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ILCOR CONSENSUS STATEMENT

Post-cardiac arrest syndrome: Epidemiology, pathophysiology, treatment, and prognostication A Scientific Statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke☆,☆☆,*

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KEYWORDS
Post-cardiac arrest syndrome;

Summary
Aim of the review: To review the epidemiology, pathophysiology, treatment and prognostication in relation to the post-cardiac arrest syndrome.

☆ A Spanish translated version of the summary of this article appears as Appendix in the online version at doi:10.1016/j.resuscitation.2008.09.017.

☆☆ Endorsed by the American College of Emergency Physicians, Society for Academic Emergency Medicine, Society of Critical Care Medicine, and Neurocritical Care Society.

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Therapeutic hypothermia

Methods: Relevant articles were identified using PubMed, EMBASE and an American Heart Association EndNote master resuscitation reference library, supplemented by hand searches of key papers. Writing groups comprising international experts were assigned to each section. Drafts of the document were circulated to all authors for comment and amendment.
Results: The 4 key components of post-cardiac arrest syndrome were identified as (1) post-cardiac arrest brain injury, (2) post-cardiac arrest myocardial dysfunction, (3) systemic ischaemia/reperfusion response, and (4) persistent precipitating pathology.
Conclusions: A growing body of knowledge suggests that the individual components of the post-cardiac arrest syndrome are potentially treatable.

Consensus process

The contributors of this statement were selected to ensure expertise in all the disciplines relevant to post-cardiac arrest care. In an attempt to make this document universally applicable and generalisable, the authorship comprised clinicians and scientists who represent many specialties in many regions of the world. Several major professional groups whose practice is relevant to post-cardiac arrest care were asked and agreed to provide representative contributors. Planning and invitations took place initially by email followed a series of telephone conferences and face-to-face meetings of the co-chairs and writing group members. International writing teams were formed to generate the content of each section, corresponding to the major subheadings of the final document. Two team leaders from different countries led each writing team. Individual contributors were assigned by the writing group co-chairs to work on one or more writing team, generally reflecting their areas of expertise. Relevant articles were identified using PubMed, EMBASE and an American Heart Association EndNote master resuscitation reference library, supplemented by hand searches of key papers. Drafts of each section were written and agreed upon by the writing team authors and then sent to the co-chairs for editing and amalgamation into a single document. The first draft of the complete document was circulated among writing team leaders for initial comment and editing. A revised version of the document was circulated among all contributors and consensus was achieved before submission of the final version independent peer review and approval for publication.

Background

This scientific statement outlines current understanding and identifies knowledge gaps in the pathophysiology, treatment, and prognosis of patients who regain spontaneous circulation after cardiac arrest. The purpose is to provide a resource for optimizing post-cardiac arrest care and pinpointing the need for research focused on gaps in knowledge that would potentially improve outcomes of patients resuscitated from cardiac arrest.

Resumption of spontaneous circulation after prolonged complete whole-body ischaemia is an unnatural pathophysiological state created by successful cardiopulmonary resuscitation (CPR). In the early 1970s, Dr. Vladimir Negovsky recognised that the pathology caused by complete whole-body ischaemia and reperfusion was unique in that it had a clearly definable aetiology, time course, and constellation of pathological processes.[1–3] Negovsky named this state *postresuscitation disease*. Although appropriate at the time, the term *resuscitation* is now used more broadly to include treatment of various shock states in which circulation has not ceased. Moreover, the term *postresuscitation* implies that the act of resuscitation has ended. Negovsky himself stated that a second, more complex phase of resuscitation begins when patients regain spontaneous circulation after cardiac arrest.[1] For these reasons, we propose a new term: *post-cardiac arrest syndrome*.

The first large multicentre report on patients treated for cardiac arrest was published in 1953.[4] The in-hospital mortality rate for the 672 adults and children whose ''heart beat was restarted'' was 50%. More than a half-century later, the location, aetiology, and treatment of cardiac arrest have changed dramatically, but the overall prognosis following return of spontaneous circulation (ROSC) has not improved. The largest modern report of cardiac arrest epidemiology was published by the National Registry of CPR in 2006.[5] Among the 19,819 adults and 524 children who regained any spontaneous circulation, in-hospital mortality rates were 67% and 55%, respectively. In a recent study of 24,132 patients in the United Kingdom who were admitted to critical care units after cardiac arrest, the in-hospital mortality rate was 71%.[6]

In 1966 the National Academy of Sciences—National Research Council Ad Hoc Committee on Cardiopulmonary Resuscitation published the original consensus statement on CPR.[7] This document described the original ABCDs of resuscitation, in which A represents airway; B, breathing; C, circulation; and D, definitive therapy. Definitive therapy includes not only the management of pathologies that cause cardiac arrest but also those that result from cardiac arrest. Post-cardiac arrest syndrome is a unique and complex combination of pathophysiological processes, including (1) post-cardiac arrest brain injury, (2) post-cardiac arrest myocardial dysfunction, and (3) systemic ischaemia/reperfusion response. This state is often complicated by a fourth component: the unresolved pathological process that caused the cardiac arrest. A growing body of knowledge suggests that the individual components of post-cardiac arrest syndrome are potentially treatable. The first intervention proved to be clinically effective is therapeutic hypothermia.[8,9] These studies provide the essential proof of concept that interventions initiated after ROSC can improve outcome.

Several barriers impair implementation and optimization of post-cardiac arrest care. Post-cardiac arrest patients are

treated by multiple teams of providers both outside and inside the hospital. There is evidence of considerable variation in post-cardiac arrest treatment and patient outcome between institutions.[10,11] Therefore, a well-thought-out multidisciplinary approach for comprehensive care must be established and executed consistently. Such protocols have already been shown to improve outcomes at individual institutions when compared with historical controls.[12–14] Another potential barrier is the limited accuracy of early prognostication. Optimized post-cardiac arrest care is resource-intensive and should not be continued when the effort is clearly futile. However, the reliability of early prognostication (<72 h after arrest) remains limited, and the impact of emerging therapies (e.g., hypothermia) on accuracy of prognostication has yet to be elucidated. Reliable approaches must be developed to avoid premature prognostication of futility without creating unreasonable hope for recovery or consuming healthcare resources inappropriately.

The majority of research on cardiac arrest over the past half-century has focused on improving the rate of ROSC, and significant progress has been made. However, many interventions improve ROSC without improving long-term survival. The translation of optimized basic life support (BLS) and advanced life support (ALS) interventions into the best possible outcomes is contingent on optimal post-cardiac arrest care. This requires effective implementation of what is already known and enhanced research to identify therapeutic strategies that will give patients who are resuscitated from cardiac arrest the best chance for survival with good neurological function.

Epidemiology of the post-cardiac arrest syndrome

The tradition in cardiac arrest epidemiology, based largely on the Utstein consensus guidelines, has been to report percentages of patients who survive to sequential end points such as ROSC, hospital admission, hospital discharge, and various points thereafter.[15,16] Once ROSC is achieved, however, the patient is technically alive. A more useful approach to studying post-cardiac arrest syndrome is to report deaths during various phases of post-cardiac arrest care. In fact, this approach reveals that rates of early mortality in patients achieving ROSC after cardiac arrest vary dramatically between studies, countries, regions, and hospitals.[10,11] The cause of these differences is multifactorial but includes variability in patient populations, reporting methods, and potentially post-cardiac arrest care.[10,11]

Epidemiological data on patients who regain spontaneous circulation after out-of-hospital cardiac arrest suggest regional and institutional variation in in-hospital mortality rates. During the ALS phase of the Ontario Prehospital Advanced Life Support Trial (OPALS), 766 patients achieved ROSC after out-of-hospital cardiac arrest.[17] In-hospital mortality rates were 72% for patients with ROSC and 65% for patients admitted to the hospital. Data from the Canadian Critical Care Research Network indicates a 65% in-hospital mortality rate for 1483 patients admitted to the intensive care unit (ICU) after out-of-hospital arrest.[18] In the United Kingdom, 71.4% of 8987 patients admitted to the ICU after out-of-hospital cardiac arrest died before being discharged from the hospital.[6] In-hospital mortality rates for patients with out-of-hospital cardiac arrest who were taken to 4 different hospitals in Norway averaged 63% (range 54–70%) for patients with ROSC, 57% (range 56–70%) for patients arriving in the emergency department (ED) with a pulse, and 50% (range 41–62%) for patients admitted to the hospital.[10] In Sweden the 1-month mortality rate for 3853 patients admitted with a pulse to 21 hospitals after out-of-hospital cardiac arrest ranged from 58% to 86%.[11] In Japan, one study reported that patients with ROSC after witnessed out-of-hospital cardiac arrest of presumed cardiac origin had an in-hospital mortality rate of 90%.[19] Among 170 children with ROSC after out-of-hospital cardiac arrest, the in-hospital mortality rate was 70% for those with any ROSC, 69% for those with ROSC > 20 min, and 66% for those admitted to the hospital.[20] In a comprehensive review of nontraumatic out-of-hospital cardiac arrest in children, the overall rate of ROSC was 22.8%, and the rate of survival to discharge was 6.7%, resulting in a calculated post-ROSC mortality rate of 70%.[21]

The largest published in-hospital cardiac arrest database (NRCPR) includes data from >36,000 cardiac arrests.[5] Recalculation of the results of this report reveals that the in-hospital mortality rate was 67% for the 19,819 adults with any documented ROSC, 62% for the 17,183 adults with ROSC > 20 min, 55% for the 524 children with any documented ROSC, and 49% for the 460 children with ROSC > 20 min. It seems intuitive to expect that advances in critical care over the past 5 decades would result in improvements in rates of hospital discharge after initial ROSC. However, epidemiological data to date fail to support this view.

Some variability between individual reports may be attributed to differences in the numerator and denominator used to calculate mortality. For example, depending on whether ROSC is defined as a brief (approximately >30 s) return of pulses or spontaneous circulation sustained for >20 min, the denominator used to calculate postresuscitation mortality rates will differ greatly.[15] Other denominators include sustained ROSC to the ED or hospital/ICU admission. The lack of consistently defined denominators precludes comparison of mortality among a majority of the studies. Future studies should use consistent terminology to assess the extent to which post-cardiac arrest care is a contributing factor.

The choice of denominator has some relationship to the site of post-cardiac arrest care. Patients with fleeting ROSC are affected by interventions that are administered within seconds or minutes, usually at the site of initial collapse. Patients with ROSC that is sustained for >20 min receive care during transport or in the ED before hospital admission. Perhaps it is more appropriate to look at mortality rates for out-of-hospital (or immediate post-ROSC), ED, and ICU phases separately. A more physiological approach would be to define the phases of post-cardiac arrest care by time rather than location. The immediate postarrest phase could be defined as the first 20 min after ROSC. The early postarrest phase could be defined as the period between 20 min and 6–12 h after ROSC when early interventions might be most effective. An intermediate phase might be between 6–12 and 72 h when injury pathways are still active and aggressive treatment is typically instituted. Finally, a

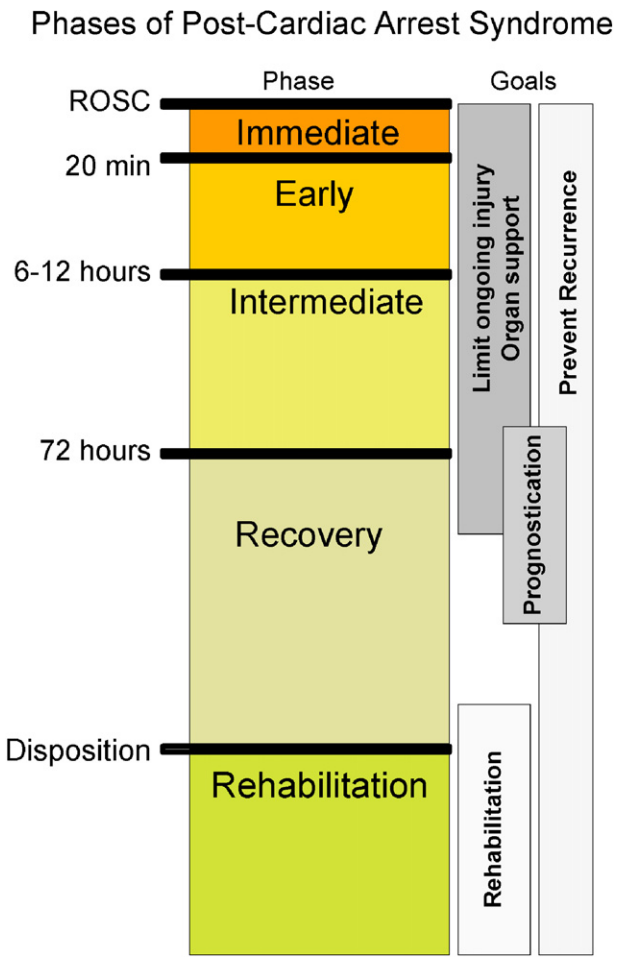

Figure 1 Phases of post-cardiac arrest syndrome.

period beyond 3 days could be considered the recovery phase when prognostication becomes more reliable and ultimate outcomes are more predictable (Figure 1). For both epidemiological and interventional studies, the choice of denominator should reflect the phases of post-cardiac arrest care that are being studied.

Beyond reporting post-cardiac arrest mortality rates, epidemiological data should define the neurological and functional outcomes of survivors. The updated Utstein reporting guidelines list Cerebral Performance Category (CPC) as a core data element.[15] For example, examination of the latest NRCPR database report reveals that 68% of 6485 adults and 58% of 236 children who survived to hospital discharge had a good outcome, defined as CPC 1 (good cerebral performance) or CPC 2 (moderate cerebral disability). In one study, 81% of 229 out-of-hospital cardiac arrest survivors were categorized as CPC 1 and 2, although this varied between 70% and 90% in the 4 hospital regions.[10] In another study, 75% of 51 children who survived out-of-hospital cardiac arrest had either paediatric CPC 1 and 2 or returned to their baseline neurological state.[20] The CPC is an important and useful outcome tool, but it lacks the sensitivity to detect clinically significant differences in neurological outcome. The report of the recent Utstein consensus symposium on post-cardiac arrest care research anticipates more refined assessment tools, including tools that evaluate quality of life.[16]

Two other factors related to survival after initial ROSC are limitations set on subsequent resuscitation efforts and the timing of withdrawal of therapy. The perception of a likely adverse outcome (correct or not) may well create a self-fulfilling prophesy. The timing of withdrawal of therapy is poorly documented in the resuscitation literature. Data from the NRCPR on in-hospital cardiac arrest indicate that 63% of patients were declared ''do not attempt resuscitation'' (DNAR) after the index event, and in 43% of these, life support was withdrawn.[22] In the same report, the median survival time of patients who died after ROSC was 1.5 days, long before futility could be accurately prognosticated in most cases. Among 24,132 comatose survivors of either in- or out-of-hospital cardiac arrest who were admitted to UK critical care units, treatment was withdrawn in 28.2% at a median of 2.4 days (interquartile range 1.5—4.1 days).[6] The reported incidence of inpatients with clinical brain death and sustained ROSC after cardiac arrest ranges from 8% to 16%.[22,23] Although clearly a poor outcome, these patients can and should be considered for organ donation. A number of studies have reported no difference in transplant outcomes whether the organs were obtained from appropriately selected post-cardiac arrest patients or from other brain-dead donors.[23–25] Non-heart-beating organ donation has also been described after failed resuscitation attempts following in- and out-of-hospital cardiac arrest,[26,27] but these have generally been cases in which sustained ROSC is never achieved. 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.

Despite variability in reporting techniques, there is surprisingly little evidence to suggest that the in-hospital mortality rate of patients who achieve ROSC after cardiac arrest has changed significantly in the past half-century. To minimise artefactual variability, epidemiological and interventional post-cardiac arrest studies should incorporate well-defined standardised methods to calculate and report mortality rates at various stages of post-cardiac arrest care, as well as long-term neurological outcome.[16] Overriding these issues is a growing body of evidence that post-cardiac arrest care impacts mortality rate and functional outcome.

Pathophysiology of the post-cardiac arrest syndrome

The high mortality rate of patients who initially achieve ROSC after cardiac arrest can be attributed to a unique pathophysiological process involving multiple organs. Although prolonged whole-body ischaemia initially causes global tissue and organ injury, additional damage occurs during and after reperfusion.[28,29] The unique features of post-cardiac arrest pathophysiology are often superimposed on the disease or injury that caused the cardiac arrest as well as underlying co-morbidities. Therapies that focus on individual organs may compromise other injured organ systems. The 4 key components of post-cardiac arrest syndrome are (1) post-cardiac arrest brain injury, (2) post-cardiac arrest myocardial dysfunction, (3) systemic ischaemia/reperfusion response, and (4) persistent precipitating pathology (Table 1). The severity of these disorders after ROSC is not uniform and will vary in individual patients, based on the severity of the ischaemic insult, the cause of

Table 1 Post-cardiac arrest syndrome: pathophysiology, clinical manifestations, and potential treatments.

Syndrome	Pathophysiology	Clinical manifestation	Potential treatments
Post-cardiac arrest brain injury	• Impaired cerebrovascular autoregulation • Cerebral oedema (limited) • Postischaemic neurodegeneration	• Coma • Seizures • Myoclonus • Cognitive dysfunction • Persistent vegetative state • Secondary Parkinsonism • Cortical stroke • Spinal stroke • Brain death	• Therapeutic hypothermia[177] • Early haemodynamic optimization • Airway protection and mechanical ventilation • Seizure control • Controlled reoxygenation (SaO_2 94%-96%) • Supportive care
Post-cardiac arrest myocardial dysfunction	• Global hypokinesis (myocardial stunning) • Reduced cardiac output • ACS	• Early revascularization of AMI[171,373] • Hypotension • Dysrhythmias • Cardiovascular collapse	• Early haemodynamic optimization • Intravenous fluid[97] • Inotropes[97] • IABP[13,160] • LVAD[161] • ECMO[361]
Systemic ischaemia/ reperfusion response	• Systemic inflammatory response syndrome • Impaired vasoregulation • Increased coagulation • Adrenal suppression • Impaired tissue oxygen delivery and utilisation • Impaired resistance to infection	• Ongoing tissue hypoxia/ischaemia • Hypotension • Cardiovascular collapse • Pyrexia (fever) • Hyperglycaemia • Multiorgan failure • Infection	• Early haemodynamic optimization • Intravenous fluid • Vasopressors • High-volume haemofiltration[374] • Temperature control • Glucose control[220] • Antibiotics for documented infection
Persistent precipitating pathology	• Cardiovascular disease (AMI/ACS, cardiomyopathy) • Pulmonary disease (COPD, asthma) • CNS disease (CVA) • Thromoboembolic disease (PE) • Toxicologic (overdose, poisoning) • Infection (sepsis, pneumonia) • Hypovolaemia (haemorrhage, dehydration)	• Specific to aetiology, but complicated by concomitant PCAS	• Disease-specific interventions guided by patient condition concomitant PCAS

ACS indicates acute coronary syndrome; AMI, acute myocardial infarction; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; EMCO, extracorporeal membrane oxygenation; COPD, chronic obstructive pulmonary disease; CNS, central nervous system; CVA, cerebrovascular accident PE, pulmonary embolism; and PCAS, post-cardiac arrest syndrome.

cardiac arrest, and the patient's prearrest state of health. If ROSC is rapidly achieved after onset of cardiac arrest, the post-cardiac arrest syndrome will not occur.

Post-cardiac arrest brain injury

Post-cardiac arrest brain injury is a common cause of morbidity and mortality. In one study of patients who survived to ICU admission but subsequently died in the hospital, brain injury was the cause of death in 68% after out-of hospital cardiac arrest and in 23% after in-hospital cardiac arrest.[30] The unique vulnerability of the brain is attributed to its limited tolerance of ischaemia as well as its unique response to reperfusion. The mechanisms of brain injury triggered by cardiac arrest and resuscitation are complex and include excitotoxicity, disrupted calcium homeostasis, free radical formation, pathological protease cascades, and activation of cell death signaling pathways.[31–33] Many of these pathways are executed over hours to days after ROSC.

Histologically, selectively vulnerable neuron subpopulations in the hippocampus, cortex, cerebellum, corpus striatum, and thalamus degenerate over hours to days.[34–38] Both neuronal necrosis and apoptosis have been reported after cardiac arrest. The relative contribution of each cell death pathway remains controversial, however, and is dependent partly on patient age and the neuronal subpopulation under examination.[39–41] The relatively protracted duration of injury cascades and histological change suggests a broad therapeutic window for neuroprotective strategies following cardiac arrest.

Prolonged cardiac arrest can also be followed by fixed and/or dynamic failure of cerebral microcirculatory reperfusion despite adequate cerebral perfusion pressure (CPP).[42,43] This impaired reflow can cause persistent ischaemia and small infarctions in some brain regions. The cerebral microvascular occlusion that causes no-reflow has been attributed to intravascular thrombosis during cardiac arrest and has been shown to be responsive to thrombolytic therapy in preclinical studies.[44] The relative contribution of fixed no-reflow is controversial, however, and appears to be of limited significance in preclinical models when the duration of untreated cardiac arrest is <15 min.[44,45] Serial measurements of regional cerebral blood flow (CBF) using stable xenon/computed tomography (CT) after 10.0—12.5 min of untreated cardiac arrest in dogs demonstrated dynamic and migratory hypoperfusion rather then fixed no-flow.[43,46] In the recent Thrombolysis in Cardiac Arrest (TROICA) trial, tenectaplase given to patients with out-of-hospital cardiac arrest of presumed cardiac aetiology did not increase 30-day survival compared with placebo (B.J.B., personal communication, 26th February 2008).

Despite cerebral microcirculatory failure, macroscopic reperfusion is often hyperaemic in the first few minutes after cardiac arrest because of elevated CPP and impaired cerebrovascular autoregulation.[47,48] These high initial perfusion pressures can theoretically minimise impaired reflow.[49] Yet, hyperaemic reperfusion can potentially exacerbate brain oedema and reperfusion injury. In one human study, hypertension (mean arterial pressure (MAP) >100 mmHg) in the first 5 min after ROSC was not associated with improved neurological outcome, but MAP during the first 2 h after ROSC was positively correlated with neurological outcome.[50] Although resumption of oxygen and metabolic substrate delivery a the microcirculatory level is essential, a growing body of evidence suggests that too much oxygen during the initial stages of reperfusion can exacerbate neuronal injury through production of free radicals and mitochondrial injury (see section 'Oxygenation').[51,52]

Beyond the initial reperfusion phase, several factors can potentially compromise cerebral oxygen delivery and possibly secondary injury in the hours to days after cardiac arrest. These include hypotension, hypoxaemia, impaired cerebrovascular autoregulation, and brain oedema. However, human data are limited to small case series. Autoregulation of CBF is impaired for some time after cardiac arrest. During the subacute period, cerebral perfusion varies with CPP instead of being linked to neuronal activity.[47,48] In humans, in the first 24—48 h after resuscitation from cardiac arrest, there is increased cerebral vascular resistance, decreased CBF, decreased cerebral metabolic rate of oxygen consumption ($CMRO_2$), and decreased glucose consumption.[53–56] Although the results of animal studies are contradictory in terms of the coupling of CBF and $CMRO_2$ during this period,[57,58] human data indicate that global CBF is adequate to meet oxidative metabolic demands.[53,55] Improvement of global CBF during secondary delayed hypoperfusion by giving the calcium channel blocker nimodipine had no impact on neurological outcome in humans.[56] These results do not rule out the potential presence of regional microcirculatory reperfusion deficits that have been observed in animal studies despite adequate CPP.[43,46] Overall, it is likely that the CPP necessary to maintain optimal cerebral perfusion will vary among individual post-cardiac arrest patients at various time points after ROSC.

There is limited evidence that brain oedema or elevated intracranial pressure (ICP) directly exacerbates post-cardiac arrest brain injury. Although transient brain oedema is observed early after ROSC, most commonly after asphyxial cardiac arrest, it is rarely associated with clinically relevant increases in ICP.[59–62] In contrast, delayed brain oedema, occurring days to weeks after cardiac arrest, has been attributed to delayed hyperaemia; this is more likely the consequence rather than the cause of severe ischaemic neurodegeneration.[60–62] No published prospective trials have examined the value of monitoring and managing ICP in post-cardiac arrest patients.

Other factors that can impact brain injury after cardiac arrest are pyrexia, hyperglycaemia, and seizures. In a small case series, patients with temperatures >39 °C in the first 72 h after out-of-hospital cardiac arrest had a significantly increased risk of brain death.[63] When serial temperatures were monitored in 151 patients for 48 h after out-of-hospital cardiac arrest, the risk of unfavorable outcome increased (odds ratio (OR) 2.3 [95% confidence interval (CI) 1.2—4.1]) for every degree Celsius that the peak temperature exceeded 37 °C.[64] A subsequent multicentre retrospective study of patients admitted after out-of-hospital cardiac arrest reported that a maximal recorded temperature >37.8 °C was associated with increased in-hospital mortality (OR 2.7 [95% CI 1.2—6.3]).[10] Recent data demonstrating neuroprotection with therapeutic hypothermia further supports the role of body temperature in the evolution of post-cardiac arrest brain injury.

Hyperglycaemia is common in post-cardiac arrest patients and is associated with poor neurological outcome after out-of-hospital cardiac arrest.[10,65–70] Animal studies suggest that elevated postischaemic blood glucose concentrations exacerbate ischaemic brain injury,[71,72] and this effect can be mitigated by intravenous insulin therapy.[73,74] Seizures in the post-cardiac arrest period are associated with worse prognosis and are likely to be caused by, as well as exacerbate, post-cardiac arrest brain injury.[75]

Clinical manifestations of post-cardiac arrest brain injury include coma, seizures, myoclonus, varying degrees of neurocognitive dysfunction (ranging from memory deficits to persistent vegetative state), and brain death (Table 1).[75–83] Of these conditions, coma and related disorders of arousal and awareness are a very common acute presentation of post-cardiac arrest brain injury. Coma precipitated by global brain ischaemia is a state of unconsciousness that is unresponsive to both internal and external stimuli.[84,85] This state represents extensive dysfunction of brain areas

responsible for arousal (ascending reticular formation, pons, midbrain, diencephalon, and cortex) and awareness (bilateral cortical and subcortical structures).[84,86–89] The lesser vulnerability or earlier recovery of the brainstem and diencephalon[90,91] may lead to either a vegetative state, with arousal and preservation of sleep–wake cycles but with persistent lack of awareness of self and environment,[92] or a minimally conscious state showing inconsistent but clearly discernible behavioral evidence of consciousness.[93] With heightened vulnerability of cortical areas, many survivors will regain consciousness but have significant neuropsychological impairment,[94] myoclonus, and seizures. Impairment in movement and coordination may arise from motor-related centres in the cortex, basal ganglia, and cerebellum.[95] These clinical conditions, representing most of the poor functional outcome (CPC 3 and 4), continue to challenge healthcare providers and should be a major focus of research.

Post-cardiac arrest myocardial dysfunction

Post-cardiac arrest myocardial dysfunction also contributes to the low survival rate after in- and out-of-hospital cardiac arrest.[30,96,97] A significant body of preclinical and clinical evidence, however, indicates that this phenomenon is both responsive to therapy and reversible.[97–102] Immediately after ROSC, heart rate and blood pressure are extremely variable. It is important to recognise that normal or elevated heart rate and blood pressure immediately after ROSC can be caused by a transient increase in local and circulating catecholamine concentrations.[103,104] When post-cardiac arrest myocardial dysfunction occurs, it can be detected within minutes of ROSC by appropriate monitoring. In swine studies, the ejection fraction decreases from 55% to 20% and left ventricular end-diastolic pressure increases from 8–10 to 20–22 mmHg as early as 30 min after ROSC.[101,102] During the period with significant dysfunction, coronary blood flow is not reduced, indicating a true stunning phenomenon rather than permanent injury or infarction. In one series of 148 patients who underwent coronary angiography after cardiac arrest, 49% of subjects had myocardial dysfunction manifested by tachycardia and elevated left ventricular end-diastolic pressure, followed approximately 6 h later by hypotension (MAP < 75 mmHg) and low cardiac output (cardiac index < 2.2 L min^{-1} m^{-2}).[97]

This global dysfunction is transient, and full recovery can occur. In a swine model with no antecedent coronary or other left ventricular dysfunction features, the time to recovery appears to be between 24 and 48 h.[102] Several case series have described transient myocardial dysfunction after human cardiac arrest. Cardiac index values reached their nadir at 8 h after resuscitation, improved substantially by 24 h, and almost uniformly returned to normal by 72 h in patients who survived out-of-hospital cardiac arrest.[97] More sustained depression of ejection fraction among in- and out-of-hospital post-cardiac arrest patients has been reported with continued recovery over weeks to months.[99] The responsiveness of post-cardiac arrest global myocardial dysfunction to inotropic drugs is well documented in animal studies.[98,101] In swine, dobutamine infusions of 5–10 μg kg^{-1} min^{-1} dramatically improve systolic (left ventricular ejection fraction) and diastolic (isovolumic relaxation of left ventricle) dysfunction after cardiac arrest.[101]

Systemic ischaemia/reperfusion response

Cardiac arrest represents the most severe shock state, during which delivery of oxygen and metabolic substrates is abruptly halted and metabolites are no longer removed. CPR only partially reverses this process, achieving cardiac output and systemic oxygen delivery (DO_2) that is much less than normal. During CPR a compensatory increase in systemic oxygen extraction occurs, leading to significantly decreased central ($ScvO_2$) or mixed venous oxygen saturation.[105] Inadequate tissue oxygen delivery can persist even after ROSC because of myocardial dysfunction, pressor-dependent haemodynamic instability, and microcirculatory failure. Oxygen debt (the difference between predicted oxygen consumption [normally 120–140 mL kg^{-1} min^{-1}] and actual consumption multiplied by time duration) quantifies the magnitude of exposure to insufficient oxygen delivery. Accumulated oxygen debt leads to endothelial activation and systemic inflammation[106] and is predictive of subsequent multiple organ failure and death.[107,108]

The whole-body ischaemia/reperfusion of cardiac arrest with associated oxygen debt causes generalized activation of immunological and coagulation pathways, increasing the risk of multiple organ failure and infection.[109–111] This condition has many features in common with sepsis.[112,113] As early as 3 h after cardiac arrest, blood concentrations of various cytokines, soluble receptors, and endotoxin increase, and the magnitude of these changes are associated with outcome.[112] Soluble intercellular adhesion molecule-1 (sICAM-1), soluble vascular-cell adhesion molecule-1 (sVCAM-1), and P- and E-selectins are increased during and after CPR, suggesting leucocyte activation or endothelial injury.[114,115] Interestingly, hyporesponsiveness of circulating leucocytes, as assessed *ex vivo*, has been studied extensively in patients with sepsis and is termed *endotoxin tolerance*. Endotoxin tolerance after cardiac arrest may protect against an overwhelming proinflammatory process, but it may induce immunosuppression with an increased risk of nosocomial infection.[112,116]

Activation of blood coagulation without adequate activation of endogenous fibrinolysis is an important pathophysiological mechanism that may contribute to microcirculatory reperfusion disorders.[117,118] Intravascular fibrin formation and microthromboses are distributed throughout the entire microcirculation, suggesting a potential role for interventions that focus on haemostasis. Coagulation/anticoagulation and fibrinolysis/antifibrinolysis systems are activated in patients who undergo CPR,[117] particularly those who recover spontaneous circulation.[118] Anticoagulant factors such as antithrombin, protein S, and protein C are decreased and are associated with a very transient increase in endogenous activated protein C soon after the cardiac arrest–resuscitation event.[118] Early endothelial stimulation and thrombin generation may be responsible for the tremendous increase in protein C activation, followed rapidly by a phase of endothelial dysfunction in which the endothelium may be unable to generate an adequate amount of activated protein C.

The stress of total body ischaemia/reperfusion affects adrenal function. Although an increased plasma cortisol level occurs in many patients after out-of-hospital cardiac arrest, relative adrenal insufficiency, defined as failure to respond to corticotrophin (i.e., $<9\ \mu g\ mL^{-1}$ increase in cortisol), is common.[119,120] Furthermore, basal cortisol levels measured from 6 to 36 h after the onset of cardiac arrest were lower in patients who subsequently died from early refractory shock (median $27\ \mu g\ dL^{-1}$; interquartile range 15—47) than in patients who died later from neurological causes (median $52\ \mu g\ dL^{-1}$; interquartile range 28—72).[119]

Clinical manifestations of systemic ischaemic-reperfusion response include intravascular volume depletion, impaired vasoregulation, impaired oxygen delivery and utilisation, and increased susceptibility to infection. In most cases these pathologies are both responsive to therapy and reversible. Data from clinical research on sepsis suggest that outcomes are optimized when interventions are both goal directed and initiated as early as possible.

Persistent precipitating pathology

The pathophysiology of post-cardiac arrest syndrome is commonly complicated by persisting acute pathology that caused or contributed to the cardiac arrest itself. Diagnosis and management of persistent precipitating pathologies such as acute coronary syndrome (ACS), pulmonary diseases, haemorrhage, sepsis, and various toxidromes can complicate and be complicated by the simultaneous pathophysiology of the post-cardiac arrest syndrome.

There is a high probability of identifying an ACS in the patient who is resuscitated from cardiac arrest. In out-of-hospital cardiac arrest studies, acute myocardial infarction (AMI) has been documented in ~50% of adult patients.[13,121,122] An acute coronary occlusion was found in 40 of 84 (48%) consecutive patients who had no obvious non-cardiac aetiology but had undergone coronary angiography after resuscitation from out-of-hospital cardiac arrest.[123] Nine of the patients with acute coronary occlusion did not have chest pain or ST-segment elevation. Elevations in troponin T measured during treatment of cardiac arrest suggest that an ACS precedes out-of-hospital cardiac arrest in 40% of patients.[124] Injury to the heart during initial resuscitation reduces the specificity of cardiac biomarkers for identifying ACS after ROSC. At 12 h after ROSC from out-of-hospital cardiac arrest, troponin T has been reported to be 96% sensitive and 80% specific for diagnosis of AMI, whereas creatine kinase MB (CK-MB) is 96% sensitive and 73% specific.[125] In the NRCPR registry, only 11% of adult in-hospital arrests were attributed to MI or acute ischaemia.[5] The proportion of in-hospital patients who achieved ROSC and are diagnosed with ACS has not been reported in this population.

Another thromboembolic disease to consider after cardiac arrest is pulmonary embolism. Pulmonary emboli have been reported in 2—10% of sudden deaths.[5,126—129] No reliable data are available to estimate the likelihood of pulmonary embolism among patients who achieve ROSC after either in- or out-of-hospital cardiac arrest.

Haemorrhagic cardiac arrest has been studied extensively in the trauma setting. The precipitating causes (multiple trauma with and without head injury) and methods of resuscitation (blood volume replacement and surgery) differ sufficiently from other situations causing cardiac arrest that haemorrhagic cardiac arrest should be considered a separate clinical syndrome.

Primary pulmonary disease such as chronic obstructive pulmonary disease (COPD), asthma, or pneumonia can lead to respiratory failure and cardiac arrest. When cardiac arrest is caused by respiratory failure, pulmonary physiology may be worse after restoration of circulation. Redistribution of blood into pulmonary vasculature can lead to frank pulmonary oedema or at least increased alveolar—arterial oxygen gradients after cardiac arrest.[130] Preclinical studies suggest that brain injury after asphyxiation-induced cardiac arrest is more severe than after sudden circulatory arrest.[131] For example, acute brain oedema is more common after cardiac arrest caused by asphyxia.[60] It is possible that perfusion with hypoxemic blood during asphyxia preceding complete circulatory collapse is harmful.

Sepsis is a cause of cardiac arrest, acute respiratory distress syndrome (ARDS), and multiple organ failure. Thus, there is a predisposition for exacerbation of post-cardiac arrest syndrome when cardiac arrest occurs in the setting of sepsis. 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.[30]

Other precipitating causes of cardiac arrest may require specific treatment during the post-cardiac arrest period. For example, drug overdose and intoxication may be treated with specific antidotes, and environmental causes such as hypothermia may require active temperature control. Specific treatment of these underlying disturbances must then be coordinated with specific support for post-cardiac arrest neurological and cardiovascular dysfunction.

Therapeutic strategies

Care of the post-cardiac arrest patient is time-sensitive, occurs both in- and out-of-hospital, and is sequentially provided by multiple diverse teams of healthcare providers. Given the complex nature of post-cardiac arrest care, it is optimal to have a multidisciplinary team develop and execute a comprehensive clinical pathway tailored to available resources. Treatment plans for post-cardiac arrest care must accommodate a spectrum of patients, ranging from the awake, haemodynamically stable survivor to the unstable comatose patient with persistent precipitating pathology. In all cases, treatment must focus on reversing the pathophysiological manifestations of the post-cardiac arrest syndrome with proper prioritization and timely execution. Such a plan enables physicians, nurses, and other healthcare professionals to optimize post-cardiac arrest care and prevents premature withdrawal of care before long-term prognosis can be established. This approach improved outcomes at individual institutions when compared with historical controls.[12,13,132]

Table 2 Post-cardiac arrest syndrome: monitoring options.

1. General intensive care monitoring
Arterial catheter
Oxygen saturation by pulse oximetry
Continuous ECG
CVP
$ScvO_2$
Temperature (bladder, esophagus)
Urine output
Arterial blood gases
Serum lactate
Blood glucose, electrolytes, CBC, and general blood sampling
Chest radiograph
2. More advanced haemodynamic monitoring
Echocardiography
Cardiac output monitoring (either non-invasive or PA catheter)
3. Cerebral monitoring
EEG (on indication/continuously): early seizure detection and treatment
CT/MRI

CVP indicates central venous pressure; $ScvO_2$, central venous oxygen saturation; CBC, complete blood count; PA, pulmonary artery; EEG, electroencephalogram; and CT/MRI, computed tomography/magnetic resonance imaging.

General measures

The general management of post-cardiac arrest patients should follow the standards of care for most critically ill patients in the ICU setting. This statement focuses on the components of care that specifically impact the post-cardiac arrest syndrome. The time-sensitive nature of therapeutic strategies will be highlighted, as well as the differential impact of therapeutic strategies on individual components of the syndrome.

Monitoring

Post-cardiac arrest patients generally require intensive care monitoring; this can be divided into 3 categories (Table 2): general intensive care monitoring, more advanced haemodynamic monitoring, and cerebral monitoring. General intensive care monitoring (Table 2) is the minimum requirement; additional monitoring should be added depending on the status of the patient and local resources and experience. The impact of specific monitoring techniques on post-cardiac arrest outcome, however, has not been prospectively validated.

Early haemodynamic optimization

Early haemodynamic optimization or early goal-directed therapy (EGDT) is an algorithmic approach to restoring and maintaining the balance between systemic oxygen delivery and demands. The key to the success of this approach is initiation of monitoring and therapy as early as possible and achievement of goals within hours of presentation. This approach focuses on optimization of preload, arterial oxygen content, afterload, contractility, and systemic oxygen utilisation. EGDT has been studied in randomized prospective clinical trials of postoperative patients and patients with severe sepsis.[133–135] The goals in these studies have included central venous pressure (CVP) 8—12 mmHg, MAP 65—90 mmHg, $ScvO_2 > 70\%$, hematocrit > 30% or Hb > 8 g dL^{-1}, lactate ≤ 2 mmol L^{-1}, urine output ≥ 0.5 mL kg^{-1} h^{-1}, and oxygen delivery index > 600 mL min^{-1} m^{-2}. The primary therapeutic tools are intravenous fluids, inotropes, vasopressors, and blood transfusion. The benefits of EGDT include modulation of inflammation, reduction of organ dysfunction, and reduction of healthcare resource consumption.[133–135] In severe sepsis EGDT also has been shown to reduce mortality.[133]

The systemic ischaemia/reperfusion response and myocardial dysfunction of post-cardiac arrest syndrome have many characteristics in common with sepsis.[112] Therefore, it has been hypothesized that early haemodynamic optimization might improve the outcome of post-cardiac arrest patients. The benefit of this approach has not been studied in randomized prospective clinical trials, however. Moreover, the optimal goals and strategies to achieve those goals could be different in post-cardiac arrest syndrome, given the concomitant presence of post-cardiac arrest brain injury, myocardial dysfunction, and persistent precipitating pathologies.

The optimal MAP for post-cardiac arrest patients has not been defined by prospective clinical trials. The simultaneous need to perfuse the postischaemic brain adequately without putting unnecessary strain on the postischaemic heart is unique to the post-cardiac arrest syndrome. The loss of cerebrovascular pressure autoregulation makes cerebral perfusion dependent on CPP (CPP = MAP — ICP). Because sustained elevation of ICP during the early post-cardiac arrest phase is uncommon, cerebral perfusion is predominantly dependent on MAP. If fixed or dynamic cerebral microvascular dysfunction is present, an elevated MAP could theoretically increase cerebral oxygen delivery. In one human study, hypertension (MAP > 100 mmHg) during the first 5 min after ROSC was not associated with improved neurological outcome[50]; however, MAP during the first 2 h after ROSC was positively correlated with neurological outcome. Good outcomes have been achieved in published studies in which the MAP target was as low as 65—75 mmHg[13] to as high as 90—100 mmHg[9,12] for patients admitted after out-of-hospital cardiac arrest. The optimal MAP in the post-cardiac arrest period might be dependent on the duration of cardiac arrest, with higher pressures needed to overcome the potential no-reflow phenomenon observed with >15 min of untreated cardiac arrest.[42,43,136] At the opposite end of the spectrum, a patient with an evolving AMI or severe myocardial dysfunction might benefit from the lowest target MAP that will ensure adequate cerebral oxygen delivery.

The optimal CVP goal for post-cardiac arrest patients has not been defined by prospective clinical trials, but a range of 8—12 mmHg is used in most published studies. An important consideration is the potential for persistent precipitating pathology that could cause elevated CVP independent of volume status, such as cardiac tamponade, right-sided AMI, pulmonary embolism, and tension pneumothorax or any dis-

ease that impairs myocardial compliance. There is also a risk of precipitating pulmonary oedema in the presence of post-cardiac arrest myocardial dysfunction. The post-cardiac arrest ischaemia/reperfusion response causes intravascular volume depletion relatively soon after the heart is restarted, and volume expansion is usually required. There is no evidence indicating an advantage for any specific type of fluid (crystalloid or colloid) in the post-cardiac arrest phase. There are some animal data indicating that hypertonic saline may improve myocardial and cerebral blood flow when given during CPR,[137,138] but there are no clinical data to indicate an advantage for hypertonic saline in the post-cardiac arrest phase.

The balance between systemic oxygen delivery and consumption can be monitored indirectly with mixed venous oxygen saturation (SvO_2) or $ScvO_2$. The optimal $ScvO_2$ goal for post-cardiac arrest patients has not been defined by prospective clinical trials, and the value of continuous $ScvO_2$ monitoring remains to be demonstrated. One important caveat is that a subset of post-cardiac arrest patients have elevated central or mixed venous oxygen saturations despite inadequate tissue oxygen delivery, a phenomenon that is more common in patients given high doses of epinephrine during CPR.[139] This phenomenon, termed ''venous hyperoxia,'' can be attributed to impaired tissue oxygen utilisation caused by microcirculatory failure or mitochondrial failure.

Additional surrogates for oxygen delivery include urine output and lactate clearance. Two of the EGDT randomized prospective trials described above used a urine output target of $\geq 0.5\,mL\,kg^{-1}\,24\,h^{-1}$.[133,135] A higher urine output goal of $>1\,mL\,kg^{-1}\,h^{-1}$ is reasonable in postarrest patients treated with therapeutic hypothermia, given the higher urine production during hypothermia[13]; however, urine output could be misleading in the presence of acute or chronic renal insufficiency. Lactate concentrations are elevated early after ROSC because of the total body ischaemia of cardiac arrest. This limits the usefulness of a single measurement during early haemodynamic optimization. Lactate clearance has been associated with outcome in patients with ROSC after out-of-hospital cardiac arrest.[140,141] However, lactate clearance can be impaired by convulsive seizures, excessive motor activity, hepatic insufficiency and hypothermia.

The optimal goal for haemoglobin concentration in the post-cardiac arrest phase has not been defined. The original early goal-directed therapy in sepsis study used a transfusion threshold hematocrit of 30, but relatively few patients received a transfusion, and the use of this transfusion threshold, even for septic shock, is controversial.[133] Subgroup analysis of patients with a closed head injury enrolled in the Transfusion Requirements in Critical Care trial showed no difference in mortality rates when haemoglobin concentration was maintained at $10-12\,g\,dL^{-1}$ compared with $7-9\,g\,dL^{-1}$.[142] A post-cardiac arrest care protocol published by a group from Norway included a haemoglobin target of $9-10\,g\,dL^{-1}$.[13]

In summary, the value of haemodynamic optimization or early goal-directed therapy in post-cardiac arrest care has yet to be demonstrated in randomized prospective clinical trials, and there is little evidence about the optimal goals in post-cardiac arrest syndrome. On the basis of the limited available evidence, reasonable goals for post-cardiac arrest syndrome include an MAP of 65—100 mmHg (taking into consideration the patient's normal blood pressure, cause of arrest, and severity of any myocardial dysfunction), CVP of 8—12 mmHg, $ScvO_2 > 70\%$, urine output $> 1\,mL\,kg^{-1}\,h^{-1}$ and a normal or decreasing serum or blood lactate level. Goals for haemoglobin concentration during post-cardiac arrest care remain to be defined.

Oxygenation

Existing guidelines emphasize the use of an F_{IO_2} of 1.0 during CPR, and clinicians will frequently maintain ventilation with 100% oxygen for variable periods after ROSC. Although it is important to ensure that patients are not hypoxemic, a growing body of preclinical evidence suggests that hyperoxia during the early stages of reperfusion harms postischaemic neurons by causing excessive oxidative stress.[51,52,143,144] Most relevant to post-cardiac arrest care, ventilation with 100% oxygen for the first hour after ROSC resulted in worse neurological outcome compared with immediate adjustment of the F_{IO_2} to produce an arterial oxygen saturation of 94—96%.[145]

On the basis of preclinical evidence alone, unnecessary arterial hyperoxia should be avoided, especially during the initial post-cardiac arrest period. This can be achieved by adjusting the F_{IO_2} to produce an arterial oxygen saturation of 94—96%. However, controlled reoxygenation has yet to be studied in randomized prospective clinical trials.

Ventilation

Although cerebral autoregulation is either absent or dysfunctional in most patients in the acute phase after cardiac arrest,[47] cerebrovascular reactivity to changes in arterial carbon dioxide tension seems to be preserved.[53,55,146,147] Cerebrovascular resistance may be elevated for at least 24 h in comatose survivors of cardiac arrest.[55] There are no data to support the targeting of a specific $PaCO_2$ after resuscitation from cardiac arrest; however, extrapolation of data from studies of other cohorts suggest ventilation to normocarbia is appropriate. Studies in brain-injured patients have shown that the cerebral vasoconstriction caused by hyperventilation may produce potentially harmful cerebral ischaemia.[148—150] Hyperventilation also increases intrathoracic pressure, which will decrease cardiac output both during and after CPR.[151,152] Hypoventilation may also be harmful because hypoxia and hypercarbia could increase ICP or compound metabolic acidosis, which is common shortly after ROSC.

High tidal volumes cause barotrauma, volutrauma,[153] and biotrauma[154] in patients with acute lung injury (ALI). The Surviving Sepsis Campaign recommends the use of a tidal volume of $6\,mL\,kg^{-1}$ (predicted) body weight and a plateau pressure of $\leq 30\,cm\ H_2O$ during mechanical ventilation of patients with sepsis-induced ALI or acute respiratory distress syndrome.[155] However, there are no data to support use of a specific tidal volume during post-cardiac arrest care and the use of this protective lung strategy will often result in hypercapnia, which may be harmful in the post-cardiac arrest patient. In these patients it may be necessary to use tidal volumes higher than $6\,mL\,kg^{-1}$ to prevent hypercapnia. When

inducing therapeutic hypothermia, additional blood gases may be helpful to adjust tidal volumes, because cooling will decrease metabolism and the tidal volumes required. Blood gas values can either be corrected for temperature or left uncorrected. There is no evidence to suggest that one strategy is significantly better than the other.

In summary, the preponderance of evidence indicates that hyperventilation should be avoided in the post-cardiac arrest period. Ventilation should be adjusted to achieve normocarbia and should be monitored by regular measurement of arterial blood gas values.

Circulatory support

Haemodynamic instability is common after cardiac arrest and manifests as dysrhythmias, hypotension, and low cardiac index.[97] Underlying mechanisms include intravascular volume depletion, impaired vasoregulation, and myocardial dysfunction.

Dysrhythmias can be treated by maintaining normal electrolyte concentrations and using standard drug and electrical therapies. There is no evidence to support the prophylactic use of anti-arrhythmic drugs after cardiac arrest. Dysrhythmias are commonly caused by focal cardiac ischaemia, and early reperfusion treatment is probably the best anti-arrhythmic therapy. Ultimately, survivors of cardiac arrest attributed to a primary dysrhythmia should be evaluated for placement of a pacemaker or an implantable cardioverter-defibrillator (ICD).

The first-line intervention for hypotension is to optimize right-heart filling pressures by using intravenous fluids. In one study, 3.5—6.5 L of intravenous crystalloid was required in the first 24 h following ROSC after out-of-hospital cardiac arrest to maintain right atrial pressures in the range of 8—13 mmHg.[97] In a separate study, out-of-hospital post-cardiac arrest patients had a positive fluid balance of 3.5 ± 1.6 L in the first 24 h, with a CVP goal of 8—12 mmHg.[13]

Inotropes and vasopressors should be considered if haemodynamic goals are not achieved despite optimized preload. Myocardial dysfunction after ROSC is well-described in both animal[101,102,156,157] and human[97,99,112] studies. Post-cardiac arrest global myocardial dysfunction is generally reversible and responsive to inotropes, but the severity and duration of the myocardial dysfunction may impact survival.[97] Early echocardiography will enable the extent of myocardial dysfunction to be quantified and may guide therapy. Impaired vasoregulation is also common in post-cardiac arrest patients; this may require treatment with vasopressors and is also reversible. Persistence of reversible vasopressor dependency has been reported for up to 72 h after out-of-hospital cardiac arrest despite preload optimization and reversal of global myocardial dysfunction.[97] No individual drug or combination of drugs has been demonstrated to be superior in the treatment of post-cardiac cardiovascular dysfunction. Despite improving haemodynamic values, the effect on survival of inotropes and vasopressors in the post-cardiac arrest phase has not been studied in humans. Furthermore, inotropes have the potential to exacerbate or induce focal ischaemia in the setting of ACS and coronary artery disease (CAD). The choice of inotrope or vasopressor can be guided by blood pressure, heart rate, echocardiographic estimates of myocardial dysfunction, and surrogate measures of tissue oxygen delivery such as $ScvO_2$, lactate clearance, and urine output. If a pulmonary artery catheter (PAC) or some form of non-invasive cardiac output monitor is being used, therapy can be further guided by cardiac index and systemic vascular resistance. There is no evidence that the use of a PAC or non-invasive cardiac output monitoring improves outcome after cardiac arrest.

If volume expansion and treatment with vasoactive and inotropic drugs do not restore adequate organ perfusion, consider mechanical circulatory assistance.[158,159] This treatment can support circulation in the period of transient severe myocardial dysfunction that often occurs for 24—48 h after ROSC.[97] The intra-aortic balloon pump (IABP) is the most readily available device to augment myocardial perfusion; it is generally easy to insert with or without radiological imaging, and its use after cardiac arrest has been recently documented in some studies.[13,160] If additional cardiac support is needed, then more invasive treatments such as percutaneous cardiopulmonary bypass (PCPB), extracorporeal membrane oxygenation (ECMO), or transthoracic ventricular assist devices can be considered.[161,162] In a recent systematic review of published case series in which PCPB was initiated during cardiac arrest and then gradually weaned after ROSC ($n = 675$), an overall in-hospital mortality rate of 55% was reported.[162] The clinical value of initiating these interventions after ROSC for cardiovascular support has not been determined.

Management of acute coronary syndrome

Coronary artery disease is present in the majority of out-of-hospital cardiac arrest patients,[163—165] and AMI is the most common cause of sudden cardiac death.[165] One autopsy study reported coronary artery thrombi in 74 of 100 subjects who died of ischaemic heart disease within 6 h of symptom onset, and plaque fissuring in 21 of 26 subjects in the absence of thrombus.[166] A more recent review reported acute changes in coronary plaque morphology in 40—86% of cardiac arrest survivors and in 15—64% of autopsy studies.[167]

The feasibility and success of early coronary angiography and subsequent percutaneous coronary intervention (PCI) after out-of-hospital cardiac arrest is well-described in a number of relatively small case series and studies with historical controls.[13,14,123,160,168—172] A subset of these studies focus on early primary PCI in post-cardiac arrest patients with ST elevation myocardial infarction (STEMI).[14,168—171] Although inclusion criteria and the outcomes reported are variable, average intervals from symptom onset or CPR to balloon inflation ranged from 2 to 5 h, angiographic success rates ranged from 78% to 95%, and overall in-hospital mortality ranged from 25% to 56%. In several of these studies, PCI was combined with therapeutic hypothermia. One retrospective study reported 25% in-hospital mortality among 40 consecutive comatose post-cardiac arrest patients with STEMI who received early coronary angiography/PCI and mild therapeutic hypothermia compared with a 66% in-hospital mortality rate for matched historical controls who underwent PCI without therapeutic hypothermia.[14] In this study 21 (78%) of 27 hypothermia-treated 6-month survivors

had a good neurologic outcome (CPC of 1 or 2) compared with only 6 (50%) of 12 non-hypothermia-treated 6-month survivors.

Studies with broader inclusion criteria (not limited to STEMI) have also shown promising results. In one such study, 77% of all out-of-hospital cardiac arrest survivors with presumed cardiac aetiology underwent immediate coronary angiography, revealing CAD in 97%, of which >80% had total occlusion of a major coronary artery.[13] Nearly half of these patients underwent reperfusion interventions with the majority by percutaneous coronary intervention and a minority by coronary artery bypass graft (CABG). Among patients admitted after ROSC, the overall in-hospital mortality decreased from 72% before the introduction of a comprehensive post-cardiac arrest care plan (which included this intensive coronary reperfusion strategy and therapeutic hypothermia) to 44% ($P < 0.001$), and >90% of survivors were neurologically normal.[13]

Chest pain and ST elevation may be poor predictors of acute coronary occlusion in post-cardiac arrest patients.[123] Given that acute coronary occlusion is the most common cause of out-of-hospital cardiac arrest, prospective studies are needed to determine if immediate coronary angiography should be performed in all patients after ROSC. It is feasible to initiate cooling before coronary angiography, and patients can be transported to the angiography laboratory while cooling continues.[13,14,160]

If there are no facilities for immediate PCI, in-hospital thrombolysis is recommended for patients with ST elevation who have not received prehospital thrombolysis.[173,174] Although the efficacy and risk thrombolytic therapy has been well characterised in post-cardiac arrest patients,[174–176] the potential interaction of mild therapeutic hypothermia and thrombolytic therapy has not be formally studied. Theoretical considerations include possible impact on the efficacy of thrombolysis and the risk of haemorrhage. CABG is indicated in the post-cardiac arrest phase for patients with left main coronary artery stenosis or 3-vessel CAD. In addition to acute reperfusion, management of ACS and CAD should follow standard guidelines.

In summary, patients resuscitated from cardiac arrest and who have ECG criteria for STEMI should undergo immediate coronary angiography with subsequent PCI if indicated. Furthermore, given the high incidence of ACS in patients with out-of-hospital cardiac arrest and limitations of ECG-based diagnosis, it is appropriate to consider immediate coronary angiography in all post-cardiac arrest patients in whom ACS is suspected. If PCI is not available, thrombolytic therapy is an appropriate alternative for post-cardiac arrest management of STEMI. Standard guidelines for management of ACS and CAD should be followed.

Other persistent precipitating pathologies

Other causes of out-of-hospital cardiac arrest include pulmonary embolism, sepsis, hypoxaemia, hypovolaemia, hypokalaemia, hyperkalaemia, metabolic disorders, accidental hypothermia, tension pneumothorax, cardiac tamponade, toxins, intoxication or cerebrovascular catastrophes. The incidence of these causes is potentially higher for in-hospital cardiac arrest.[5] These potential causes of cardiac arrest that persist after ROSC should be diagnosed promptly and treated.

Therapeutic hypothermia

Therapeutic hypothermia should be part of a standardised treatment strategy for comatose survivors of cardiac arrest.[13,177,178] Two randomized clinical trials and a meta-analysis 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 ROSC.[8,9,179] Patients in these studies were cooled to 33 °C or the range of 32–34 °C for 12–24 h. The Hypothermia After Cardiac Arrest (HACA) study included a small subset of patients with in-hospital cardiac arrest.[8] Four studies with historical control groups reported benefit after therapeutic hypothermia in comatose survivors of out-of-hospital non-VF arrest[180]and all rhythm arrests.[12,13,132] Other observational studies provide evidence possible benefit after cardiac arrest from other initial rhythms and in other settings.[181,182] Mild hypothermia is the only therapy applied in the post-cardiac arrest setting that has been shown to increase survival rates. The patients who may benefit from this treatment have not been fully elucidated, and the ideal induction technique (alone or in combination), target temperature, duration, and rewarming rate have yet to be established.

Animal studies demonstrate a benefit of very early cooling either during CPR or within 15 min of ROSC when cooling is maintained for only a short duration (1–2 h).[183,184] When prolonged cooling is used (>24 h), however, less is known about the therapeutic window. Equivalent neuroprotection was produced in a rat model of cardiac arrest when a 24-h period of cooling was initiated either at the time of ROSC or delayed by 1 h.[185] In a gerbil forebrain ischaemia model, sustained neuroprotection was achieved when hypothermia was initiated at 1, 6, or 12 h after reperfusion and maintained for 48 h[186]; however, neuroprotection did decrease when the start of therapy was delayed. The median time to achieve target temperature in the HACA trial was 8 h (IQR 6–26),[8] whereas in the Bernard study, average core temperature was reported to be 33.5 °C within 2 h of ROSC.[9] Clearly, additional clinical studies are needed to optimize this therapeutic strategy.

The practical approach of therapeutic hypothermia can be divided into 3 phases: induction, maintenance, and rewarming. Induction can be instituted easily and inexpensively with intravenous ice-cold fluids (30 mL/kg of saline 0.9% or Ringer's lactate)[187–191] or traditional ice packs placed on the groin and armpits and around the neck and head. In most cases it is easy to cool patients initially after ROSC because their temperature normally decreases within the first hour.[10,64] Initial cooling is facilitated by concomitant neuromuscular blockade with sedation to prevent shivering. Patients can be transferred to the angiography laboratory with ongoing cooling using these easily applied methods.[13,14] Surface or internal cooling devices (as described below) can also be used either alone or in combination with the above measures to facilitate induction.[182,192]

In the maintenance phase, effective temperature monitoring is needed to avoid significant temperature fluctuations. This is best achieved 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 internal cooling devices which are usually inserted into a femoral or subclavian vein. Less sophisticated methods, such as cold wet blankets placed on the torso and around the extremities, or ice packs combined with ice-cold fluids, can also be effective; but these methods may be more time consuming for nursing staff, result in greater temperature fluctuations, and do not enable controlled rewarming.[193] Ice-cold fluids alone cannot be used to maintain hypothermia.[194]

The rewarming phase can be regulated using the external or internal devices used for cooling or by other heating systems. The optimal rate of rewarming is not known, but current consensus is to rewarm at about 0.25—0.5 °C/h.[181] Particular care should be taken during the cooling and rewarming phases because metabolic rate, plasma electrolyte concentrations, and haemodynamic conditions may change rapidly.

Therapeutic hypothermia is associated with several complications.[195] Shivering is common, particularly during the induction phase.[196] Mild hypothermia increases systemic vascular resistance, which reduces cardiac output. A variety of arrhythmias may be induced by hypothermia, but bradycardia is the most common.[182] Hypothermia induces a diuresis and coexisting hypovolaemia will compound haemodynamic instability. Diuresis may produce electrolyte abnormalities including hypophosphatemia, hypokalaemia, hypomagnesemia and hypocalcemia and these, in turn, may cause dysrhythmias.[195,197] The plasma concentrations of these electrolytes should be measured frequently and electrolytes should be replaced to maintain normal values. Hypothermia decreases insulin sensitivity and insulin secretion, which results in hyperglycaemia.[9] This should be treated with insulin (see Section 'Glucose control'). Effects on platelet and clotting function account for impaired coagulation and increased bleeding. Hypothermia can impair the immune system and increase infection rates.[198] In the HACA study, pneumonia was more common in the cooled group but this did not reach statistical significance.[8] The serum amylase may increase during hypothermia but its significance is unclear. The clearance of sedative drugs and neuromuscular blockers is reduced by up to 30% at a temperature of 34 °C.[199]

Magnesium sulphate, a naturally occurring NMDA receptor antagonist, reduces shivering thresholds and can be given to reduce shivering during cooling.[200] Magnesium is also a vasodilator, and therefore increases cooling rates.[201] It has anti-arrhythmic properties, and there are some animal data indicating that magnesium provides added neuroprotection in combination with hypothermia.[202] Magnesium sulphate 5 g can be infused over 5 h, which covers the period of hypothermia induction. The shivering threshold can also be reduced by warming the skin — the shivering threshold is reduced by 1 °C for every 4 °C increase in skin temperature.[203] Application of a forced air warming blanket reduces shivering during intravascular cooling.[204]

If therapeutic hypothermia is not feasible or contraindicated, then, at a minimum, pyrexia must be prevented. Pyrexia is common in the first 48 h after cardiac arrest.[63,205,206] The risk of a poor neurological outcome increases for each degree of body temperature >37 °C.[64]

In summary, both preclinical and clinical evidence strongly support mild therapeutic hypothermia as an effective therapy for the post-cardiac arrest syndrome. Unconscious adult patients with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32—34 °C for at least 12—24 h.[177] Most experts currently recommend cooling for at least 24 h. Although data support cooling to 32—34 °C, the optimal temperature has not been determined. Induced hypothermia might also benefit unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest from a nonshockable rhythm or in-hospital cardiac arrest.[177] Although the optimal timing of initiation has not been clinically defined, current concensus is to initiate cooling as soon as possible. The therapeutic window, or time after ROSC at which therapeutic hypothermia is no longer beneficial, is also not defined. Rapid intravenous infusion of ice-cold 0.9% saline or Ringer's lactate (30 mL kg^{-1}) is a simple, effective method for initiating cooling. Shivering should be treated by ensuring adequate sedation or neuromuscular blockade with sedation. Bolus doses of neuromuscular blocking drugs are usually adequate, but infusions are occasionally necessary. Slow rewarming is recommended (0.25—0.5 °C/h), although the optimum rate for rewarming has not been clinically defined. If therapeutic hypothermia is not undertaken, pyrexia during the first 72 h after cardiac arrest should be treated aggressively with antipyretics or active cooling.

Sedation and neuromuscular blockade

If patients do not show adequate signs of awakening within the first 5—10 min after ROSC, tracheal intubation (if not already achieved), mechanical ventilation, and sedation will be required. Adequate sedation will reduce oxygen consumption, which is further reduced with therapeutic hypothermia. Use of published sedation scales for monitoring these patients (e.g., the Richmond or Ramsay Scales) may be helpful.[207,208] Both opioids (analgesia) and hypnotics (e.g., propofol or benzodiazepines) should be used. During therapeutic hypothermia, optimal sedation can prevent shivering, and achieve target temperature earlier. If shivering occurs despite deep sedation, neuromuscular blocking drugs (as an intravenous bolus or infusion) should be used with close monitoring of sedation and neurological signs such as seizures. Because of the relatively high incidence of seizures after cardiac arrest, continuous electroencephalographic (EEG) monitoring for patients during sustained neuromuscular blockade is advised.[209] The duration of action of neuromuscular blockers is prolonged during hypothermia.[199]

Although it has been common practice to sedate and ventilate patients for at least 24 h after ROSC, there are no secure data to support routines of ventilation, sedation, or

neuromuscular blockade after cardiac arrest. The duration of sedation and ventilation may be influenced by the use of therapeutic hypothermia.

In summary, critically ill post-cardiac arrest patients will require sedation for mechanical ventilation and therapeutic hypothermia. Use of sedation scales for monitoring may be helpful. Adequate sedation is particularly important for prevention of shivering during induction of therapeutic hypothermia, maintenance, and rewarming. Neuromuscular blockade may facilitate induction of therapeutic hypothermia, but if continuous infusions of neuromuscular blocking drugs become necessary, continuous EEG monitoring should be considered.

Seizure control and prevention

Seizures or myoclonus or both occur in 5—15% of adult patients who achieve ROSC and 10—40% of those who remain comatose.[75,76,210,211] Seizures increase cerebral metabolism by up to 3-fold.[212] No studies directly address the use of prophylactic anticonvulsant drugs after cardiac arrest in adults. Anticonvulsants such as thiopental, and especially phenytoin, are neuroprotective in animal models,[213—215] but a clinical trial of thiopental after cardiac arrest showed no benefit.[216] Myoclonus can be particularly difficult to treat; phenytoin is often ineffective. Clonazepam is the most effective antimyoclonic drug, but sodium valproate and levetiracetam may also be effective.[83] Effective treatment of myoclonus with propofol has been described.[217] With therapeutic hypothermia, good neurological outcomes have been reported in patients initially displaying severe post-arrest status epilepticus.[218,219]

In summary, prolonged seizures may cause cerebral injury and should be treated promptly and effectively with benzodiazepines, phenytoin, sodium valproate, propofol, or a barbiturate. Each of these drugs can cause hypotension, and this must be treated appropriately. Clonazepam is the drug of choice for the treatment of myoclonus. Maintenance therapy should be started after the first event once potential precipitating causes (e.g., intracranial haemorrhage, electrolyte imbalance) are excluded. Prospective studies are needed to determine the benefit of continuous EEG monitoring.

Glucose control

Tight control of blood glucose (4.4—6.1 mmol L^{-1} or 80—110 mg dL^{-1}) with insulin reduced hospital mortality rates in critically ill adults in a surgical ICU[220] and appeared to protect the central and peripheral nervous system.[221] When the same group repeated this study in a medical ICU, the overall mortality rate was similar in the intensive insulin and control groups.[222] Among the patients with an ICU stay of $\geq$3 days, intensive insulin therapy reduced the mortality rate from 52.5% (control group) to 43% ($P = 0.009$). Of the 1200 patients in the medical ICU study, 61 had neurological disease; the mortality rate among these patients was the same in the control and treatment groups (29% versus 30%).[222] Two studies indicate that the median length of ICU stay for ICU survivors after admission following cardiac arrest is approximately 3.4 days.[6,13]

Hyperglycaemia is common after cardiac arrest. Blood glucose concentrations must be monitored frequently in these patients and hyperglycaemia treated with an insulin infusion. Recent studies indicate that post-cardiac arrest patients may be treated optimally with a target range for blood glucose concentration of up to 8 mmol L^{-1} (144 mg dL^{-1}).[13,223,224] In a recent study, 90 unconscious survivors of out-of-hospital VF cardiac arrest were cooled and randomized into 2 treatment groups: a strict glucose control (SGC) group, with a blood glucose target of 4—6 mmol L^{-1} (72—108 mg dL^{-1}), and a moderate glucose control (MGC) group, with a blood glucose target of 6—8 mmol L^{-1} (108—144 mg dL^{-1}).[223] Episodes of moderate hypoglycaemia (<3.0 mmol L^{-1} or 54 mg dL^{-1}) occurred in 18% of the SGC group and 2% of the MGC group ($P = 0.008$); however, there were no episodes of severe hypoglycaemia (<2.2 mmol L^{-1} or 40 mg dL^{-1}). There was no difference in mortality. A target glucose range with an upper value of 8.0 mmol L^{-1} (144 mg dL^{-1}) has been suggested by others.[13,224,225] The lower value of 6.1 mmol L^{-1} may not reduce mortality any further but instead may expose patients to the potentially harmful effects of hypoglycaemia.[223] The incidence of hypoglycaemia in another recent study of intensive insulin therapy exceeded 18%,[226] and some have cautioned against its routine use in the critically ill.[227,228] Regardless of the chosen glucose target range, blood glucose must be measured frequently,[13,223] especially when insulin is started and during cooling and rewarming periods.

Neuroprotective pharmacology

Over the past 3 decades investigators have used animal models of global cerebral ischaemia to study numerous neuroprotective modalities, including anesthetics, anticonvulsants, calcium and sodium channel antagonists, N-methyl D-aspartate (NMDA)-receptor antagonists, immunosuppressants, growth factors, protease inhibitors, magnesium, and γ-aminobutyric acid (GABA) agonists. Many of these targeted pharmacological neuroprotective strategies that focus on specific injury mechanisms have shown benefit in preclinical studies. Yet, none of the interventions tested thus far in prospective clinical trials have improved outcomes after out-of-hospital cardiac arrest.[216,229—231]

There are many negative or neutral studies of targeted neuroprotective trials in humans with acute ischaemic stroke. Over the past 10 years the Stroke Therapy Academic Industry Roundtable (STAIR) has made recommendations for preclinical evidence of drug efficacy and enhancing acute stroke trial design and performance in studies of neuroprotective therapies in acute stroke.[232] Despite improved trial design and relatively large human clinical trials, results from neuroprotective studies remain disappointing.[233—235]

In summary, there is inadequate evidence to recommend any pharmacological neuroprotective strategies to reduce brain injury in post-cardiac arrest patients.

Adrenal dysfunction

Relative adrenal insufficiency occurs frequently after successful resuscitation of out-of-hospital cardiac arrest and is associated with increased mortality (see Section 'Epi-

demiology of the post-cardiac arrest syndrome').[119,236] One small study has demonstrated increased ROSC when patients with out-of-hospital cardiac arrest were treated with hydrocortisone,[237] but the use of steroids has not been studied in the post-cardiac arrest phase. The use of low-dose steroids, even in septic shock, for which they are commonly given, remains controversial.[238] Although relative adrenal insufficiency may exist after ROSC, there is no evidence that treatment with steroids improves long-term outcomes. Therefore, routine use of steroids after cardiac arrest is not recommended.

Renal failure

Renal failure is common in any cohort of critically ill patients. In a recent study of comatose survivors of out-of-hospital cardiac arrest, 5 of 72 (7%) received haemodialysis, and the incidence was the same with or without the use of therapeutic hypothermia.[14] In another study, renal function was impaired transiently in out-of-hospital post-cardiac arrest patients treated with therapeutic hypothermia, required no interventions, and returned to normal by 28 days.[239] The indications for starting renal replacement therapy in comatose cardiac arrest survivors are the same as those used for critically ill patients in general.[240]

Infection

Complications inevitably occur during the treatment of post-cardiac arrest patients as they do during the treatment of any critically ill patients. Although several studies have shown no statistical difference in complication rates between patients with out-of-hospital cardiac arrest who are treated with hypothermia and those who remain normothermic, these studies are generally underpowered to show this conclusively.[12,132] Pneumonia caused by aspiration or mechanical ventilation is probably the most important complication in comatose post-cardiac arrest patients, occurring in up to 50% of patients after out-of-hospital cardiac arrest.[8,13] In comparison with other intubated critically ill patients, post-cardiac arrest patients are at particularly high risk of developing pneumonia within the first 48 h of intubation.[241]

Placement of implantable cardioverter-defibrillators

In survivors with good neurological recovery, insertion of an ICD is indicated if subsequent cardiac arrests cannot be reliably prevented by other treatments (such as a pacemaker for atrioventricular block, transcatheter ablation of a single ectopic pathway, or valve replacement for critical aortic stenosis).[242–250] For patients with underlying coronary disease, an ICD is strongly recommended if myocardial ischaemia was not identified as the single trigger of sudden cardiac death or if it cannot be treated by coronary revascularization. Systematic implementation of ICD therapy should be considered for survivors of sudden cardiac death with persistent low (<30%) left ventricular ejection fraction. Detection of asynchrony is important because stimulation at multiple sites may further improve prognosis when combined with medical treatment (diuretics, β-blockers, angiotensin-converting enzyme [ACE] inhibitors) in patients with low left ventricular ejection fraction.[250]

Long-term management

Issues related to long-term management are beyond the scope of this scientific statement but include cardiac and neurological rehabilitation and psychiatric disorders.

Post-cardiac arrest prognostication

With the brain's heightened susceptibility to global ischaemia, the majority of cardiac arrest patients who are successfully resuscitated have impaired consciousness, and some remain in a vegetative state. The need for protracted high-intensity care of neurologically devastated survivors presents an immense burden to healthcare systems, patients' families, and society in general.[251,252] To limit this burden, clinical factors and diagnostic tests are used to prognosticate functional outcome. With the limitation of care or withdrawal of life-sustaining therapies as a likely outcome of prognostication, studies have focused on poor long-term prognosis (vegetative state or death) based on clinical or test findings that indicate irreversible brain injury. A recent study showed that prognostication based on neurological examination and diagnostic modalities influenced the decision of physicians and families on the timing of withdrawal of life-sustaining therapies.[253]

Recently several systematic reviews evaluated predictors of poor outcome, including clinical circumstances of cardiac arrest and resuscitation, patient characteristics, neurological examination, electrophysiological studies, biochemical markers, and neuroimaging.[254–256] Despite a large body of research in this area, the timing and optimal approach to prognostication of futility is controversial. Most importantly, the impact of therapeutic hypothermia on the overall accuracy of clinical prognostication has undergone only limited prospective evaluation.

This section approaches important prognostic factors as a manifestation of specific neurological injury in the context of the overall neurological presentation. Having been the most studied factor with widest applicability even in institutions with limited technologies and expertise, the primary focus is on neurological examination, with the use of adjunctive prognostic factors to enhance the accuracy of predicting poor outcome. We will present classical factors in patients not treated with hypothermia followed by recent studies on the impact of therapeutic hypothermia on prognostic factors and clinical outcome.

Prognostication in patients not treated with hypothermia

Pre-cardiac arrest factors

Many studies have identified factors associated with poor functional outcome after resuscitation, but no studies have shown a reliable predictor of outcome. Advanced age is associated with decreased survival after resuscitation,[257–259] but

at least one study suggested that advanced age did not predict poor neurological outcome in survivors.[260] Race[261–263] and poor pre-cardiac arrest health, including conditions such as diabetes,[259,264] sepsis,[265] metastatic cancer,[266] renal failure,[267] homebound lifestyle,[266] and stroke[267] were associated with outcome but not enough to be reliable predictors of function. The prearrest Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores also were not reliable predictors.[266,268]

Intra-cardiac arrest factors

Many factors during the resuscitation process have been associated with functional outcome, but no single factor has been identified as a reliable predictor. Some association with poor functional outcome has been made between a long interval between collapse and the start of CPR and increased duration of CPR to ROSC,[260,269] but high false-positive rates make these unreliable for predicting poor outcome.[254] Furthermore, the quality of CPR is likely to influence outcome. Lack of adherence to established CPR guidelines,[270–272] including failure to deliver a shock or achieve ROSC before transport,[273] and long preshock pauses with extended interruption to assess rhythms and provide ventilation have been associated with poor outcome.[270,272] A maximum end-tidal carbon dioxide ($ETCO_2$) of <10 mmHg (as a marker of cardiac output during CPR) is associated with worse outcomes.[274–279] Other arrest-related factors associated with poor outcome that are unreliable as predictors are asystole as the initial cardiac rhythm[280,281] and noncardiac causes of arrest.[260,282]

Post-cardiac arrest factors

The bedside neurological examination remains one of the most reliable and widely validated predictors of functional outcome after cardiac arrest.[76,254–256] With sudden interruption of blood flow to the brain, higher cortical functions, such as consciousness, are lost first, whereas lower brainstem functions, such as spontaneous breathing activity, are lost last.[283] Not surprisingly, retention of any neurological function during or immediately after CPR portends a good neurological outcome. The absence of neurological function immediately after ROSC, however, is not a reliable predictor of poor neurological outcome. The reliability and validity of neurological examination as a predictor of poor outcome depends on the presence of neurological deficits at specific time points after ROSC.[255,256] Findings of prognostic value include the absence of pupillary light reflex, corneal reflex, facial movements, eye movements, gag, cough, and motor response to painful stimuli. Of these, the absence of pupillary light response, corneal reflex, or motor response to painful stimuli at day 3 provide the most reliable predictor of poor outcome (vegetative state or death).[211,254,256] On the basis of a systematic review of the literature, it was reported that absent brainstem reflexes or a Glasgow Coma Scale (GCS) motor score of $\leq$2 at 72 h had a false-positive rate (FPR) of 0% (95% CI 0–3%) for predicting poor outcome.[254] In a recent prospective trial it was reported that absent pupillary or corneal reflexes at 72 h had a 0% FPR (95% CI 0–9%), whereas absent motor response at 72 h had a 5% FPR (95% CI 2–9%) for poor outcome.[211] Poor neurological outcome is expected with these findings because of the extensive brain injury involving the upper brainstem (midbrain), which is the location of the ascending reticular formation (responsible for arousal) and where the pupillary light response and motor response to pain is facilitated.[284] When the neurological examination is used as the basis for prognostication, it is important to consider that physiological and pathological factors (hypotension, shock, and severe metabolic abnormalities) and interventions (paralytics, sedatives, and hypothermia) may influence the findings and lead to errors in interpretation.[254] Therefore, adequate efforts must be undertaken to stabilize the patient medically before prognosis is determined. Use of the bedside neurological examination can also be compromised by complications such as seizures and myoclonus, which, if prolonged and repetitive, may carry their own grave prognosis.[285] Although status myoclonus has been regarded as a reliable predictor of poor outcome (FPR 0% [95% CI 0–8.8%]),[254] it may be misdiagnosed by non-neurologists.

Combinations of neurological findings have been studied in an attempt to find a simple summary scale such as the GCS,[286] which is based on the patient's best verbal, eye, and motor responses. The GCS score – especially a low motor component score – is associated with poor outcome.[287–289] The importance of brainstem reflexes in the assessment of brain injury has been incorporated into a GCS-style scale called the Full Outline of UnResponsiveness (FOUR) scale; the FOUR score includes the 4 components of eye, motor, and cranial nerve reflexes (i.e., pupillary light response) and respiration.[290] Some of the best predictors of neurological outcome are cranial nerve findings and motor response to pain. A measure that combines these findings, such as the FOUR score, may have better utility. Unfortunately, no studies have been undertaken to assess the utility of the FOUR score in cardiac arrest survivors.

Neurophysiological tests

The recording of somatosensory-evoked potentials (SSEP) is a neurophysiological test of the integrity of the neuronal pathways from a peripheral nerve, spinal cord, or brainstem to the cerebral cortex.[291,292] The SSEP is probably the best and most reliable prognostic test because it is influenced less by common drugs and metabolic derangements. The N20 component (representing the primary cortical response) of the SSEP with median nerve stimulation is the best studied evoked-potential waveform in prognostication.[211,256,293–295] In an unresponsive cardiac arrest survivor, the absence of the bilateral N20 component of the SSEP with median nerve stimulation from 24 h to one week after ROSC very reliably predicts poor outcome (FPR for poor outcome = 0.7%, 95% CI 0.1–3.7).[254–256] The presence of the N20 waveform in comatose survivors, however, did not reliably predict a good outcome.[296] It also has been suggested that the absence of the N20 waveform is better than the bedside neurological examination as a predictor of poor outcome.[211] Widespread implementation of the SSEP in postresuscitation care requires advanced neurological training; this investigation can be completed and interpreted only in specialized centres. Other evoked potentials such as brainstem auditory and visual and long-latency evoked-potential tests have not been thoroughly tested or widely replicated for their prognostic value in brain injury after cardiac arrest.[296–299]

Electroencephalography has been extensively studied as a tool for evaluating the depth of coma and extent of damage after cardiac arrest. Many malignant EEG patterns have been associated with poor functional outcome, the most reliable of which appear to be generalized suppression to <20 μV, burst-suppression pattern with generalized epileptiform activity, and generalized periodic complexes on a flat background.[254] However, the predictive value of individual patterns is poorly understood because most studies categorize a panel of patterns as malignant. A meta-analysis of studies reporting malignant EEG patterns within the first 3 days after ROSC calculated an FPR of 3% (95% CI 0.9—11%).[254] The authors concluded that the EEG alone was insufficient to prognosticate futility. Electroencephalography is non-invasive and easy to record even in unstable patients, but its widespread application is hampered by the lack of a unified classification system, lack of consistent study design, the need for EEG expertise, and its susceptibility to numerous drugs and metabolic disorders.[291,293,294,300—303] Recent advances in the analysis of electroencephalography and continuous bedside recording have addressed many of these limitations. Quantitative EEG (QEEG) analysis will enable non-neurologists to use this technology at the bedside.[301,302,304] Given the capability of the EEG to monitor brain activity continuously, future research can focus on developing better methods to prognosticate early, track the brain's real-time response to therapies, help understand the impact of neurological injury caused by seizures, and develop novel treatment strategies.[209]

Neuroimaging and monitoring modalities

Neuroimaging is performed to define structural brain injury related to cardiac arrest. The absence of a well-designed study has limited the use of neuroimaging in the prediction of outcome after cardiac arrest. The most common type of neuroimaging studied has been cranial CT. Cranial CT studies can show widespread injury to the brain with changes in oedema characteristics.[61,305] Acquiring MRI studies is challenging in critically ill patients because of restrictions on the type of equipment that can be placed in the room; however, this is becoming less problematic, and MRI studies in the critically ill are increasingly being undertaken. Some limited studies have shown that diffuse cortical abnormalities in diffusion-weighted imaging (DWI) or fluid-attenuated inversion recovery (FLAIR) are associated with poor outcome.[306] Functional neuroimaging with magnetic resonance spectroscopy[307] and positron emission tomography (PET) showing metabolic abnormality (i.e., increasing lactate) in the brain are associated with poor outcome.[308] Other neurological factors that define neurological injury but were not reliable predictors of outcome are ICP/CPP,[309] brain energy metabolism,[310] CBF by xenon CT,[311] and jugular bulb venous oxygen concentrations.[312]

At this time the practical utility of neuroimaging, especially CT scans, is limited to excluding intracranial pathologies such as haemorrhage or stroke. The limited studies available hinder the effective use of neuroimaging for prognostication. Nonetheless, neuroimaging continues to be useful for understanding the brain's response to cardiac arrest. Well-designed prospective studies are needed to fully understand the utility of neuroimaging techniques at key times after resuscitation. Functional neuroimaging has been used successfully to characterise injury in other areas of the brain. The development of portable imaging devices and improved functional neuroimaging studies may provide a way to study the utility of neuroimaging during the acute period, not only as a prognostic tool but also to guide treatment.

Biochemical markers

Biochemical markers derived initially from cerebrospinal fluid (CSF) (creatine phosphokinase [CPK]-BB)[313,314] or peripheral blood (neuron-specific enolase [NSE] and S100β) have been used to prognosticate functional outcome after cardiac arrest. The ease of obtaining samples has favored blood-based biochemical markers over those in CSF. NSE is a cytoplasmic glycolytic enzyme found in neurons, cells, and tumors of neuroendocrine origin; concentrations increase in serum a few hours after injury. One study showed that an NSE cutoff of >71.0 $\mu g\,L^{-1}$ drawn between 24 and 48 h after ROSC was required to achieve an FPR of 0% (95% CI 0—43%) for predicting poor outcome with a sensitivity of 14%.[315] Another study showed that serum NSE concentrations >33 $\mu g\,L^{-1}$ drawn between 24 and 72 h after ROSC predicted poor outcome after one month with an FPR of 0% (95% CI 0—3%).[211] Numerous other studies show varying thresholds from 30 to 65 $\mu g\,L^{-1}$ for poor outcome and mortality.[316—322]

The biochemical marker S100β is a calcium-binding protein from astroglial and Schwann cells. In cardiac arrest survivors, one study showed that an S100β cutoff of >1.2 $\mu g\,L^{-1}$ drawn between 24 and 48 h after ROSC was required to achieve an FPR of 0% (95% CI 0—14%), with a sensitivity of 45%.[315] Other less robust studies show similar high specificity with low sensitivity.[319,320,323—326]

Although a recommendation has been made on the use of biochemical markers, specifically NSE > 33 $\mu g\,L^{-1}$ as a predictor of poor outcome,[254] care must taken. This caution is based on problems such as lack of standardisation in study design and patient treatment, wide variability of threshold values to predict poor outcome, and differing measurement techniques. These limitations make it difficult to analyze these studies in aggregate. A well-designed study to standardise these tests at strategic times after cardiac arrest is necessary to determine their benefit.

Multimodality prediction of neurological outcome

More accurate prognostication can potentially be achieved by using several methods to investigate neurological injury. Some studies have suggested that combining neurological examination with other adjunctive tests enhances the overall accuracy and efficiency of prognosticating poor outcome.[255,293,299,327] No clinical decision rule or multimodal prognostication protocol has been prospectively validated, however.

Prognostication in hypothermia-treated patients

Therapeutic hypothermia improved survival and functional outcome for one in every 6 comatose cardiac arrest survivors treated.[179] As a neuroprotective intervention, hypothermia alters the progression of neurological injury; hypothermia alters the evolution of recovery when patients who received

therapeutic hypothermia are compared with those who did not. Therefore, prognostication strategies established in patients who were not treated with hypothermia might not accurately predict the outcome of those treated with hypothermia. Hypothermia may mask neurological examination or delay the clearance of medication, such as sedative or neuromuscular blocking drugs that may mask neurological function.[199,254,328] Although the incidence of seizures in the HACA study was similar in the hypothermia and placebo groups,[8] there is some concern that seizures may be masked when a neuromuscular blocking drug is used.[219]

There are no studies detailing the prognostic accuracy of the neurological examination in cooled post-cardiac arrest patients. SSEPs and biochemical markers have undergone limited investigation in this patient population. One study found bilateral absence of cortical N20 responses at 24—28 h after cardiac arrest in 3 of 4 hypothermia-treated patients with permanent coma [FPR 0% (95% CI 0—100%); sensitivity 75% (95% CI 30—95%)].[329] An earlier study from the same group found that the 48-h NSE and S100 values which achieved a 0% FPR for poor outcome were 2—3 times higher in patients treated with hypothermia compared with the normothermic control group [NSE > 25 versus 8.8 $\mu g\,L^{-1}$; S100β 0.23 versus 0.12 $\mu g\,L^{-1}$].[317]

In summary, there are both theoretical and evidence-based concerns suggesting that the approach to early prognostication might need to be modified when post-cardiac arrest patients are treated with therapeutic hypothermia. The relative impact of hypothermia on prognostic accuracy appears to vary among individual strategies, and is inadequately studied. The recovery period after hypothermia therapy has not been clearly defined, and early withdrawal of life-sustaining therapies may not be in the best interest of patients and their families. Until more is known about the impact of therapeutic hypothermia, prognostication should probably be delayed, but the optimal time has yet to be determined. Ideally bedside monitoring systems need to be developed to enable tracking of evolving brain injury and the brain's response to therapy (e.g., hypothermia).

Paediatrics: special considerations

In children, cardiac arrests are caused typically by respiratory failure, circulatory shock or both. In contrast to adults, children rarely develop sudden arrhythmogenic VF arrests from coronary artery disease. Arrhythmogenic VF/ventricular tachycardia (VT) arrests occur in 5—20% of out-of-hospital paediatric cardiac arrests and approximately 10% of in-hospital paediatric arrests.[5,20,330—332]

Although clinical data are limited, differences in both cardiac arrest aetiology and developmental status are likely to contribute to differences between adult and paediatric post-cardiac arrest syndrome.[97,330,333—335] For example, the severity and duration post-cardiac arrest myocardial stunning in paediatric animal models is substantially less than in adult animals.[102,336—338]

In terms of treatment, there is a critical knowledge gap for postarrest interventions in children.[339] Therefore, management strategies are based primarily on general principles of intensive care or extrapolation of evidence obtained from adults, newborns, and animal studies.[8,9,12,13,195,333,334,340—346] Based upon this extrapolation, close attention to temperature management (avoidance of hyperthermia and consideration of induction of hypothermia), glucose management (control of hyperglycaemia and avoidance of hypoglycaemia[347—349]), blood pressure (avoidance of age-adjusted hypotension), ventilation (avoidance of hyper- or hypocarbia and avoidance of over ventilation), and haemodynamic support (maintenance of adequate cardiac output to meet metabolic demand) are recommended by consensus for children post-cardiac arrest, but are not supported by specific interventional studies in the post-arrest setting.

Temperature management

Mild hypothermia is a promising neuroprotective and cardioprotective treatment in the postarrest phase[177,179,350] and is a well-established treatment in adult survivors of cardiac arrest.[12,13] Studies of hypoxic-ischaemic encephalopathy in newborns indicate that mild hypothermia is safe and feasible and may be neuroprotective,[340—342,344,351—355] although the pathophysiology of newborn hypoxic-ischaemic encephalopathy differs from cardiac arrest and the post-cardiac arrest syndrome. Furthermore, pyrexia is common after cardiac arrest in children and is associated with poor neurological outcome.[356] Therefore post-cardiac arrest pyrexia should be actively prevented and treated. Although post-cardiac arrest-induced hypothermia is a rational therapeutic approach, it has not been adequately evaluated in children. Despite this, several centres treat children after cardiac arrest with therapeutic hypothermia based on extrapolation of the adult data.[357] There are several physical and pharmacological methods for temperature control, all feasible in the paediatric intensive care environment, with specific advantages and disadvantages.[187,189,358—360]

Extracorporeal membrane oxygenation

Perhaps the ultimate technology to control postresuscitation temperature and haemodynamic parameters is ECMO. Several studies have shown that placing children on ECMO during prolonged CPR (E-CPR) can result in good outcomes. In one report, 66 children were placed on ECMO during CPR over 7 years.[361] The median duration of CPR before establishment of ECMO was 50 min, and 35% (23 of 66) of these children survived to hospital discharge. These children had only brief periods of no flow and excellent CPR during the low-flow period, as well as excellent haemodynamic support and temperature control during the postresuscitation phase. According to the Extracorporeal Life Support registry, E-CPR has become one of the most common indications for ECMO therapy over the past few years.

Paediatric cardiac arrest centres

High-quality multimodal postarrest care improves survival and neurological outcome in adults.[13]

Paediatric post-cardiac arrest care requires specifically adapted equipment and training to deliver critical interventions rapidly and safely to avoid latent errors and

Table 3 Barriers to implementation.

Structural barriers
Resources — human and financial — often perceived as a major problem but, in reality, it is more frequently a logistical issue
Organizational
Leadership
Scientific — a low level of evidence may make implementation more difficult
Personal barriers
Intellectual — lack of awareness that a guidelines exists
Poor attitude — inherent resistance to change
Motivation — change requires effort
Environmental barriers
Political — a recommendation by one organization may not be adopted by another
Economical
Cultural — these may impact the extent of treatment deeded appropriate in the postresuscitation phase
Social

preventable morbidity and mortality. Survival of children after in-hospital arrest is greater when they are treated in hospitals that employ specialized paediatric staff.[362] These data suggest that development of regionalized paediatric cardiac arrest centres may improve outcomes after paediatric cardiac arrests, similar to improvements with trauma centres and regionalized neonatal intensive care. For now, stabilization and transfer of paediatric postarrest patients to optimally equipped and staffed specialized paediatric facilities should be encouraged.[363,364]

Challenges to implementation

Publication of clinical guidelines alone is frequently inadequate to change practice. There are often several barriers to changing clinical practice, and these will need to be identified and overcome before changes can be implemented. The purpose of the following section is to provide insight into the challenges and barriers to implementing optimized post-cardiac arrest care.

Existing studies showing poor implementation

In 2003 the advanced life support task force of the International Liaison Committee on Resuscitation (ILCOR) published an advisory statement on the use of therapeutic hypothermia.[177] This statement recommended that comatose survivors of out-of-hospital VF cardiac arrest should be cooled to 32—34 °C for 12—24 h. Despite this recommendation, which was based on the results of 2 randomized controlled trials, implementation of therapeutic hypothermia has been slow. A survey of all ICUs in the United Kingdom showed that by 2006 only 27% of units had ever used mild hypothermia to treat post-cardiac arrest patients.[365] Similar findings were reported in surveys in the United States[366,367] and Germany.[368] Successful implementation has been described by several centres, however.[12—14,132,160,369]

Table 4 Implementation strategies.

Select a local champion — an influential and enthusiastic person should lead local implementation of guidelines
Develop a simple, pragmatic protocol — a simple local treatment protocol should be developed with contributions from all relevant disciplines
Identify weak links in the local system
Prioritize interventions
Develop educational materials
Pilot phase

Barriers to implementation

The numerous barriers to implementation of guidelines have been recently described and may be classified as structural, personal, or environmental (Table 3).[370]

Implementation strategies

Clinical guidelines that are evidence-based and strongly supported by well recognised and respected professional organizations are more likely to be adopted by practicing clinicians. Many strategies to improve implementation have been described (Table 4).[370,371]

Monitoring of implementation

All clinical practices should be audited, especially when change is implemented. By measuring current performance against defined standards (e.g., time to achieve target temperature when using therapeutic hypothermia), it is possible to identify which local protocols and practices need modification. Process as well as clinical factors should be monitored as part of the quality program. The iterative process of reaudit and further change as necessary should enable optimal performance. Ideally the standards against which local practice is audited are established at the national or international level. This type of benchmarking exercise is now common practice throughout many healthcare systems.

Resource issues

Many of the interventions applied in the postresuscitation period do not require expensive equipment. The more expensive cooling systems have some advantages but are by no means essential. Maintenance of an adequate mean arterial blood pressure and control of blood glucose are also relatively inexpensive interventions. In some healthcare systems the lack of 24-h interventional cardiology systems makes it difficult to implement timely PCI, but in most cases it should still be possible to achieve reperfusion with thrombolytic therapy.

Practical problems

Postresuscitation care is delivered by many different groups of healthcare providers in multiple locations. Pre-

Table 5 Critical knowledge gaps related to post-cardiac arrest syndrome.

Epidemiology
- What epidemiological mechanism can be developed to monitor trends in post-cardiac arrest outcomes?

Pathophysiology
- What is the mechanism(s) and time course of post-cardiac arrest coma?
- What is the mechanism(s) and time course of post-cardiac arrest delayed neurodegeneration?
- What is the mechanism(s) and time course of post-cardiac arrest myocardial dysfunction?
- What is the mechanism(s) and time course of impaired oxygen delivery and utilisation after cardiac arrest?
- What is the role of intravascular coagulation in post-cardiac arrest organ dysfunction and failure?
- What is the mechanism(s), time course, and significance of post-cardiac arrest adrenal insufficiency?

Therapy

1. What is the optimal application of therapeutic hypothermia in the post-cardiac arrest patient?
   a. Which patients benefit?
   b. What is the optimal target temperature, onset, duration, and rewarming rate?
   c. What is the most effective cooling technique — external versus internal?
   d. What are the indications for neuromuscular blockade?
2. Which patients should have early PCI?
3. What is the optimal therapy for post-cardiac arrest myocardial dysfunction?
   a. Pharmacological
   b. Mechanical
4. What is the clinical benefit of controlled reoxygenation?
5. What is the clinical benefit of early haemodynamic optimization according to protocol?
6. What are the optimal goals (parameters and target ranges) for early haemodynamic optimization?
   a. MAP?
   b. CVP?
   c. Central or mixed venous oxygen saturation?
   d. Haemoglobin concentration and transfusion threshold?
   e. Lactate level or lactate clearance rate?
   f. Urine output
   g. Oxygen delivery?
   h. Other?
7. What is the clinical benefit of glucose control and what is the optimal target glucose range?
8. What is the clinical benefit of high-volume haemofiltration?
9. What is the clinical benefit of early glucocorticoid therapy?
10. What is the clinical benefit of prophylactic anticonvulsants?
11. What is the clinical benefit of a defined period of sedation and ventilation?
12. What is the clinical benefit of neuroprotective agents?

Prognosis
- What is the optimal decision rule for prognostication of futility?
- What is the impact of therapeutic hypothermia on the reliability of prognostication of futility?

Paediatrics
- What is the evidence specific to children for the knowledge gaps listed above?
- What is the role of ECMO in paediatric cardiac arrest and postarrest support?

Barriers
- What is the most effective approach to implement therapeutic hypothermia and optimized post-cardiac arrest care?
- What is the value of regionalization of post-cardiac arrest care to specialized centres?

PCI indicates percutaneous coronary intevention; MAP, mean arterial pressure; CVP, central venous pressure; and EMCO, extracorporeal membrane oxygenation.

hospital treatment by EMS may involve both paramedics and physicians, and continuation of treatment in-hospital will involve emergency physicians and nurses, cardiologists, neurologists, critical care physicians and nurses, and cardiac catheter laboratory staff. Treatment guidelines will have to be disseminated across all these specialty groups. Implementation in all these environments may also be challenging; e.g., maintenance of

hypothermia during cardiac catheterization may be problematic.

Therapies such as primary PCI and therapeutic hypothermia may not be available 24 h in many hospitals admitting comatose post-cardiac arrest patients. For this reason, the concept of 'regional cardiac arrest centres' (similar in concept to level one trauma centres) has been proposed.[372] The concentration of post-cardiac arrest patients in regional centres may improve outcome (this is not yet proven) and should help to facilitate research.

Critical knowledge gaps

In addition to summarizing what is known about the pathophysiology and management of post-cardiac arrest syndrome, a goal of this statement is to highlight what is not known. Table 5 outlines the critical knowledge gaps identified by the writing group. The purpose of this list is to stimulate preclinical and clinical research that will lead to evidence-based optimization of post-cardiac arrest care.

Appendix A. Disclosures

Writing group and reviewer disclosures can be found at doi:10.1016/j.resuscitation.2008.09.017.

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