Clinical Medicine 2011, Vol 11, No 6: 605–8

Advances in post-resuscitation care

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It is now widely recognised that interventions applied after return of spontaneous circulation (ROSC) impact significantly on the quality of survival, and there is considerable variation in post-cardiac arrest treatment and patient outcome between hospitals.[1] This review addresses some recent advances in the treatment and prognostication of comatose survivors of cardiac arrest.

These patients frequently develop the post-cardiac arrest syndrome (PCAS).

Primary percutaneous coronary intervention (PCI) is the preferred method for restoring coronary perfusion when cardiac arrest has been caused by ST-elevation myocardial infarction (STEMI). Many cardiac arrest survivors with non-STEMI may also benefit from urgent coronary angiography and PCI. Targeted temperature management using mild hypothermia is now generally accepted as part of a treatment strategy for comatose survivors of cardiac arrest, but its use makes prognostication difficult and unreliable.

Post-cardiac arrest syndrome

The prolonged period of systemic ischaemia during cardiac arrest and the subsequent reperfusion response that occurs after ROSC cause PCAS,[2] comprising:

- post-cardiac arrest brain injury
- post-cardiac arrest myocardial dysfunction
- the systemic ischaemia/reperfusion response
- any persistent precipitating pathology.

All components of the PCAS need to be addressed if outcome is to be optimised.[3] Guidance is available from two sources.[4,5]

Post-cardiac arrest myocardial dysfunction

Out-of-hospital cardiac arrest (OHCA) is caused most commonly by coronary artery disease. Early and complete restoration of perfusion is the fundamental goal of the treatment of STEMI with or without cardiac arrest. Reperfusion can be achieved with PCI, fibrinolysis or both.

Primary percutaneous coronary intervention

If a first medical contact-to-balloon time of less than 90 minutes can be achieved, primary PCI is the preferred treatment because it is much more likely than fibrinolytic therapy to establish full reperfusion. This is also likely to be true for resuscitation from cardiac arrest associated with STEMI, although this has never been tested in a randomised trial.

Post-resuscitation electrocardiogram (ECG)

An early post-resuscitation 12-lead ECG is less reliable for predicting acute coronary occlusion than in those who have not had a cardiac arrest. In a recent French study:[6]

- 435 (61%) of 714 admitted to hospital after OHCA had no obvious extracardiac cause for their arrest and underwent coronary angiography with PCI if indicated
- at least one coronary artery lesion was found in 304 (70%) of the above 435 patients
- 96% of the 134 patients with ST-segment elevation on the ECG had at least one coronary lesion and 99 (74%) underwent successful PCI.

Among the 301 patients with other ECG patterns, of particular interest is that 176 (58%) had at least one coronary lesion and 78 (26%) underwent successful PCI.

This study confirms that in the setting of OHCA the predictive value of the ECG for coronary artery occlusion is poor, suggesting that immediate coronary artery angiography should be considered in all OHCA patients with no obvious non-cardiac cause of arrest. Controversially, this includes patients without ECG evidence of STEMI.

Blood pressure

Arterial hypotension is common among cardiac arrest survivors admitted to the intensive care unit (ICU). The optimum post-resuscitation blood pressure has not been defined but is likely to depend on the patient's normal level. It must be high enough to maintain cerebral perfusion despite impaired cerebral autoregulation, but not excessively high because this would increase myocardial work in the face of possible myocardial ischaemia.

Global myocardial dysfunction

Global myocardial dysfunction, which can be quantified with early and serial echocardiography, is common after cardiac arrest but typically recovers over 48–72 hours.[7] Treatment with an inotrope, such as dobutamine, or an intra-aortic balloon pump may be required. Monitoring of cardiac output may be helpful because the inflammatory response associated with the PCAS may result in significant vasodilatation, which may require treatment with a vasopressor such as noradrenaline.[2]

Optimising neurological outcome after cardiac arrest

Although the long-term quality of life for most cardiac arrest survivors is good,[8] post-cardiac arrest brain injury is a common cause of morbidity and mortality. In patients surviving to ICU admission but subsequently dying in hospital, brain injury is the cause of death in 68% after OHCA and 23% after in-hospital cardiac arrest.[2] Control of tissue oxygenation, glucose and temperature may all impact significantly on outcome and are considered separately below.

Controlled re-oxygenation

During the initial stages of reperfusion, excessive tissue oxygen concentrations may increase neuronal damage by driving the production of free radicals which then cause mitochondrial injury. In an animal study, neurological outcome was optimised during the initial phases of resuscitation by controlled re-oxygenation, with ventilation using the minimum FiO_2 required to maintain adequate oxygen saturation of arterial blood (94–96%), compared with 100% oxygen.[9]

These animal data are supported by a clinical registry study including more than 6,000 patients. Based on the first documented arterial blood gas sample, post-resuscitation hyperoxaemia was associated with worse outcome compared with both normoxaemia and hypoxaemia.[10] However, another clinical registry study of over 12,000 patients that used the lowest PaO_2 value and controlled for more potential confounders (such as sickness severity) did not show a convincing association between hyperoxaemia and mortality.[11] Hypoxia was associated with increased mortality.

Based on these conflicting data, unnecessary arterial hyperoxia should be avoided, particularly during the initial post-cardiac arrest period, but only when arterial oxygenation can be monitored reliably, thereby avoiding the risk of hypoxaemia.

Glucose control

Hyperglycaemia is common after cardiac arrest. For non-diabetic patients, there is a U-shaped relationship between maximum and minimum blood glucose and hospital survival: both high and low glucose values are associated with decreased survival.[12] One study showed that tight blood glucose control (4.4–6.1 mmol/l) with insulin reduced hospital mortality rates in surgical ICU patients.[13] However, another study of over 6,000 ICU patients reported an increased 90-day mortality among those randomised to tight glucose control (4.5–6.0 mmol/l) compared with a target blood glucose of 10.0 mmol/l.[14] Severe hypoglycaemia (blood glucose <2.2 mmol/l) occurred in 6.8% of patients in the intensive-control group and 0.5% of the control group ($p<0.001$).

There is evidence that increased variability in glucose values also affects outcome adversely.[15] The current consensus is that following ROSC blood glucose should be maintained at 10 mmo/l or below and hypoglycaemia avoided.[5]

Targeted temperature management

Therapeutic hypothermia is now generally accepted as part of a standardised treatment for comatose survivors of cardiac arrest,[2,16] but its use is based mainly on evidence from one randomised trial and a pseudo-randomised trial.[2] These studies demonstrated improvement in neurological outcome after discharge from hospital in patients who had an out-of-hospital ventricular fibrillation cardiac arrest, who were still comatose (on arrival at hospital) and who were cooled to 32–34°C for 12–24 hours after ROSC.

The evidence for benefit of hypothermia after cardiac arrest from other rhythms or in a hospital setting is based mainly on observational studies with either historical or concurrent controls.[17,18] A recent French registry study documented no improvement in outcome when hypothermia was used following cardiac arrest from non-shockable rhythms (pulseless electrical activity or asystole).[19]

Some investigators remain concerned that the quality of the evidence supporting therapeutic hypothermia after cardiac arrest remains poor, and have embarked on a prospective trial comparing temperature control at 36°C versus 33°C after cardiac arrest from any rhythm.[20] Given that hypothermia cannot be assumed to benefit all post-cardiac arrest patients, the term 'targeted temperature management' has been deemed by some to be preferable to 'therapeutic hypothermia'.

Hypothermia can be induced easily and inexpensively with intravenous (iv) ice-cold fluids (30 ml/kg of saline 0.9% or Ringer's lactate) or traditional ice packs, placed in the groins, armpits and around the neck and head. By starting cooling pre-hospital, it is possible to achieve the target temperature more rapidly, which may maximise the neuroprotection provided by mild hypothermia. Nasopharyngeal cooling, achieved by instilling perfluorocarbon via nasal prongs, is a novel way of inducing hypothermia during cardiac arrest.[21] Initial cooling is facilitated by concomitant neuromuscular blockade, with sedation to prevent shivering. The use of magnesium may improve the efficiency of cooling because it is a vasodilator and reduces the shivering threshold. Surface or internal cooling devices can also be used alone or in combination with the above

Key points

The post-cardiac arrest syndrome comprises post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, the systemic ischaemia/reperfusion response, and persistent precipitating pathology

Primary percutaneous coronary intervention (PCI) is the preferred method for restoring coronary perfusion when cardiac arrest has been caused by ST-elevation myocardial infarction (STEMI); many cardiac arrest survivors with non-STEMI may also benefit from urgent coronary angiography and PCI

Targeted temperature management using mild hypothermia is now generally accepted as part of a treatment strategy for comatose survivors of cardiac arrest

Use of mild hypothermia makes prognostication difficult and unreliable

KEY WORDS: percutaneous coronary intervention, post-cardiac arrest syndrome, prognostication, therapeutic hypothermia

Table 1. Complications associated with therapeutic hypothermia. Adapted from reference 3 with permission from Wolters Kluwer.

Shivering	
Dysrhythmias	Bradycardia is the most common
Diuresis	May cause hypovolaemia and electrolyte abnormalities: • hypophosphataemia • hypokalaemia • hypomagnesaemia • hypocalcaemia
Decreased insulin sensitivity and insulin secretion	Hyperglycaemia
Impaired coagulation and increased bleeding	
Impairment of the immune system	Increased infection rates (eg pneumonia)
Hyperamylasaemia	
Reduced drug clearance	eg clearance of sedative drugs and neuromuscular blockers reduced by up to 30% at 34°C

measures to facilitate induction. The patient can be transferred to the angiography laboratory while cooling is maintained.[6]

In the maintenance phase, a cooling method with effective temperature monitoring that avoids temperature fluctuations is preferred. This is best achieved with external or internal cooling devices that include continuous temperature feedback to achieve a set target temperature.[22] Rewarming should be controlled at about 0.25ºC/hour.[23] The complications of therapeutic hypothermia are listed in Table 1.[23,24]

Prognostication

Predicting the eventual outcome of those remaining comatose after initial resuscitation from cardiac arrest remains extremely difficult.[25] All the well-established guidelines, such as those of the American Academy of Neurology,[26] were based on data generated before the widespread implementation of hypothermia. The use of hypothermia and the increased sedation often given with this therapy can delay recovery of motor reaction for 5–6 days after cardiac arrest. In recent studies, two of 14 patients who had been treated with hypothermia and had motor responses no better than extension at day 3 regained awareness,[27] and six comatose survivors of cardiac arrest similarly treated improved beyond vegetative state despite developing post-anoxic status epilepticus.[28]

Some experts now recommend a multimodal approach to prognostication. For example, the presence of at least two of four independent predictors reliably indicates a poor outcome (positive predictive value 1.0):[29]

- incomplete recovery of brainstem reflexes
- myoclonus
- an unreactive electroencephalogram (EEG)
- absent cortical somatosensory evoked potentials.

The major limitation to these recommendations is that in most hospitals it is often difficult or impossible to access some of these more sophisticated neurological investigations.

Cardiac arrest centres

There is considerable variation between hospitals in the outcomes of patients admitted to ICUs after cardiac arrest, with some evidence that mortality is lower among those admitted to ICUs that treat a high volume of post-cardiac arrest patients.[1] The need for 24/7 access to PCI facilities, competence in the use of targeted temperature management and availability of sophisticated neurological investigations implies that these patients might be treated optimally in specialist cardiac arrest centres.

Conclusions

Survivors from cardiac arrest develop a PCAS comprising:

- post-cardiac arrest brain injury
- post-cardiac arrest myocardial dysfunction
- the systemic ischaemia/reperfusion response
- any persistent precipitating pathology.

Post-resuscitation care treatment that includes targeted temperature management and primary PCI improves survival and neurological outcome in cardiac arrest survivors. Predicting outcome in comatose survivors of cardiac arrest who have been treated with mild hypothermia is challenging and may not be achievable with acceptable reliability until at least 5–6 days after cardiac arrest.

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