After a cardiopulmonary arrest and return of spontaneous circulation (ROSC), 80% of patients are comatose for a varying period of time. A considerable number of these remain unconscious due to hypoxic-ischaemic cerebral dysfunction and progress to brain death or persistent vegetative state. However, 20% will survive and regain consciousness. As meaningful neurological recovery only occurs in a small proportion of patients and treatment is complex, expensive, possibly prolonged, and very difficult for relatives it would be helpful to be able to prognosticate on individual patients from an early stage. Many approaches have been examined to try to predict the outcome of post cardiopulmonary resuscitation (CPR) coma. These include:

- Premorbid, peri-arrest, and immediate post-arrest variables
- Serial neurological examinations looking for normal or abnormal signs or both
- Electrophysiological investigations
- Neuroimaging
- Neurobiochemical investigations

The purpose of this review is to determine the appropriate emergency management of patients resuscitated to a coma state following cardiorespiratory arrest.

**REVIEW METHODS**

The Medline database (1996–2003) was searched using the Ovid search engine. MeSH headings of “Cardiorespiratory arrest survival”, “Cardiorespiratory arrest outcome”, “Cardiac arrest survival” and “Cardiac arrest outcome” were used. These were combined with those from the MeSH headings “Coma”, “Neurological outcome” and “Encephalopathy”. The search was restricted to “humans”, “adults” and “English language”. A total of 136 papers were identified of which 25 were directly relevant to at least a part of the review question. All of the references in the chosen papers were examined to identify other relevant referenced papers. The EMBASE database and the Cochrane Library Issue 3, 2004, were also searched but provided no additional data. The journals Resuscitation and Critical Care Medicine were also handsearched from 1998 to 2003.

**DISCUSSION**

Premorbid, peri-arrest, and immediate post-arrest variables

Premorbid, peri-arrest, and post-arrest variables have been extensively examined, largely in retrospective analyses. Most studies have analysed survival rather than neurological outcome.

**Premorbid factors**

**Age**

Schultz et al reported a retrospective review of 75 post-arrest patients and showed a significant difference in survival between patients under the age of 60 years and those over the age of 80 years (15% v 4%, respectively). They did not examine neurological outcome. However, Berger and Kelley in a prospective analysis of 255 inhospital cardiopulmonary arrests in non-critical patients demonstrated age was not an independent predictor of survival. Varon and Kelley reported substantial survival among the elderly after an inhospital arrest with eight survivors from 89 patients (11%) over the age of 70 years. Parish et al reported, in a retrospective review of 2813 cardiorespiratory arrests, that age was unrelated to survival where the initial rhythm was pulseless ventricular tachycardia (VT), ventricular fibrillation (VF), or asystole, but it was related if the rhythm was pulseless electrical activity (PEA). The latter was thought to reflect the poor premorbid state associated with a PEA arrest. Importantly Rogove et al reported in a prospective study of 774 patients that old age did not negate good cerebral outcome after cardiorespiratory arrest.

**Premorbid health and performance status**

Berger and Kelley reported that patients’ admission diagnoses and comorbidities predicted outcome from inhospital cardiorespiratory arrest. This is reflected in the increased mortality rate from a PEA arrest, a common endpoint of severe illness. Three morbidity scores have been developed as a guide to “Do Not Attempt Resuscitation” (DNAR) decisions but the information they provide is relevant to prognosis after an arrest. The Prognosis after Resuscitation (PAR) score was developed from a meta-analysis of 14 post-arrest studies in 1992 and uses seven variables: cancer, sepsis, poor performance status, pneumonia, creatinine >130 mg/L, and age over 70 as positive scores, and recent myocardial infarction as a negative score. Prospective validation in 274 consecutive
resuscitated patients demonstrated that a score of >4 predicted non-survival. Bowker and Stewart\textsuperscript{13} compared the PAR to other morbidity scoring systems in a group of elderly patients and showed that they were all more complex to use due to multiple variables, in one case the score had not been validated prospectively, and they provided no additional information. Unfortunately although 100% specific and therefore of use in DNAR decisions, the PAR score does not help in the majority of post-arrest patients who will have low scores. It also does not predict a good neurological outcome in those predicted to survive.

**Peri-arrest factors**

Schultz \textit{et al}\textsuperscript{24} reported that the duration of the cardiorespiratory arrest was related to outcome. They reported survival rates of 48% for less than 10 minutes duration and 2% for longer than 10 minutes. Other studies have confirmed this highly biologically plausible finding using surrogate markers for duration of arrest. Behringer \textit{et al} reported an unfavourable cerebral performance category was associated with significantly greater cumulative doses of adrenaline (epinephrine).\textsuperscript{13} This was confirmed by Denton and Thomas who also correlated the number of DC shocks with poor outcome.\textsuperscript{14} Saklayen \textit{et al}\textsuperscript{25} confirmed a shorter duration of arrest was associated with a better outcome and that this correlated with a witnessed arrest or resuscitation by a health professional indicating earlier effective intervention. They also demonstrated that pulseless VT or VF arrests had a better outcome than PEA arrests, and that arrests in the emergency department or coronary care unit had a better outcome than those in intensive care unit (ITU) or a general ward. The latter finding reflects both the arrest rhythm and the premorbid state of the patients. Andreasson \textit{et al} quantified these observations in cardiorespiratory arrests in hospital.\textsuperscript{13} They showed a survival rate of 64% from VT/VF arrest, 24% from asystole, and 10% from a PEA arrest. Monitored patients had a survival rate of 52% while unmonitored patients had a survival rate of 27%.

**Post-arrest factors**

Various post-arrest physiological variables have been investigated as proposed prognostic indicators post cardiorespiratory arrest with ROSC. Schultz \textit{et al} examined initial PaO\textsubscript{2} after ROSC and showed that a level of <50 mm Hg correlated with survival of 1% compared with 13% with a level >50 mm Hg. APACHE II scores were shown to correlate with outcome by Denton and Thomas.\textsuperscript{14} However, Berger and Kelley\textsuperscript{4} showed that although APACHE II scores correlated with ITU survival, there was no correlation with hospital discharge. Niskanen \textit{et al}, using an APACHE II score of 25 or greater as a cut-off, showed a correlation with poor outcome but the positive predictive value was only 71%.\textsuperscript{14}

Arterial blood gas analysis after ROSC has also been investigated. Schultz \textit{et al} showed no correlation between initial pH and survival. Denton and Thomas\textsuperscript{26} showed correlation between arterial bicarbonate concentration on the first blood gas analysis in ITU and outcome but showed no correlation with pH of the same sample or initial bicarbonate level following ROSC. Mullner \textit{et al}\textsuperscript{25} showed a trend for higher levels of serum lactate after ROSC to correlate with poor neurological outcome but a level of greater than 16 mmol/l was required for 100% specificity. Buunk \textit{et al}\textsuperscript{27} examined oxygen delivery following ROSC as a prognostic indicator by comparing mixed venous (SmvO\textsubscript{2}) and jugular bulb venous (SjO\textsubscript{2}) oxygen saturation. Post-arrest SjO\textsubscript{2} was about 10% lower than the SmvO\textsubscript{2}. In non-survivors SjO\textsubscript{2} steadily increased due to reduced cerebral oxygen consumption secondary to loss of functional tissue. At 24 hours an SjO\textsubscript{2} greater than SmvO\textsubscript{2} had a positive predictive value for poor outcome of 93%. Denton and Thomas\textsuperscript{28} also demonstrated that an inotrope requirement after ROSC correlated with a poor outcome. This was confirmed by Langhelle \textit{et al}\textsuperscript{25} in a retrospective cohort analysis of 459 patients who had an out of hospital cardiorespiratory arrest. They demonstrated that hypotension, oliguria, base deficit of 3.5 or more, plasma glucose of greater than 10.6 mmol/l, or core body temperature of >37.8 °C within 24 hours of ROSC were each independently related to poor outcome. The latter two factors are consistent with other studies of outcome from hypoxic-ischaemic coma. These have demonstrated that hyperglycaemia following an arrest has a statistically significant impact on the risk of poor neurological outcome whereas for every degree Celsius above 37 °C the risk of an unfavourable neurological outcome increases with an odds ratio of 2.26.\textsuperscript{13} 13

**Serial neurological examination**

**Abnormal neurological signs**

Myoclonus in comatose patients following ROSC was reported to be an agonal sign by Wijdicks \textit{et al} as all patients with myoclonus died.\textsuperscript{29} However, since that report this finding has been contradicted in a number of case reports. Morris \textit{et al}\textsuperscript{30} reported three survivors with mild disability and in a literature review found five similar cases. Snyder \textit{et al}\textsuperscript{10} reported seizure activity in 30% of patients following ROSC; 17% of those with myoclonus, 33% of those with partial seizures, and 50% of those with generalised, complex seizures survived. Overall the survival rate for those with seizure activity was 32% compared with 43% for those with no seizure activity. A further report by Krumholz \textit{et al}\textsuperscript{31} showed no relation between seizure activity and neurological outcome, except in a subgroup with status, which predicted a higher risk of persistent unconsciousness or brain death.

Jorgenson and Holm examined neurological outcome over one year in 231 patients post cardiorespiratory arrest with ROSC.\textsuperscript{32} They divided outcome into four categories: brain death, persistent unconsciousness, persistent disability after awakening and complete recovery. They reviewed both electroencephalographic (EEG) activity (see later) and the presence of abnormal neurological signs in an attempt to predict individual neurological outcome. Brain stem areflexia was an agonal sign (brain death) noted at any time after ROSC predicted brain death with 100% specificity and sensitivity. Myoclonus was unhelpful in prediction occurring in 65 patients with brain death or persistent unconsciousness and 27 with persistent disability after awakening or complete recovery. Adding the presence of myoclonus at any time to the presence of no EEG activity at 1 hour after ROSC only marginally improved the predictive value—that is, 53 with brain death or persistent unconsciousness versus 13 with persistent disability after awakening or complete recovery. A systematic review in 1998 combining 33 studies of prognostic indicators post-arrest with ROSC demonstrated the poor predictive value of seizure activity. Specificity and sensitivity for poor outcome were 25–92% and 16–85%, respectively.\textsuperscript{25}

**Glasgow Coma Score**

The Glasgow Coma Scale (GCS) has been extensively investigated as a predictor of individual outcome following cardiac arrest with ROSC. Zandsbergen \textit{et al} in a systematic review showed that a GCS of 5 or less in the first 24 hours was not helpful in predicting outcome.\textsuperscript{27} Mullie \textit{et al} in a study of 133 patients showed that of 54 patients with a GCS of 4 or less 48 hours after ROSC only one recovered consciousness. A GCS of 10 or more at the same time predicted good recovery in 40 of 49 patients.\textsuperscript{28} Bassetti \textit{et al} combined a GCS of 8 or less with abnormal somatosensory evoked potentials at 48 hours to produce a 97% specificity for
brain death or persistent unconsciousness. Grubb et al. showed that a GCS of 8 or less was absolutely predictive of poor outcome at 72 hours. However, this study included small numbers of patients in this category. A systematic review in 2004 of clinical signs in prognostication following cardiac arrest with ROSC demonstrated that an absent motor response at 72 hours had a likelihood ratio for death or poor neurological outcome of 9.2 (95% CI 2.1 to 49.4). This indicates it is impossible to use a low GCS as an absolute predictor of poor outcome though it suggests a low probability of a good outcome. It should be noted that a significant limitation in all prognostication studies is that in many cases active support has been withdrawn as soon as the patient appears to demonstrate poor neurological recovery and this may bias results in favour of a poor outcome.

Temporal recovery of normal cerebral function
Persistent brainstem dysfunction is an indicator of poor prognosis post arrest with ROSC as the adult cerebral cortex is more susceptible to the effects of anoxia than the brainstem. In view of this brainstem reflex activity has been examined as a predictor of individual outcome. The simplest clinical examination is the pupillary response to light. Numerous studies have raised doubts about the specificity of pupillary responses due to small numbers of patients who make a good recovery despite no response to light. Longstreth et al., for example, reported 4 out of 39 patients with absent pupillary responses had a good outcome. However in these studies there is usually a failure to examine the temporal relation between the time of testing and final outcome. Zandbergen et al. in a systematic review in 1998 reported three independent factors with 100% specificity for poor outcome. These were absence of pupillary response to light on day 3, absent motor response to pain on day 3, and abnormal evoked potential tests within one week (see below).

Jorgenson examined the natural course of neurological recovery following CPR and demonstrated that although the magnitude and duration of the hypoxic-ischaemic cerebral insult prior to ROSC determined if cerebral function could be restored, in all cases where neurological recovery occurred, it occurred in the same sequence. Brain stem functions recovered in the same sequential order irrespective of initial neurological status or eventual outcome and this recovery of function followed a specific temporal course. The initial phase was a phase of exclusive presence of cranial nerve reflexes. Stagnation of recovery in terms of lack of time-related recovery of function predicted either brain death or persistent unconsciousness. Stagnation of recovery did not occur in those with persistent disability after awakening or complete recovery and these findings did not aid in prediction of final outcome between these groups. The study determined the recovery sequence as follows: initially recovery of spontaneous ventilation, then pupillary light response, then coughing/swallowing then presence of a ciliospinal reflex. It also examined critical time limits for neurological recovery. Pupillary responsivity to light at two minutes following ROSC had a positive predictive value of 1.0 for persistent disability after awakening or complete recovery whereas absence of responsivity at 20 minutes after ROSC had a negative predictive value of 0.98. Absence of a cough/swallow response at 30 minutes after ROSC had a negative predictive value for persistent disability after awakening or complete recovery of 1.0. Presence of a ciliospinal reflex at 20 minutes following ROSC had a positive predictive value of 1.0 for persistent disability after awakening or complete recovery and absence at 30 minutes after ROSC gave a negative predictive value of 0.98.

Further work by Jorgensen and Holm examined additional potential unique discriminative signs in 231 patients following arrest with ROSC. They demonstrated that absence of the caloric vestibular reflex at eight hours after ROSC had a negative predictive value of 1.0 for complete recovery or persistent disability after awakening. They also demonstrated that by using a combination of early EEG with division of patients into those with no activity versus some activity at one hour after ROSC they could use the time of recovery of speech in each group to differentiate persistent disability after awakening and complete recovery. For example, speech at 24 hours in those with some EEG activity at one hour has a positive predictive value for complete recovery of 1.0.

Electrophysiological investigations
Sensory evoked potentials
Sensory (especially somatosensory) evoked potentials (SEP) have been investigated for their potential in prediction of outcome from coma for over 20 years. They have the advantage of being a non-invasive bedside test with high reproducibility. They are less susceptible to electrical interference than EEGs. Madi et al. published a study in 1993 of 66 patients investigated with SSEP between 4 and 48 hours after ROSC. In 17 patients with “favourable outcome” a normal response was demonstrated whereas in 49 with a “poor outcome” the evoked response was delayed or absent. However, further studies have qualified these initial findings. A study of SEP in 62 patients within 24 hours of ROSC demonstrated an abnormal SEP was associated with a “poor prognosis” but a normal SEP did not predict recovery. Nakabayashi et al., Chen et al., and Sandroni et al. demonstrated a 100% negative predictive value for a good outcome (persistent disability after awakening or complete recovery) with delayed or absent SEPs but a poor positive predictive value for normal SEPs. Nakabayashi demonstrated that of 12 patients with normal cortical response on SSEP, eight recovered consciousness. Chen demonstrated that bilaterally absent or low amplitude SSEP predicted brain death or persistent unconsciousness while with a normal SSEP the rate of complete recovery was only 44%. This lack of sensitivity was confirmed in a systematic review in 1998. This showed that bilateral absence of early cortical response to SEP within the first week had a positive likelihood ratio of poor outcome of 12 (CI 5.3 to 27.2). Specificity was 100%, but sensitivity was 28–73%.

Gendo et al. recorded serial SEPs at 4, 12, 24, and 48 hours after ROSC. They demonstrated that SEPs improved significantly between 4 and 24 hours with no improvement afterwards. Newer studies of SEPs following ROSC have tended to adopt a policy of investigation at 24 hours in view of these findings.

It has been suggested that as the somatosensory cortex is relatively resistant to hypoxic-ischaemic injury it may be preserved even when other cortical areas are severely affected. This would explain why absence/delay of SEP reinforces the likelihood of poor outcome whereas their preservation does not necessarily predict a favourable outcome.

Electroencephalography
EEG studies have been used to try to predict individual outcome from coma following cardiac arrest. There have been few studies examining temporal changes in EEG making single examinations difficult to interpret. EEG patterns can also be affected by confounding factors such as electrical interference, sedative medications, and septic or metabolic encephalopathies.
Synke produced a five point grading system in 1990 for EEG at 24 hours after ROSC and reported a 98.4% prognostic accuracy. Yamashita et al in a prospective study of 79 patients 24 hours following ROSC used a similar scale. They reported that grades I and II made a full recovery and grades IV and V were characterised by persistent unconsciousness or brain death. However, Rothstein in a prospective study of 40 patients demonstrated that a "malignant EEG pattern" within 48 hours of ROSC predicted a poor outcome (persistent unconsciousness or brain death) in only 42% of cases. Jorgensen and Holm took EEGs of 231 patients one hour following ROSC. In patients with no EEG activity, brain death or persistent unconsciousness was the final outcome in 68% compared with 28% in those with some EEG activity. However, although a good outcome was less likely with no EEG activity, 12% of such patients made a complete recovery. They concluded that recovery following arrest with ROSC is dictated by the severity of the hypoxic-ischaemic cerebral insult as reflected by the EEG evidence of cortical activity. However, the course and rate of recovery must be influenced by other factors as the entire spectrum of outcomes is noted regardless of initial EEG status. 

A systematic review in 1998 suggested that a burst suppression or isoelectric pattern on EEG within the first week predicted poor outcome (persistent unconsciousness or brain death). The positive likelihood ratio of poor outcome was 9.0 (CI 2.5 to 33.1).

**Neuroimaging**

There are a number of case reports and small retrospective reviews of neuroimaging after cardiac arrest with ROSC. Computed tomography (CT), magnetic resonance imaging and positron emission tomography have all demonstrated loss of distinction between grey and white matter, developing cerebral atrophy, and hypodensities in the basal ganglia consistent with the high metabolic requirements of the cerebral cortex and basal ganglia. Few studies have tried to use neuroimaging to predict outcome in comatose patients. Torbey et al carried out a retrospective review of 25 patients who had CT of the brain within 24 hours of ROSC. They showed that loss of distinction between grey and white matter on CT predicted poor outcome especially at the basal ganglia level and produced a qualitative analysis that suggested a cut-off for loss of distinction and guaranteed poor outcome. This was based on a small sample and has yet to be validated.

**Neurobiochemical investigations**

Biochemical markers have been investigated in coma patients following ROSC. Their utility in possible prediction of outcome is based on the fact that they reflect cerebral structural damage rather than function. This suggests the possibility of correlating their level directly with outcome measures.

**Cerebrospinal fluid creatine kinase-BB isoenzyme**

The brain is rich in creatine kinase (CK)-BB isoenzyme and has no CK-MM or CK-MB activity. CK-BB activity is unaffected by confounding factors that can reversibly affect cerebral function and reflects structural injury. Animal and human studies have demonstrated a correlation between cerebrospinal fluid (CSF) CK-BB after arrest and ROSC and the degree of brain injury. The peak CK-BB level occurs 48–72 hours after ROSC. Tirschwell et al tested CSF CK-BB 48–72 hours after ROSC in 351 patients. They reported a sensitivity of 0.82, a specificity of 0.85, and a positive predictive value of 0.96 for never awakening for CK-BB levels greater than 50 IU/l. A higher CK-BB cut-off of 205 IU/l increased specificity to 100% and positive predictive value to 1.0 with a reduced sensitivity of 48%.

**Serum neurope-specific enolase**

Serum neurope-specific enolase (NSE) levels reflect structural cerebral damage. A small study in 43 patients with daily serum levels for seven days post arrest with ROSC demonstrated that an NSE level greater than 33 ng/ml predicts persistent unconsciousness or brain death. The specificity was 100% with a sensitivity of 80%. Unfortunately the temporal relationship was unclear. Other small studies have confirmed a correlation between NSE levels and outcome. Zingler et al measured serial NSE levels after ROSC and demonstrated that an NSE level of greater than 43 ng/ml on day 2 had a specificity of 100% and a sensitivity of 91% for a poor outcome.

**Serum astroglial protein S-100**

Serum S-100 levels reflect structural cerebral damage. Rosen et al in a study of 41 patients post out of hospital cardiac arrest demonstrated a significantly higher level of S-100 in non-survivors. An S-100 level of 0.2 ng/ml or greater on day 2 had a positive predictive value of 100% for death within 14 days whereas a level of less than 0.2 had a positive predictive value for survival of 89%. Bottiger et al in a study of 66 patients post out of hospital cardiac arrest demonstrated that S-100 levels two hours following ROSC were significantly higher in patients with brain damage (including survivors) than in those who recovered with no brain damage. A systematic review of the predictive utility of biochemical markers of brain damage in 2001 concluded that although the results for CK-BB were interesting and produced no false positive results the small numbers and poor methodology in all trials made the combined results for any marker insufficiently accurate to provide a solid basis for non-treatment decisions.

**THERAPEUTIC HYPOTHERMIA**

The management of hypoxic-ischaemic coma after a cardiorespiratory arrest should now include induced mild hypothermia. An advisory statement from the International Liaison Committee on Resuscitation in 2003 has recommended cooling to 32–34 °C for 12–24 hours for all patients after ROSC following out of hospital cardiac arrest where the initial rhythm was VF. The statement also recommends consideration in other rhythms and in hospital arrests. This advice is largely based on two prospective randomised studies which reported numbers needed to treat for a favourable neurological outcome at six months as 67 and 4. It is unclear how therapeutic hypothermia will affect the normal temporal sequence of cerebral recovery. Importantly the interval between ROSC and attainment of the required core temperature had an interquartile range of 4–16 hours in one study. Examination will however be compromised by the associated requirement for sedation and paralysis.

**CONCLUSION**

A wide range of investigations has been utilised to try to predict individual outcome from coma due to hypoxic-ischaemic encephalopathy after cardiorespiratory arrest with ROSC.

- Age is not a significant factor in outcome provided the arrest is not an endstage event as indicated by a PEA rhythm.

- Comorbidity and premorbid performance status are good individual predictors of poor outcome following cardiorespiratory arrest and ROSC. However they can only be
used to identify a small subgroup with poor outcome and do not predict awakening in survivors.

- Prolonged resuscitation (or surrogate markers for prolonged resuscitation) is associated with poor outcome as would be expected with hypoxic-ischaemic pathology. However it is impossible to absolutely predict poor outcome from arrest duration alone once ROSC is achieved.

- Arrest rhythms reflect the patient’s premorbid state and predict outcome but provide no individual prognostic evidence. The better survival from emergency department or coronary care unit arrests is a function of early intervention and an increased probability of a reversible cause but once ROSC is achieved, again individual prognosis is difficult to assess if the patient is comatose.

- Measured physiological variables demonstrate that the worse the post-arrest milieu the more likely there is to be a poor neurological outcome but none are sufficiently sensitive indicators to predict outcome.

- Abnormal neurological signs are unhelpful in prediction of outcome and may simply reflect the normal course of cerebral recovery following a hypoxic-ischaemic insult. Only features consistent with brain death at any time provide an absolute prediction for brain death.

- A GCS score of 8 or less or an absent motor response at

- Very early prediction of poor outcome may be possible where features of brain death are present or where early recovery of specific cranial nerve reflexes fails to occur. However this temporal sequence may be altered by therapeutic hypothermia.

- All patients who remain comatose after ROSC and who do not have significant pre-morbid features should progress to a period of supportive care in the ITU. Therapeutic hypothermia, usually requiring sedation and paralysis, should be considered.

- Individual prognosis cannot be determined in the emergency department.

- Neuroimaging after ROSC has not been studied extensively and at present is unhelpful in prognostication.

- Neurobiochemical markers reflect structural cerebral damage and therefore should predict neurological outcome rather than reflect current function. However their individual predictive value is variable and is unhelpful before 48 hours have elapsed. At present they are at best adjuncts to assessment of neurological outcome.

Competing interests: none declared

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