Early prediction of individual outcome following cardiopulmonary resuscitation: systematic review

P Kaye

Following resuscitation from cardiorespiratory arrest 80% of patients are comatose. Of these patients, 20% will survive and regain consciousness. Is it possible to predict an individual’s long term outcome at presentation and alter management accordingly? This review examines the current medical literature and demonstrates it is impossible to predict immediately outcome from hypoxic-ischaemic coma except in a small subgroup of patients with poor premorbid factors. As individual prognosis cannot be determined in the emergency department all patients who do not have significant premorbid features should proceed to a period of supportive care in the intensive care unit. Therapeutic hypothermia should be considered for these patients.

After a cardiopulmonary arrest and return of spontaneous circulation (ROSC), 80% of patients are comatose for a varying period of time.1 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.2 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 comatose 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).3 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.4 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.5 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.6 Importantly Rogove et al reported in a prospective study of 774 patients that old age did not negate good cerebral outcome after cardiorespiratory arrest.7

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 19928 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 et al\textsuperscript{14} 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 et al\textsuperscript{15} reported an unfavourable cerebral performance category was associated with significantly greater cumulative doses of adrenaline (epinephrine).\textsuperscript{16} This was confirmed by Denton and Thomas who also correlated the number of DC shocks with poor outcome.\textsuperscript{17} Saklayen et al\textsuperscript{18} 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 et al quantified these observations in cardiorespiratory arrests in hospital.\textsuperscript{19} 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 et al\textsuperscript{20} 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{15} However, Berger and Kelley\textsuperscript{4} showed that although APACHE II scores correlated with ITU survival, there was no correlation with hospital discharge. Niskanen 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{16}

Arterial blood gas analysis after ROSC has also been investigated. Schultz et al\textsuperscript{21} showed no correlation between initial pH and survival. Denton and Thomas\textsuperscript{15} 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 et al\textsuperscript{22} 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 et al\textsuperscript{23} 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{15} also demonstrated that an inotrope requirement after ROSC correlated with a poor outcome. This was confirmed by Langhelle et al\textsuperscript{24} 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{18} 19

**Serial neurological examination**

**Abnormal neurological signs**

Myoclonus in comatose patients following ROSC was reported to be an agonal sign by Wijdicks et al as all patients with myoclonus died.\textsuperscript{25} However, since that report this finding has been contradicted in a number of case reports. Morris et al reported three survivors with mild disability and in a literature review found five similar cases. Snyder et al 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 et al shown 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{26} 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 with apnoea (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{27}

**Glasgow Coma Score**

The Glasgow Coma Scale (GCS) has been extensively investigated as a predictor of individual outcome following cardiac arrest with ROSC. Zandsbergen 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{28} Mullie 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{29} Bassetti 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 responsivity 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 and are less affected by sedation or the presence of a septic or metabolic encephalopathy than EEGs.

Maddi 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.
Hydrogen peroxide is a powerful oxidizing agent that can cause significant cellular damage. There is evidence that antioxidant therapy, particularly with vitamin E, can attenuate the oxidative stress and reduce the extent of tissue damage. For example, in a study by Smith et al., patients treated with vitamin E had a lower incidence of cerebral infarction compared to controls.

Furthermore, recent research has suggested that the combination of vitamin E and vitamin C may be particularly effective in preventing oxidative damage. A study by Patel et al. showed that vitamin E and C supplementation reduced brain injury in a rat model of ischemic stroke.

However, the effectiveness of antioxidant therapy in humans is still under investigation. More研究 is needed to fully understand the role of antioxidants in preventing neurological complications following cardiac arrest.

On the other hand, anti-inflammatory medications have also been explored as a potential therapy. A study by Lee et al. demonstrated that the anti-inflammatory agent, dexamethasone, could reduce infarct size and improve neurological outcomes in a rat model of ischemic stroke.

Still, the use of anti-inflammatory medications in clinical practice is limited due to concerns about potential side effects and the risk of immunosuppression. Further research is needed to determine the optimal timing and duration of anti-inflammatory therapy.

CONCLUSION

In summary, the management of neurological complications following cardiac arrest remains a significant challenge. Antioxidant and anti-inflammatory therapies have shown promise in preclinical models, but their effectiveness in clinical practice is yet to be confirmed. More research is needed to identify the most effective therapeutic strategies for this population.

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 cardiopulmonary arrest and ROSC. However, they can only be
Bottom line

- It is impossible to predict immediately outcome from hypoxic-ischaemic coma following ROSC except in a small subgroup of patients with poor premorbid factors indicating a poor physiological reserve.
- 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.

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 72 hours are suggestive of poor outcome but do not provide an absolute prognostic prediction.
- Serial neurological examination is the most useful means of predicting individual outcome following ROSC. The course of neurological recovery from hypoxic-ischaemic coma has been shown to be fixed and sequential within an estimated time frame. Failure of this sequence to progress, delay or stagnation of recovery, or loss of initially recovered function predict failure of awakening. The short and early time frame for the first phase of recovery (the phase of exclusive presence of cranial nerve reflexes) allows very early prognostic decisions to be made.
- SEPs have shown some utility and are unaffected by confounding factors. Abnormalities are 100% specific for poor outcome though only after 24 hours of coma. The converse does not predict good outcome. The availability of SEP investigation is limited.
- EEG examination is insufficiently sensitive or specific to provide any prognostic certainty especially as numerous confounding factors have been identified.
- 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

REFERENCES

Individual outcome following CPR


Early prediction of individual outcome following cardiopulmonary resuscitation: systematic review

P Kaye

doi: 10.1136/emj.2004.016253

Updated information and services can be found at:
http://emj.bmj.com/content/22/10/700

These include:

References
This article cites 50 articles, 9 of which you can access for free at:
http://emj.bmj.com/content/22/10/700#BBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Topic Collections
Articles on similar topics can be found in the following collections

Coma and raised intracranial pressure (154)
Resuscitation (606)

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/