the prognostic reliability of MRI at different time points and sequences at fixed time points after CPR, for example at day 1 or 2 and day 7. This would elucidate if any additional information on functional outcome will be provided, but it has to be realized that in many hospitals an MRI is impossible in ventilated ICU patients because of all the technical problems with the large magnetic field.
Discussion

**Improvement of outcome**

Research concerning prediction of outcome in patients with postanoxic coma after CPR is constantly on the move, as new potential treatment options are introduced and evaluated. This might lead to different outcome in these patients and might also affect reliability of prognostic variables. Already mentioned examples of measures which attribute to improvement of outcome are change of the compression/ventilation ratio, implementation of the Automatic External Defibrillator (AED), on field administration of amiodarone, and treatment with therapeutic hypothermia.

After successful CPR, a complex pathophysiological process occurs. The term post-cardiac arrest syndrome includes four components on which (potential) treatment should be focused: post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology. This section will discuss some important subjects of current research of different treatment options in the post-CPR period with regard to neuroprotection.

**Target Temperature Management**

*Hypothermia treatment*

Treatment with hypothermia is considered beneficial in patients after CPR because hypothermia is associated with lower levels of proinflammatory cytokines and free radicals, a reduced hyperexcitatory state of the brain, a lower cerebral metabolic rate, reduced permeability of the blood-brain barrier and anticoagulant effects. Lower temperatures may also decrease intracranial pressure. After the publication of two positive randomized controlled trials this treatment was soon incorporated in the international guidelines and has become standard care in many countries. However, a recent systematic review concluded that the evidence is still inconclusive, even in patients with ventricular fibrillation/ventricular tachycardia as initial rhythms and out-of-hospital CPR. The major limitation of the existing literature is the occurrence of untreated fever in the control patient and the poor methodological quality of the studies. Controlled normothermia might be as effective, or even more effective, since the potential side effects of hypothermia will be diminished. Currently, the optimal target temperature is studied in the international multicenter Target Temperature Management Study (NCT01020916), which investigates whether a controlled temperature of 36°C has a similar effect as a controlled temperature of 33°C.
Rewarming and fever

The current recommendation is to rewarm the patients after therapeutic hypothermia at a rate of maximal 0.25-0.5 °C/h, but the optimal rewarming rate is unknown. A recent study (177 patients) showed that longer duration of passive rewarming was associated with increased in-hospital mortality. Our retrospective study showed that patients who needed active rewarming after therapeutic hypothermia did not have a higher risk for a poor outcome when compared to patients who rewarmed spontaneously. In addition, speed of rewarming had no effect on outcome. However, the number of patients with a high rewarming rate was very small which limited robust conclusions.

Another consensus in the current guidelines is that hyperthermia or fever should be avoided. In patients who were not treated with hypothermia after CPR, fever occurred in up to 83% and was associated with an unfavorable neurologic recovery and a prolonged length of stay on ICU. In the two studies concerning patients treated with hypothermia after CPR, fever was found in 47-76% of the patients. However, in these patients, it was not associated with in-hospital mortality, nor with poor outcome after 6 months.

Future research should investigate the optimal rate of rewarming, the possible benefits of fever treatment, different sedation regimens and the best methods to monitor patients during hypothermia and rewarming. In daily practice, such studies would be quite a challenge as large numbers of patients and strict treatment protocols will be needed.

Other methods of neuroprotection

Controlled re-oxygenation

As adenosine triphosphate production needs oxygen, one could assume that immediate restoration of the oxygen supply is very important after return of spontaneous circulation. Animal studies, however, indicate that hyperoxemia in the initial phase of reperfusion exacerbates neuronal damage due to free radical production and mitochondrial injury. Clinical data are conflicting. One retrospective study, using data from a large clinical registry, found significant higher in-hospital mortality for the hyperoxemia group. This study had significant limitations and further research is necessary to establish optimal oxygenation strategies. Current consensus is to aim for normoxemia and to avoid hypoxemia.

Helium

Helium inhalation has shown promising results in reducing ischemia and reperfusion injury with reduction of cerebral and myocardial infarct volumes in animal studies. Preliminary results of a safety and feasibility study in patients after CPR showed that...
helium ventilation can be applied safely to patients after CPR\textsuperscript{55}. Further research with this potential therapeutic agent is needed.

\textit{Erythropoietin}

Erythropoietin (EPO) had neuroprotective qualities in animal studies and was shown to be safe in a pilot study in patients after stroke\textsuperscript{56}. A subsequent randomized clinical trial showed no benefits and an unexplained higher mortality rate in patients who received EPO, especially in those who were also treated with recombinant tissue plasminogen activator (rtPA)\textsuperscript{57}. A recent animal study confirmed the negative effect of the combination of EPO with rtPA\textsuperscript{58}. Other clinical studies of EPO in patients with subarachnoid hemorrhage (phase II trial) and severe traumatic brain injury (prospective observational study) did show beneficial effects\textsuperscript{59,60}. In cardiac arrest patients, only one matched control study was performed\textsuperscript{61}. In total 18 patients were treated. A higher survival rate was found, which did not significantly differ with the control group. Potential side effects of EPO were elevated platelet count (with coronary vascular thrombosis in 1 case). Currently, the same research group investigates the efficacy EPO after cardiac arrest in a randomized multicenter single-blinded trial comparing early high dose of EPO with standard care (NCT00999583).

\textit{Other}

Thiopentone has shown to be neuroprotective in animal models, but a large clinical trial showed no benefit. Also magnesium, diazepam, calcium channel inhibition, or glucocorticoids did not show an improvement in outcome\textsuperscript{62,63}. Future research should investigate the role of potentially neuroprotective agents in the prevention of reperfusion injury and improvement of outcome after CPR.

\textbf{Outcome research and guidelines}

As previously mentioned, research concerning prediction of outcome in patients with postanoxic coma after CPR is constantly on the move, as new potential treatment options are introduced and evaluated. 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 \textit{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. For instance, the results of studies performed in the last five years in patients treated with hypothermia after CPR, such as the studies described in this thesis, should lead to changes in international 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. Although the FPRs of “absent pupillary light responses together with absent corneal reflexes” or “absent SEP after rewarming” suggest a robust reliability in patients treated with hypothermia, physicians should realize that the CIs are wide, which may lead to uncertainty. 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.

References

Discussion


