

Chapter

1

# Cardiac Arrest: Post Resuscitation Management

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## Introduction

Every year in the United Kingdom (UK) approximately 50,000 people suffer an out-of-hospital cardiac arrest (OHCA). Historically, of these arrests, only approximately 6,250 people are admitted to UK intensive care units (ICU) for post cardiac arrest care. Despite improving resuscitation practices, mortality for those who suffer an OHCA is greater than 90 percent, with many survivors being left with severe neurological impairment. However, in the last few years, there has been a major change in the way OHCA's are managed with signs of improved overall mortality and morbidity. This case will summarise the latest advances in OHCA care.

## Case

A 58-year-old man was admitted to Accident and Emergency after sustaining an OHCA. He had collapsed at home in front of his wife, who performed cardiopulmonary resuscitation immediately after calling for an ambulance. It took five minutes for the paramedic rapid response car to arrive, at which point the rhythm was noted to be ventricular fibrillation (VF). He required two biphasic DC shocks and 1 dose of 1 mg of adrenaline to restore circulation. His estimated downtime prior to return of spontaneous circulation (ROSC) was a total of 12 minutes. He was intubated on the scene by the paramedics. On arrival in hospital, 20 minutes later, he was making agonal gasping respirations which were being assisted with manual ventilation. He was maintaining a blood pressure of 135/60 mmHg with a pulse rate of 95 bpm, confirmed to be sinus rhythm on cardiac monitoring. A 12 lead electrocardiogram (ECG) revealed significant ST elevation in the anterior chest leads. He was deeply unconscious with a Glasgow Coma Scale of 3 out of 15.

No exclusions to targeted temperature management were present and this was commenced shortly after arrival to the emergency department, using cold intravenous fluids and application of a cooling helmet and vest. Sedation was maintained with propofol and alfentanil. Given the history and ECG findings, a computerised tomography (CT) scan of the head was not performed, as a neurological cause for the arrest was not suspected.

Cardiology review was urgently sought and he was subsequently transferred to the cardiac angiography suite. It was discovered that his proximal left anterior descending coronary artery was blocked and this was stented with excellent results. He was transferred to ICU, where he completed 24 hours of targeted temperature management, with a core body temperature maintained between 32 and 36°C.

Following slow passive rewarming of no greater than 0.5°C per hour, there was no recovery of consciousness with a persistent GCS of 3/15. At 72 hours post arrest, an

electroencephalogram (EEG) showed burst suppression. Subsequent somatosensory evoked potentials (SSEP) revealed bilateral absence at the N20 level. Following discussion with the family, active therapy was withdrawn as the neurological prognosis was considered hopeless.

## Discussion

ROSC is just the preliminary step in attaining complete recovery after cardiac arrest. Of those subsequently admitted to ICU, as many as 40–50 percent survive to hospital discharge, often with good neurological outcome, although many will have subtle cognitive impairments that are not immediately obvious on ICU discharge.

Complex pathophysiological processes occur during the cardiac arrest when the body is in an ischaemic (limited blood flow) state, and after ROSC when there is increased cellular activity due to reperfusion. These processes have been termed the post-cardiac arrest syndrome. The syndrome comprises: the precipitating pathology which may still persist; post-cardiac arrest brain injury; post-cardiac arrest myocardial dysfunction; and the systemic ischaemia/ reperfusion response. The severity of the syndrome is extremely variable depending on length and cause of cardiac arrest. Some patients have a very brief post-cardiac arrest syndrome and regain consciousness rapidly. Others manifest, in the first few days, signs of cardiac failure and multi-organ failure, which has many features in common with sepsis and confers significant risk of mortality. The remainder exhibit varying degrees of neurological dysfunction (seizures, myoclonus, cognitive memory impairments, coma, cortical brain death and brainstem death). Prognosticated bad neurological outcome often leads to withdrawal of active life sustaining therapy (WLST) and is consequently a late cause of death in patients.

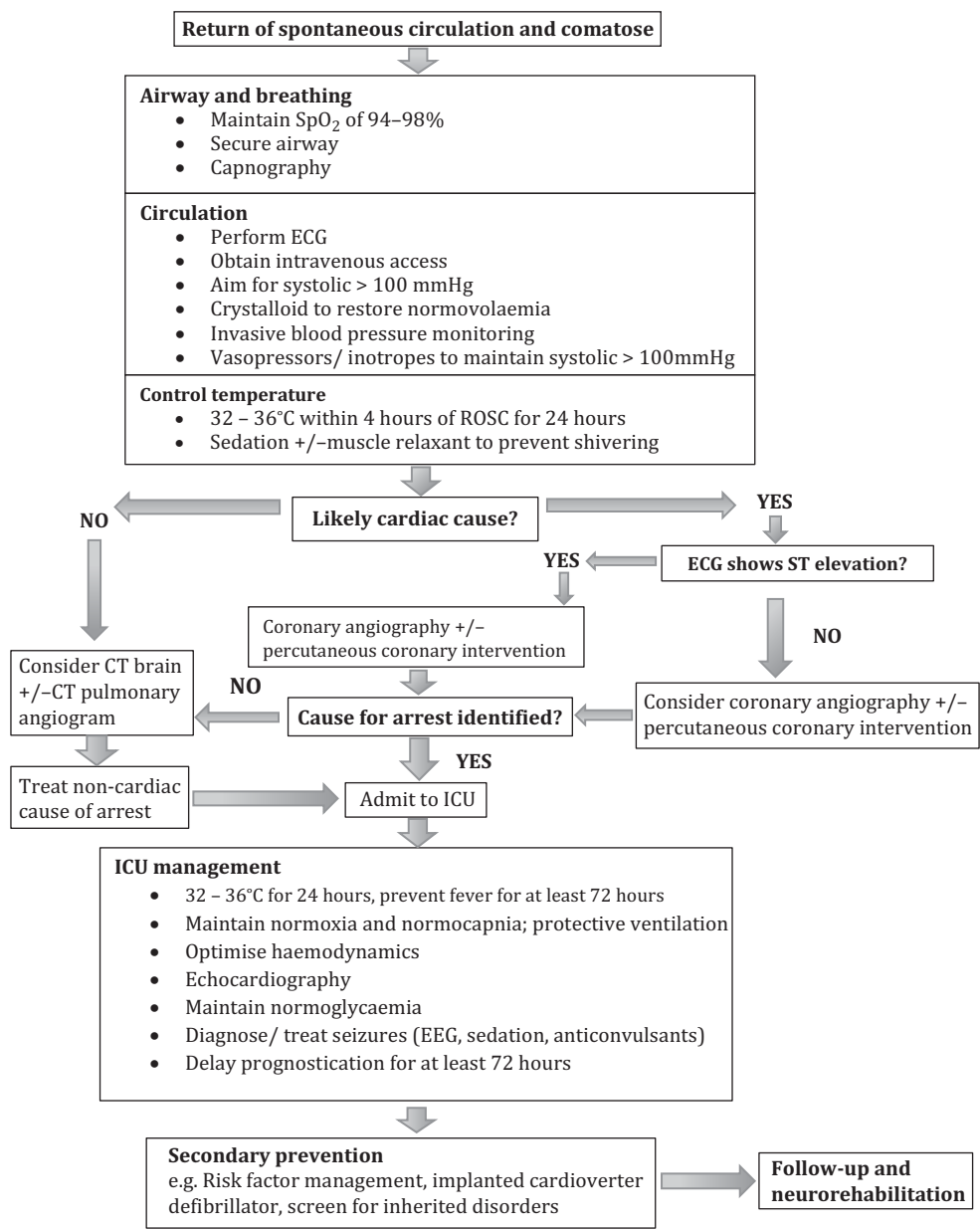
Post-cardiac arrest comatose patients have multiple treatment requirements which often need to be instigated at the scene of ROSC outside the ICU. All hospitals should follow a post-resuscitation care algorithm similar to the one outlined in Figure 1.1.

The specific requirements for targeted temperature management, coronary angiography, mechanical support and neurological prognostication will be discussed in more detail below.

## Targeted Temperature Management

Following the publication of two landmark papers in 2002, therapeutic hypothermia (32 to 34°C) became the treatment of choice for comatose patients following OHCA when the underlying rhythm was VF.<sup>[1,2]</sup> The study by Bernard et al. involved 4 Australian centres and enrolled 77 patients; the European study recruited in 9 centres across 5 European countries and enrolled 275 patients. The Australian study used alternate day randomisation, a technique which is subject to operator bias. In the European group, the control group who received normothermia actually became hyperthermia, so the perceived benefit from hypothermia may have been biased by the potential harm caused by hyperthermia. An additional criticism of both studies is that the clinicians could not be blinded to the separate treatment arms. Despite this, widespread adoption of therapeutic hypothermia occurred within the critical care community after publication of the trials.

The mechanism of the action of cooling is thought to suppress many of the pathways leading to cell death. Hypothermia decreases the cerebral metabolic rate for oxygen by



**Figure 1.1** Post-resuscitation care algorithm.<sup>[12]</sup>

approximately 6 per cent for every 1°C drop in core temperature and this may reduce the inflammatory cytokine response associated with the post-cardiac arrest syndrome.

The use of therapeutic hypothermia in non-VF arrests (i.e., asystole and pulseless electrical activity (PEA)) and in hospital cardiac arrests has remained more contentious. However in 2010, the International Liaison Committee on Resuscitation (ILCOR),

although accepting of the lower evidence strength, advocated the use of therapeutic hypothermia in comatose patients following both ‘shockable – VF/VT’ and ‘non-shockable – PEA/ Asystole’ cardiac arrests.<sup>[3]</sup>

The publication of the ‘Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest’ (TTM) study looked at 950 all rhythm OHCA patients. The study showed no difference in survival and neurological outcome between those cooled to 33°C and those cooled to 36°C.<sup>[4]</sup> While the implications of this are still to be fully realised, the term *targeted temperature management* or *temperature control* is now preferred over the previous term *therapeutic hypothermia*. The optimal duration of targeted temperature management is unknown, but a period of 24 hours is most commonly chosen.

ILCOR has subsequently produced new guidelines in 2015 which now recommend maintaining a constant target temperature between 32 to 36°C for those patients in whom temperature control is used. TTM is recommended for adults after OHCA with an initial shockable rhythm who remain unresponsive after ROSC (strong recommendation, low quality evidence). However, TTM is suggested in adults after OHCA with an initial non-shockable rhythm and in adults after in hospital cardiac arrests with any initial rhythm (weak recommendation, very low quality evidence). Whether or not certain subpopulations of cardiac arrest patients may benefit from lower or higher temperatures remains unknown; further research is required.

At present, it is unclear what target temperature individual centres will choose to adopt. There is concern that controlling temperature at 36°C will run the risk of temperature overshoot, leading to hyperthermia, which is known to be deleterious. It is likely that most centres will aim for a target temperature of 32 to 36°C for 24 hours post-ROSC in the first instance. However, if there are contra-indications to cooling e.g., arrhythmias, pre-existing medical coagulopathy (fibrinolytic therapy is not a contra-indication), electrolyte disturbance or sepsis, or direct complications that occur due to cooling at 32 to 36°C, then it is probable controlled normothermia will be attained. Hyperthermia must be meticulously avoided for 72 hours following the arrest and cooling devices may be required to achieve this. Rebound hyperthermia is common after targeted temperature management and can be difficult to control.

In this case, it was felt that a VF arrest with cardiac aetiology gave a strong indication to cool. It is very important after the cooling period not to increase the temperature too quickly. Passive rewarming at between 0.25 to 0.5°C per hour is recommended to avoid rebound hyperthermia, vasodilatation and hypotension which can lead to coronary ischaemia and deleterious effects on the heart.

## Coronary Angiography

Should we perform coronary angiography and intervention following successful resuscitation after cardiac arrest?

At present we have no trials to answer this question. The large trials looking at coronary angiography following ST elevation myocardial infarction (STEMI) specifically exclude post-cardiac arrest patients. However, case series of patients post arrest with STEMIs show 60% survival to hospital discharge thus indicating that these patients could benefit from urgent angiography.<sup>[5]</sup> In the non-STEMI population approximately 25% have acute coronary lesions.<sup>[6]</sup> It would appear that the post-cardiac arrest ECG does not accurately predict the presence, or more importantly the absence, of occluded coronary arteries.

This has led the 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations to state:

*It is reasonable to perform early angiography and primary percutaneous coronary intervention in selected patients despite the absence of ST-segment elevation on the ECG or prior clinical findings, such as chest pain, if coronary ischaemia is considered the likely cause on clinical grounds.<sup>[5]</sup>*

Therapeutic hypothermia does not preclude the use of urgent coronary intervention.

The European Association for Percutaneous Cardiovascular Interventions (EAPCI) has also recently produced a consensus statement that states coronary angiography should be immediately performed in the presence of ST elevation on an ECG in OHCA patients and considered within two hours in other patients in the absence of a non-coronary cause, particularly if there is haemodynamic instability.

It would therefore seem reasonable to perform urgent coronary angiography in OHCA patients where a cardiac cause is suspected.

Mechanical Support

The recent clinical IABP-Shock II trial of the intra-aortic balloon pump (IABP) in cardiogenic shock from acute myocardial infarction has shown that the insertion of this device does not lead to an improvement in 30 day mortality.<sup>[7]</sup> In this trial, the mortality for those in whom an IABP was inserted is 39.7% and 41.3% in the control group managed conventionally, giving a P value of 0.69. Extrapolating this data to post-cardiac arrest patients may be difficult as reversible myocardial stunning could be contributing to the cardiogenic failure. In patients with post-cardiac arrest myocardial stunning, IABP can be considered as rescue therapy but it may be unlikely to improve overall outcome.

Neurological Prognostication

Predicting the neurological outcome in a comatose cardiac arrest survivor can be very difficult. It is important that poor outcome is clearly defined. The majority of studies use Cerebral Performance Category (CPC) grades of 3 or more as poor outcome (see Table 1.1).

Multiple modalities are now used to aid this prognostication: clinical; electrophysiological; radiological and biochemical (see Table 1.2).

Table 1.1 Cerebral performance categories (CPC) and outcome class

| CPC                              | Activity level                                                                                                               | Outcome class |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------|---------------|
| 1 – Good cerebral performance    | Conscious. Can lead normal life and work. May have minor deficits.                                                           | Good          |
| 2 – Moderate cerebral disability | Conscious. Cerebral function adequate for part-time work in sheltered environment or independent activities of daily living. | Good          |
| 3 – Severe cerebral disability   | Conscious. Dependent on others for daily support because of neurological deficit.                                            | Poor          |
| 4 – Coma, vegetative state       | Not conscious. No interaction with environment.                                                                              | Poor          |
| 5 – Dead                         | Brainstem dead or dead by conventional criteria                                                                              | Poor          |

**Table 1.2** Prognostic factors false positive rate (FPR) in comatose survivors 72 hours post arrest, unless stated, by application of targeted temperature management (TTM) post arrest. 24 to 72 hours post arrest

| Prognostic factor            | FPR - No TTM | FPR - TTM |
|------------------------------|--------------|-----------|
| Corneal reflexes             | 0            | 0.05      |
| Pupillary reflexes           | 0            | 0.04      |
| Motor score M1 or M2         | 0            | 0.05      |
| Myoclonic status (<72 hours) | 0            | 0.05      |
| Serum NSE >33 mcg/ml         | 0.09         | 0.12      |
| Unfavourable EEG             | 0.03         | 0.10      |
| Bilateral absence N20 SSEP   | 0.07         | 0.06      |

In the pre-targeted temperature era, the following clinical signs predicted poor neurological signs with a false positive rate (FPR) of zero, if present 72 hours post-cardiac arrest: absent pupillary or corneal reflexes and extensor or absent motor reflex.<sup>[8,9]</sup> Myoclonic status from 24 hours onwards, in patients who have not suffered cardiac arrest secondary to respiratory causes and who have not been cooled, has been associated with a hopeless neurological prognosis.<sup>[9]</sup> However, caution in diagnosis is essential as this condition closely mimics Lance–Adams syndrome, a voluntary myoclonic syndrome, which has a good prognosis.<sup>[10]</sup> There are many other case reports that describe early onset of prolonged and generalised myoclonus which disappears on sedation holds and subsequent recovery of consciousness. If any diagnostic uncertainty is present, expert neurological opinion should be considered.

In the targeted temperature era, no clinical signs are associated with a FPR of zero. After 72 hours, pupillary reflex has the lowest FPR of 0.04, followed by corneal reflex and absent or extensor motor reflex with a FPR of 0.05. Myoclonic status after day 1 has a FPR of 0.05 after TTM.<sup>[11]</sup>

Clinical examination is inexpensive and easy to perform but can lead to bias and variability in interpretation of findings which can potentially influence management and lead to a self-fulfilling prophecy. Using clinical signs as the sole method of prognostication cannot be recommended.

Unfavourable EEG results are defined as any of the following patterns: generalised suppression; burst suppression; status epilepticus; suppression or unreactive pattern. These patterns are invariably associated with a poor outcome with a FPR of 0.1 following TTM 72 hours after the arrest.<sup>[11]</sup> EEG requires expert interpretation, which may limit availability in many hospitals.

SSEP involves monitoring brain response to electrical stimulation of peripheral nerves and specifically looks at cerebral cortical function. At time zero the median nerve is stimulated, responses are looked for at 9 to 10 ms at the brachial plexus (N9/10), 13 ms at the dorsal nerve root (N13), and 20 ms (N20) at the somatosensory cortex. Bilateral loss of the N20 response indicates cortical cell death, assuming response is seen at both the N9/10 and N13 points indicating intact peripheral nerves.

In the pre-TTM era, bilateral absence of SSEP was associated with a FPR of 0.07 up to 72 hours post-cardiac arrest. With the introduction of TTM, bilateral absence of SSEP is associated with a FPR of 0.06, 72 hours post-cardiac arrest.<sup>[11]</sup> SSEP has been adopted in some large treatment centres and is a useful test in establishing cerebral cortical death. SSEP is frequently a criterion investigation for deciding on WLST however, it requires expert

interpretation and is prone to artefact (electrical interference from muscle artefacts or the ICU environment).

Radiological techniques are useful to exclude intracerebral catastrophe in the early stages. However, as a prognostication tool, radiological findings are not reliable enough to predict neurological outcome in the early stages. The radiological CT finding of loss of grey white matter differentiation is commonly seen immediately after ROSC and is not reliable enough to prognosticate with in the initial stages. Extreme caution must be exhibited in interpretation of the initial head CT immediately after ROSC. However, CT becomes more beneficial as a prognostic tool a few days after ROSC. The grey-white matter interface can be quantitatively measured as a ratio between grey matter and white matter (GWR). The GWR threshold for prediction of poor outcome with FPR of zero ranged between 1.10 and 1.22 but the methods for GWR calculation were inconsistent amongst studies.<sup>[12]</sup>

MRI changes after global anoxic ischaemic injury due to cardiac arrest appear as hyperintensity signals in cortical areas or basal ganglia on diffusion weighted imaging sequences. MRI is more sensitive in identifying ischaemic brain injury compared with CT and often reveals extensive abnormalities when SSEP is normal. MRI is a potentially useful investigation 4 to 5 days after ROSC but is a more lengthy procedure than CT which often precludes use in haemodynamically unstable patients.<sup>[12]</sup>

Raised levels of an enzyme neurone specific enolase (NSE) have been used as a predictor of poor neurological outcome. Levels greater than 33 mcg/l following cardiac arrest are associated with poor neurological outcome with a false positive rate of 0.12.<sup>[11]</sup> However, the NSE thresholds vary in TTM treated and non-TTM treated patients. The measurement techniques are extremely heterogeneous due to variation among different analysers and an incomplete understanding of the kinetics of NSE blood concentration in the first few days after ROSC. NSE measurement is still not commonly used in clinical practice and is largely confined to the research setting.

Various algorithms for neurological prognostication exist, but some of the investigations are expensive and require expert interpretation which leads to variable uptake. This, in addition to the increasing requirement for coronary angiography and the need for implanted cardiac defibrillators after subsequent survival from cardiac arrest, has led to the view that post-cardiac arrest care should be regionalised in a similar manner to care for major trauma. Whether this centralisation of care will occur in the future remains to be seen.

## Conclusion

Cardiac arrest is a potentially devastating condition with overall poor survival. In patients in whom there is ROSC, various treatment strategies including targeted temperature management and early revascularisation can be used which may improve physiological survival.

Neurological prognostication has become less certain in the targeted temperature era with a requirement of ideally 72 hours post-ROSC to elapse before prognostication can reliably be attempted. Neurological prognostication immediately after cardiac arrest is unreliable and cannot be recommended as a reason not to admit a patient to critical care. All escalation decisions should be based purely on pre-morbidity and frailty assessment. Neurological prognostication becomes clearer in the ensuing days after the cardiac arrest.

## Key Learning Points

- Targeted temperature management (target of 36°C) is at least as effective as therapeutic hypothermia. The ILCOR guidelines in 2015 recommend to maintain a temperature

between 32 to 36°C. Active normothermia for 72 hours and avoidance of hyperthermia is very important.

- Consideration should be given to performing coronary angiography and intervention in patients in whom a cardiac cause is suspected regardless of ECG findings.
- Mechanical support with IABP does not improve cardiogenic shock survival in patients with acute myocardial infarction. The role of post-cardiac arrest is unclear; however it is likely to have a role in rescue therapy.
- No clinical or electrophysiological markers predict poor neurological outcome with a false positive rate of zero following targeted temperature management.
- A period of 72 hours should elapse post-cardiac arrest before prognostication is attempted in the targeted-temperature managed patient, unless there is clinical evidence of brainstem death.

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