The Post-cardiac Arrest Syndrome

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Introduction

Survival rates following in- and out-of-hospital cardiac arrest remain disappointingly low [1–3] but there is good evidence that interventions applied after return of spontaneous circulation influence significantly the chances of survival with good neurological outcome [4]. Among those patients admitted to an intensive care unit (ICU) after cardiac arrest, approximately two thirds will not survive to be discharged from hospital [5, 6], but there is considerable variation in post-cardiac arrest treatment and patient outcome between institutions [6, 7]. The prolonged period of systemic ischemia during cardiac arrest and the subsequent reperfusion response that occurs after return of spontaneous circulation results in a complex combination of pathophysiological processes that have been termed recently the post-cardiac arrest syndrome [8]. The components of post-cardiac arrest syndrome comprise post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology. A recent scientific statement from the International Liaison Committee on Resuscitation (ILCOR) and several other organizations provides comprehensive information about the epidemiology, pathophysiology, treatment, and prognostication of the post-cardiac arrest syndrome [8]. This chapter will highlight the main messages to come from this scientific statement.

Phases of the Post-cardiac Arrest Syndrome

The post-cardiac arrest period can be divided into four phases (**Fig. 1**) [8]. The immediate post-arrest phase is defined as the first 20 minutes after return of spontaneous circulation. This phase will be influenced by interventions that are typically applied at the site of the initial collapse. The early post-arrest phase is between 20 minutes and 6 to 12 hours after return of spontaneous circulation; early interventions applied during transport, in the emergency department and in the ICU will impact this phase. The intermediate phase is between 6 to 12 hours and 72 hours when injury pathways are still active and may be influenced by further treatment in the ICU. Finally, the recovery phase is the period beyond 3 days – this is when prognostication becomes more reliable.

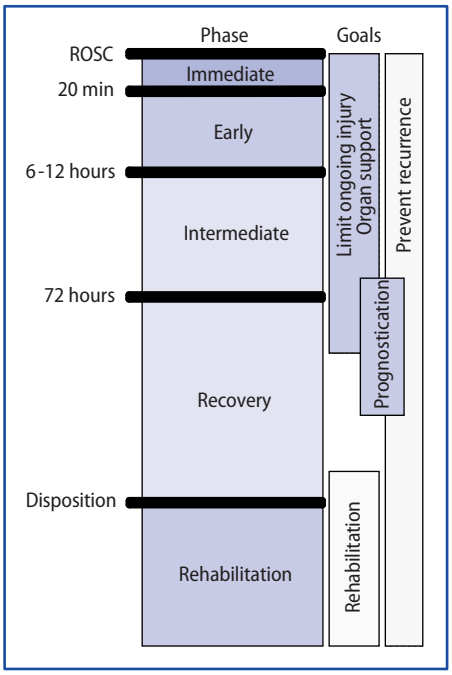

Fig. 1. Phases of post-cardiac arrest syndrome. ROSC = return of spontaneous circulation. From [8] with permission.

Pathophysiology of Post-cardiac Arrest Syndrome

The severity of the post-cardiac arrest syndrome will vary depending on the severity of the ischemic insult, the cause of cardiac arrest, and the patient's pre-arrest state of health. The post–cardiac arrest syndrome is unlikely to occur if return of spontaneous circulation is achieved rapidly.

Post-cardiac Arrest Brain Injury

Of those patients who survive to ICU admission but who die later in hospital, brain injury is the cause of death in approximately two thirds of cases after out-of hospital cardiac arrest and in about a quarter of cases after in-hospital cardiac arrest [9]. The pathophysiological processes leading to brain injury in these circumstances are complex and include excitotoxicity, disrupted calcium homeostasis, free radical formation, pathological protease cascades, and activation of cell death signaling pathways [10]. Many of these processes occur over hours to days after return of spontaneous circulation, which provides a reasonable window for potential treatment. Intravascular thrombosis may occur during prolonged cardiac arrest and, after return of spontaneous circulation, can impair cerebral microcirculatory reperfusion despite adequate cerebral perfusion pressure (CPP) [11]. This provides part of the rationale for the use of thrombolytic therapy during cardiac arrest [12]. Although there is cerebral microcirculatory failure, elevated CPP and impaired cerebrovascular autoregulation may result in high cerebral blood flow (CBF) soon after return of spontaneous circulation [13]; this may result in transient brain edema, especially after asphyxial cardiac arrest, but it is rarely associated with clinically relevant increases in intracra-

nial pressure (ICP). The CPP necessary to maintain optimal cerebral perfusion will vary among individual post-cardiac arrest patients and with the interval after return of spontaneous circulation.

Pyrexia [14], seizures [15], and hyperglycemia [16] are all associated with worse neurological outcome among post-cardiac arrest patients.

Post-cardiac Arrest Myocardial Dysfunction

Post–cardiac arrest global myocardial dysfunction is common but is often responsive to therapy and reversible [17]. In one series of 148 patients who survived out-of-hospital cardiac arrest, cardiac index was lowest at 8 hours after resuscitation and returned to normal by 72 hours [17].

Systemic Ischemia/reperfusion Response

With the onset of cardiac arrest, the delivery of oxygen and metabolic substrates and the removal of metabolites cease. Cardiopulmonary resuscitation (CPR) only partially reverses this process, achieving cardiac output and oxygen delivery that is much less than normal. The whole body ischemia/reperfusion of cardiac arrest followed by return of spontaneous circulation activates immunological and coagulation pathways causing a systemic inflammatory response syndrome (SIRS) that resembles sepsis [18, 19]. Activation of blood coagulation without adequate activation of endogenous fibrinolysis causes widespread microvascular thrombosis [20].

Persistent Precipitating Pathology

The pathophysiology of the post–cardiac arrest syndrome may be complicated by the presence of precipitating pathologies such as acute coronary syndrome (ACS), pulmonary diseases, hemorrhage and sepsis. Acute myocardial infarction is documented in approximately 50 % of adult out-of-hospital cardiac arrest patients and in many cases there is no history of chest pain and ST-segment elevation is absent [4, 21]. Pulmonary emboli have been reported in 2 % to 10 % of sudden deaths [3, 22]. The incidence of pulmonary embolism among patients who achieve return of spontaneous circulation after cardiac arrest is unknown. Multiple organ failure is a more common cause of death in the ICU after initial resuscitation from in-hospital cardiac arrest than after out-of-hospital cardiac arrest. This may reflect the greater contribution of infections to cardiac arrest in the hospital [9].

Treatment of the Post-cardiac Arrest Syndrome

Treatment of the post–cardiac arrest patient will involve several specialties. Some of these patients will have a prolonged ICU stay and require multiple organ support. There is some evidence that a coordinated multimodal approach improves outcome when compared with historical controls [4]. A post-cardiac arrest ICU care bundle has been proposed and comprises: Early coronary reperfusion and hemodynamic optimization; control of ventilation; blood glucose control; temperature control; and treatment of seizures [23].

Airway and Ventilation

There are no data supporting precise indications for intubation, ventilation, and sedation after cardiac arrest. Although cerebral autoregulation is either absent or altered in most patients in the acute phase after cardiac arrest [13], cerebrovascular reactivity to changes in arterial carbon dioxide tension is preserved [24]. Extrapolation from studies of brain-injured patients indicating that hyperventilation induces cerebral ischemia implies that ventilation to normocarbia is probably optimal.

Adequate oxygen delivery is essential, but animal data indicate that too much oxygen during the initial stages of reperfusion can exacerbate neuronal damage through production of free radicals and mitochondrial injury [25]. Animal studies have demonstrated neurological benefits of controlled reoxygenation during the initial phases of resuscitation by ventilating with the minimum FiO_2 required to maintain adequate oxygen saturation of arterial blood (SaO_2 94–96 %) [26]. Based on these data, avoid unnecessary arterial hyperoxia, particularly during the initial post-cardiac arrest period. This can be achieved by adjusting the FiO_2 to produce an SaO_2 of 94–96 %. Controlled reoxygenation has yet to be studied in randomized prospective clinical trials. The British Thoracic Society has recently published guidelines for emergency oxygen use in adult patients [27]. These recommend a target SaO_2 of 94–98 % for those critically ill patients not at risk of hypercapnic respiratory failure.

Circulation

In one review, acute changes in coronary plaque morphology were found in 40 to 86 % of cardiac arrest survivors and in 15 to 64 % of autopsy studies [28]. Several case series and studies with historical controls document the feasibility and success of early percutaneous coronary intervention (PCI) after out-of-hospital cardiac arrest [4, 21, 29]. Patients resuscitated from cardiac arrest and who have electrocardiogram (EKG) criteria for ST-segment elevation myocardial infarction (STEMI) should undergo immediate coronary angiography with subsequent PCI if indicated. Given the high incidence of ACS in patients with out-of-hospital cardiac arrest and limitations of EKG-based diagnosis, it is appropriate to consider immediate coronary angiography in all post–cardiac arrest patients in whom ACS is suspected. In the absence of a PCI facility, thrombolytic therapy is an appropriate alternative for post-cardiac arrest management of STEMI.

Following return of spontaneous circulation, myocardial dysfunction, hypovolemia and impaired vasoregulation commonly result in hemodynamic instability in the form of dysrhythmias, hypotension, and low cardiac index [17]. These patients will frequently require surprisingly large volumes of fluid (e.g., 3.5 – 6.5 l of crystalloid) to maintain adequate right-heart filling pressures [4, 17]. Myocardial dysfunction after return of spontaneous circulation is common but is generally reversible and responsive to inotropes [17, 18]. Early echocardiography will enable the extent of myocardial dysfunction to be quantified and may guide therapy. Impaired vasoregulation may occur for up to 72 hours after cardiac arrest [17]. Treatment with an inotrope and/or vasopressor may be guided by blood pressure, heart rate, plasma lactate concentration, urine output and central venous oxygen saturation ($ScvO_2$). Although a pulmonary artery catheter (PAC) or non-invasive cardiac output monitoring will enable treatment to be guided by cardiac index and systemic vascular resistance there is no evidence that use of these monitors improves outcome after cardiac arrest. If fluid resuscitation combined with inotropes and/or vasopressors

does not restore adequate organ perfusion, insertion of an intra-aortic balloon pump (IABP) may be beneficial [4].

Relative adrenal insufficiency occurs frequently after successful resuscitation of out-of-hospital cardiac arrest and is associated with increased mortality [30] but there is no evidence that treatment with steroids in the post–cardiac arrest phase improves long-term outcomes.

Early goal-directed therapy is established for sepsis [31], but there are few data to support this strategy in post–cardiac arrest syndrome. The optimal mean arterial pressure (MAP) for post-cardiac arrest patients is unknown. Loss of cerebral autoregulation implies the need for an adequate perfusion pressure to ensure optimal cerebral blood flow but a high MAP will increase myocardial afterload. On the basis of the limited available evidence, reasonable goals for post–cardiac arrest syndrome include a MAP of 65 – 100 mm Hg (taking into consideration the patient's normal blood pressure, cause of arrest, and severity of any myocardial dysfunction), central venous pressure (CVP) 8 – 12 mm Hg, $ScvO_2$ > 70 %, urine output > 1 ml/kg/h and a normal or decreasing serum or blood lactate value. The optimum hemoglobin concentration during post-cardiac arrest has not been defined.

Disability (optimizing neurological recovery)

Interventions in the post-cardiac arrest period that may determine the final neurological outcome include control of cerebral perfusion, control of seizures, control of plasma glucose concentration, and control of temperature. Maintenance of an adequate CPP has been discussed above.

Control of seizures

Seizures and/or myoclonus occur in 5 to 15 % of adult patients who achieve return of spontaneous circulation and 10 to 40 % of those who remain comatose [15, 32]. Seizures increase cerebral metabolism by up to 3-fold and should be treated promptly and effectively with benzodiazepines, phenytoin, sodium valproate, propofol, or a barbiturate. Clonazepam is the drug of choice for the treatment of myoclonus, but sodium valproate and levetiracetam may also be effective.

Glucose Control

Hyperglycemia is common after cardiac arrest. Although one study has shown that tight control of blood glucose (4.4 to 6.1 mmol/l or 80 to 110 mg/dl) with insulin reduced hospital mortality rates in a surgical ICU [33], recent studies indicate that post–cardiac arrest patients may be treated optimally with a slightly higher target range for blood glucose concentration of up to 8 mmol/l (144 mg/dl) [4, 34, 35]. The lower value of 6.1 mmol/l may not reduce mortality any further but instead may expose patients to the potentially harmful effects of hypoglycemia. Glucose control may be particularly beneficial for those patients staying in the ICU for at least 3 days [36]; the median length of ICU stay for post-cardiac arrest patients is approximately 3.4 days [4, 5]. Regardless of the chosen glucose target range, blood glucose must be measured frequently [4, 34], especially when insulin is started and during cooling and rewarming periods.

Temperature control

Therapeutic hypothermia is considered widely as part of a standardized treatment strategy for comatose survivors of cardiac arrest [4, 37, 38]. Two randomized clinical

trials showed improved outcome in adults who remained comatose after initial resuscitation from out-of-hospital ventricular fibrillation (VF) cardiac arrest and who were cooled within minutes to hours after return of spontaneous circulation [39, 40]. Patients in these studies were cooled to 33 °C or the range of 32 °C to 34 °C for 12 to 24 hours. Four studies with historical control groups reported benefit after therapeutic hypothermia in comatose survivors of out-of-hospital non-VF arrest and all rhythm arrests [8]. Other observational studies provide evidence for possible benefit after cardiac arrest from other initial rhythms and in other settings [41]. Which patients may benefit most from mild hypothermia has not been fully elucidated, and the ideal induction technique, target temperature, duration, and rewarming rate have not been determined. There is some clinical evidence that a shorter time to achieve target temperature is associated with a better neurological outcome [42].

Hypothermia can be induced easily with intravenous ice-cold fluids (30 ml/kg of 0.9 % saline or Ringer's lactate) [43] or placing ice packs on the groin and armpits and around the neck and head. Initial cooling is facilitated by concomitant neuromuscular blockade with sedation to prevent shivering. Magnesium sulfate reduces shivering threshold and can be given (5 g infused over 5 h) to reduce shivering during cooling. As it is a vasodilator, magnesium sulfate increases cooling and has antiarrhythmic properties. Patients can be transferred to the angiography laboratory while being cooled [4]. Hypothermia is best maintained with external or internal cooling devices that include continuous temperature feedback to achieve a target temperature. External devices include cooling blankets or pads with water-filled circulating systems or more advanced systems in which cold air is circulated through a tent. Intravascular cooling catheters are usually inserted into a femoral or subclavian vein. Less sophisticated methods, such as cold wet blankets and ice packs can also be used to maintain hypothermia but these methods may be more time consuming for nursing staff, result in greater temperature fluctuations, and do not enable controlled rewarming [44]. The optimal rate of rewarming is not known, but current consensus is to rewarm at about 0.25 °C to 0.5 °C per hour [41]. Therapeutic hypothermia is associated with several complications (**Table 1**); metabolic rate,

Table 1. Complications associated with therapeutic hypothermia

Shivering – particularly during the induction phase	
Increased systemic vascular resistance	
Dysrhythmias – bradycardia is the most common	
Diuresis – may cause hypovolemia and electrolyte abnormalities	
Electrolyte abnormalities:	hypophosphatemia hypokalemia hypomagnesemia hypocalcemia
Decreased insulin sensitivity and insulin secretion – hyperglycemia	
Impaired coagulation and increased bleeding	
Impairment of the immune system – increased infection rates, e.g., pneumonia	
Hyperamylasemia	
Reduced drug clearance	e.g., clearance of sedative drugs and neuromuscular blockers is reduced by up to 30 % at a temperature of 34ºC

plasma electrolyte concentrations, and hemodynamic conditions may change rapidly during both the cooling and rewarming phases.

If therapeutic hypothermia is not indicated, prevention of pyrexia is critically important. Pyrexia is common in the first 48 hours after cardiac arrest [45] and the risk of a poor neurological outcome increases for each degree of body temperature > 37 °C [14].

Post-cardiac Arrest Prognostication

Although several recent systematic reviews have evaluated predictors of poor outcome in those remaining comatose after cardiac arrest [46–48] prognostication of futility remains controversial. The situation has been compounded by the introduction of therapeutic hypothermia – there are few data on its impact on the accuracy of prognostication. The ILCOR Scientific Statement on the Post-Cardiac Arrest Syndrome summarizes most of the available data on prognostication but some of the salient points on this topic are:

- Prognosis cannot be based on the circumstances surrounding cardiac arrest and CPR.
- The reliability of all prognosticating tools is dependent on when they are applied after cardiac arrest
- Neurologic exam does not reliably prognosticate futility in the first 24 hours after return of spontaneous circulation.
- Absence of pupillary light response, corneal reflex, or motor response to painful stimuli at day 3 after return of spontaneous circulation provide the most reliable predictors of poor outcome (vegetative state or death) [32, 46, 48].
- In the comatose patient after a primary cardiac arrest, myoclonic status epilepticus reliably predicts a poor outcome [46], but it may be misdiagnosed by non-neurologists.
- Burst suppression or generalized epileptiform discharges on the electroencephalogram (EEG) predict poor outcome but this is too imprecise for use in individual cases.
- Bilateral absence of the N20 component of the somatosensory evoked potential with median nerve stimulation recorded on days 1–3 or later accurately predicts a poor outcome [46–48].
- There are too few data to determine the value of radiological investigations in predicting outcome in comatose post-cardiac arrest patients.
- Until more is known about the impact of therapeutic hypothermia, prognostication should probably be delayed but the optimal time for this has yet to be determined.

Organ Donation

The reported incidence of patients with clinical brain death following sustained return of spontaneous circulation after cardiac arrest ranges from 8 to 16 % [49, 50]. These patients can be considered for organ donation. A number of studies have reported no difference in transplant outcomes when the organs were obtained from appropriately selected post–cardiac arrest patients or from other brain-dead donors [50]. The proportion of cardiac arrest patients dying in the critical care unit and who might be suitable non-heart-beating donors has not been documented.

Conclusion

A recent scientific statement has outlined the pathophysiology, treatment, and prognosis of patients who regain spontaneous circulation after cardiac arrest. The components of post-cardiac arrest syndrome comprise post-cardiac arrest brain injury, post-cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology. Treatment may include prolonged multiple-organ support as well as time-critical input from specialists from several disciplines. Historically, about one third of post-cardiac arrest patients admitted to the ICU survive to be discharged from hospital. Studies utilizing therapeutic hypothermia and optimized post-cardiac arrest care suggest that 50 % survival with good neurologic outcome is an achievable goal.

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