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Post Cardiac Arrest Syndrome. Epidemiology, Pathophysiology, Treatment, and Prognostication A Consensus Statement From the International Liaison Committee on Resuscitation (American Heart Association, Australian and New Zealand Council on Resuscitation, European Resuscitation Council, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Asia, and the Resuscitation Council of Southern Africa); 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; and the Stroke Council

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ILCOR Consensus Statement

Post-Cardiac Arrest Syndrome

Epidemiology, Pathophysiology, Treatment, and Prognostication

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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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I. Consensus Process

The contributors to 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 generalizable, 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 e-mail, followed a series of telephone conferences and face-to-face meetings of the cochairs and writing group members. International writing teams were formed to generate the content of each section, which corresponded 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 cochairs to work on 1 or more writing teams, which generally reflected their areas of expertise. Relevant articles were identified with 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 on by the writing team authors and then sent to the cochairs 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 for independent peer review and approval for publication.

II. 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 optimization of post-cardiac arrest care and to pinpoint the need for research focused on gaps in knowledge that would potentially improve outcomes of patients resuscitated from cardiac arrest.

Resumption of spontaneous circulation (ROSC) after prolonged, complete, whole-body ischemia is an unnatural pathophysiological state created by successful cardiopulmonary resuscitation (CPR). In the early 1970s, Dr Vladimir Negovsky recognized that the pathology caused by complete whole-body ischemia and reperfusion was unique in that it had a clearly definable cause, 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 multicenter 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, cause, and treatment of cardiac arrest have changed dramatically, but the overall prognosis after ROSC has not improved. The largest modern report of cardiac arrest epidemiology was published by the National Registry of Cardiopulmonary Resuscitation (NRCPR) 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, which include (1) post-cardiac arrest brain injury, (2) post-cardiac arrest myocardial dysfunction, and (3) systemic ischemia/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. Evidence exists 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 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 hours after arrest) remains limited, and the impact of emerging therapies (eg, 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 and advanced

life support 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.

III. Epidemiology of 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 the study of 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 advanced life support 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 indicate 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% to 70%) for patients with ROSC, 57% (range 56% to 70%) for patients who arrived in the emergency department with a pulse, and 50% (range 41% to 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, 1 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 minutes, 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%, which resulted in a calculated post-ROSC mortality rate of 70%.²¹

The largest published in-hospital cardiac arrest database (the 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 minutes, 55% for the 524 children with any documented ROSC, and 49% for the 460 children with ROSC >20 minutes. 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 seconds) return of pulses or spontaneous circulation sustained for >20 minutes, the denominator used to calculate postresuscitation mortality rates will differ greatly.¹⁵ Other denominators include sustained ROSC to the emergency department 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 minutes receive care during transport or in the emergency department before hospital admission. Perhaps it is more appropriate to look at mortality rates for out-of-hospital (or immediate post-ROSC), emergency department, 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 minutes after ROSC. The early postarrest phase could be defined as the period between 20 minutes and 6 to 12 hours after ROSC, when early interventions might be most effective. An intermediate phase might be between 6 to 12 hours and 72 hours, when injury pathways are still active and aggressive treatment is typically instituted. Finally, a period beyond 3 days could be considered the recovery phase, when prognostication becomes more reliable and ultimate outcomes are more predictable (Figure). 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 to 2, although this varied between 70% and 90% in the 4 hospital regions.¹⁰ In another study, 75% of

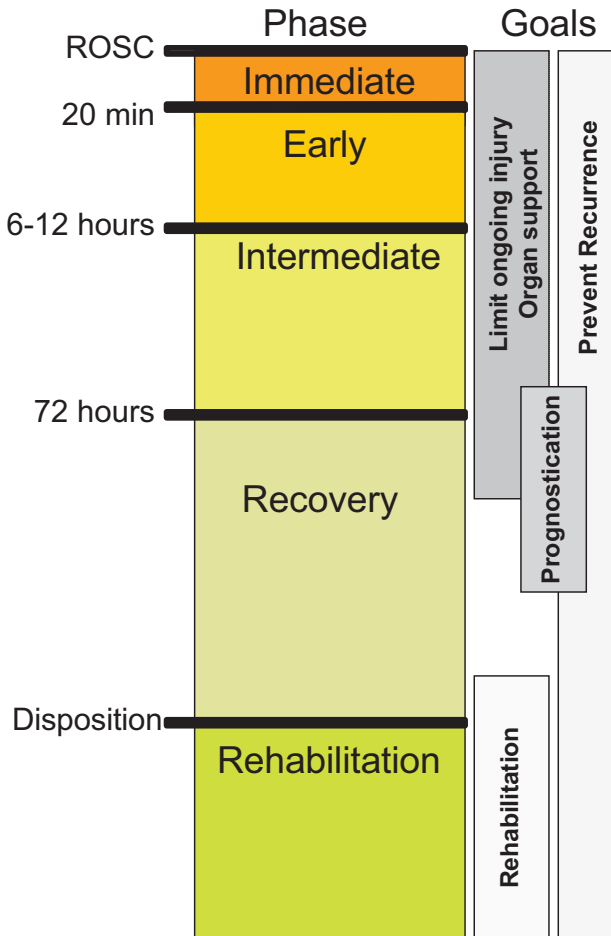


Figure. Phases of post-cardiac arrest syndrome.

51 children who survived out-of-hospital cardiac arrest had either pediatric CPC 1 to 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 prophecy. The timing of withdrawal of therapy is poorly documented in the resuscitation literature. Data from the NRCPR on in-hospital cardiac arrest indicate that “do not attempt resuscitation” (DNAR) orders were given for 63% of patients 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 critical care units in the United Kingdom, treatment was withdrawn in 28.2% at a median of 2.4 days (interquartile range 1.5 to 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 this is 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 after in- and out-of-hospital cardiac arrest,^{26,27} but these have generally been cases in which sustained ROSC was 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, surprisingly little evidence exists 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 minimize artifactual variability, epidemiological and interventional post-cardiac arrest studies should incorporate well-defined standardized 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.

IV. Pathophysiology of 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 that involves multiple organs. Although prolonged whole-body ischemia 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 comorbidities. 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 ischemia/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 ischemic insult, the cause of cardiac arrest, and the patient’s prearrest state of health. If ROSC is achieved rapidly 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 1 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 ischemia and its unique response to reperfusion. The mechanisms of brain injury triggered by cardiac arrest and resuscitation are complex and include

Table 1. Post-Cardiac Arrest Syndrome: Pathophysiology, Clinical Manifestations, and Potential Treatments

Syndrome	Pathophysiology	Clinical Manifestation	Potential Treatments
Post-cardiac arrest brain injury	<ul style="list-style-type: none"> ● Impaired cerebrovascular autoregulation ● Cerebral edema (limited) ● Postischemic neurodegeneration 	<ul style="list-style-type: none"> ● Coma ● Seizures ● Myoclonus ● Cognitive dysfunction ● Persistent vegetative state ● Secondary Parkinsonism ● Cortical stroke ● Spinal stroke ● Brain death 	<ul style="list-style-type: none"> ● Therapeutic hypothermia¹⁷⁷ ● Early hemodynamic optimization ● Airway protection and mechanical ventilation ● Seizure control ● Controlled reoxygenation (SaO₂ 94% to 96%) ● Supportive care
Post-cardiac arrest myocardial dysfunction	<ul style="list-style-type: none"> ● Global hypokinesis (myocardial stunning) ● ACS 	<ul style="list-style-type: none"> ● Reduced cardiac output ● Hypotension ● Dysrhythmias ● Cardiovascular collapse 	<ul style="list-style-type: none"> ● Early revascularization of AMI^{171, 373} ● Early hemodynamic optimization ● Intravenous fluid⁹⁷ ● Inotropes⁹⁷ ● IABP^{13, 160} ● LVAD¹⁶¹ ● ECMO³⁶¹
Systemic ischemia/reperfusion response	<ul style="list-style-type: none"> ● Systemic inflammatory response syndrome ● Impaired vasoregulation ● Increased coagulation ● Adrenal suppression ● Impaired tissue oxygen delivery and utilization ● Impaired resistance to infection 	<ul style="list-style-type: none"> ● Ongoing tissue hypoxia/ischemia ● Hypotension ● Cardiovascular collapse ● Pyrexia (fever) ● Hyperglycemia ● Multiorgan failure ● Infection 	<ul style="list-style-type: none"> ● Early hemodynamic optimization ● Intravenous fluid ● Vasopressors ● High-volume hemofiltration³⁷⁴ ● Temperature control ● Glucose control^{223, 224} ● Antibiotics for documented infection
Persistent precipitating pathology	<ul style="list-style-type: none"> ● Cardiovascular disease (AMI/ACS, cardiomyopathy) ● Pulmonary disease (COPD, asthma) ● CNS disease (CVA) ● Thromboembolic disease (PE) ● Toxicological (overdose, poisoning) ● Infection (sepsis, pneumonia) ● Hypovolemia (hemorrhage, dehydration) 	<ul style="list-style-type: none"> ● Specific to cause but complicated by concomitant PCAS 	<ul style="list-style-type: none"> ● Disease-specific interventions guided by patient condition and concomitant PCAS

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

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 a period of hours to days after ROSC. Histologically, selectively vulnerable neuron subpopulations in the hippocampus, cortex, cerebellum, corpus striatum, and thalamus degenerate over a period of 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 in part 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 after cardiac arrest.

Prolonged cardiac arrest can also be followed by fixed or dynamic failure of cerebral microcirculatory reperfusion despite adequate cerebral perfusion pressure (CPP).^{42, 43} This impaired reflow can cause persistent ischemia and small infarctions in some brain regions. The cerebral microvascular occlusion that causes the no-reflow phenomenon 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 minutes.^{44, 45} Serial measurements of regional cerebral blood flow (CBF) by stable xenon/computed tomography (CT) after 10.0 to 12.5 minutes

of untreated cardiac arrest in dogs demonstrated dynamic and migratory hypoperfusion rather than fixed no-reflow.^{43,46} In the recent Thrombolysis in Cardiac Arrest (TROICA) trial, tenecteplase given to patients with out-of-hospital cardiac arrest of presumed cardiac origin did not increase 30-day survival compared with placebo (B.J.B., personal communication, February 26, 2008).

Despite cerebral microcirculatory failure, macroscopic reperfusion is often hyperemic 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 minimize impaired reflow.⁴⁹ Yet, hyperemic reperfusion can potentially exacerbate brain edema and reperfusion injury. In 1 human study, hypertension (mean arterial pressure [MAP] >100 mm Hg) in the first 5 minutes after ROSC was not associated with improved neurological outcome, but MAP during the first 2 hours after ROSC was positively correlated with neurological outcome.⁵⁰ Although resumption of oxygen and metabolic substrate delivery at 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 on 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, hypoxemia, impaired cerebrovascular autoregulation, and brain edema; 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 to 48 hours after resuscitation from cardiac arrest, increased cerebral vascular resistance, decreased CBF, decreased cerebral metabolic rate of oxygen consumption (CMRO₂), and decreased glucose consumption are present.^{53–56} Although the results of animal studies are contradictory in terms of the coupling of CBF and CMRO₂ 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 using 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.

Limited evidence is available that brain edema or elevated intracranial pressure (ICP) directly exacerbates post-cardiac arrest brain injury. Although transient brain edema 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 edema, occurring days to weeks after cardiac arrest, has been attributed to delayed hyperemia; this is more likely the consequence rather than the cause of severe ischemic neurodegen-

eration.^{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, hyperglycemia, and seizures. In a small case series, patients with temperatures >39°C in the first 72 hours 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 hours after out-of-hospital cardiac arrest, the risk of unfavorable outcome increased (odds ratio 2.3, 95% confidence interval [CI] 1.2 to 4.1) for every degree Celsius that the peak temperature exceeded 37°C.⁶⁴ A subsequent multicenter 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 (odds ratio 2.7, 95% CI 1.2 to 6.3).¹⁰ Recent data demonstrating neuroprotection with therapeutic hypothermia further support the role of body temperature in the evolution of post-cardiac arrest brain injury.

Hyperglycemia 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 postischemic blood glucose concentrations exacerbate ischemic 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, various 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 ischemia 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 brain stem 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 centers in the cortex, basal ganglia, and cerebellum.⁹⁵ These clinical conditions, which represent 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 recognize 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 to 10 mm Hg to 20 to 22 mm Hg as early as 30 minutes after ROSC.^{101,102} During the period with significant dysfunction, coronary blood flow is not reduced, which indicates a true stunning phenomenon rather than permanent injury or infarction. In 1 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 \approx 6 hours later by hypotension (MAP $<$ 75 mm Hg) and low cardiac output (cardiac index $<$ 2.2 L \cdot min⁻¹ \cdot 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 hours.¹⁰² Several case series have described transient myocardial dysfunction after human cardiac arrest. Cardiac index values reached their nadir at 8 hours after resuscitation, improved substantially by 24 hours, and almost uniformly returned to normal by 72 hours 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 to 10 μ g \cdot kg⁻¹ \cdot min⁻¹ dramatically improve systolic (left ventricular ejection fraction) and diastolic (isovolumic relaxation of left ventricle) dysfunction after cardiac arrest.¹⁰¹

Systemic Ischemia/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, which leads 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 hemodynamic instability, and microcirculatory failure. Oxygen debt (the difference between predicted oxygen consumption [normally 120 to 140 mL \cdot kg⁻¹ \cdot min⁻¹] and actual consump-

tion multiplied by time duration) quantifies the magnitude of exposure to insufficient oxygen delivery. Accumulated oxygen debt leads to endothelial activation and systemic inflammation¹⁰⁶ and is predictive of subsequent multiple organ failure and death.^{107,108}

The whole-body ischemia/reperfusion of cardiac arrest with associated oxygen debt causes generalized activation of immunologic and coagulation pathways, which increases 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 hours after cardiac arrest, blood concentrations of various cytokines, soluble receptors, and endotoxin increase, and the magnitude of these changes is associated with outcome.¹¹² Soluble intercellular adhesion molecule-1, soluble vascular cell adhesion molecule-1, and P- and E-selectins are increased during and after CPR, which suggests leukocyte activation or endothelial injury.^{114,115} Interestingly, hyporesponsiveness of circulating leukocytes, 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, which suggests a potential role for interventions that focus on hemostasis. 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 ischemia/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 (ie, $<$ 9 μ g/mL increase in cortisol), is common.^{119,120} Furthermore, basal cortisol levels measured from 6 to 36 hours after the onset of cardiac arrest were lower in patients who subsequently died of early refractory shock (median 27 μ g/dL, interquartile range 15 to 47 μ g/dL) than in patients who died later of neurological causes (median 52 μ g/dL, interquartile range 28 to 72 μ g/dL).¹¹⁹

Clinical manifestations of systemic ischemic-reperfusion response include intravascular volume depletion, impaired vasoregulation, impaired oxygen delivery and utilization, 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, hemorrhage, sepsis, and various toxidromes can complicate and be complicated by the simultaneous pathophysiology of the post-cardiac arrest syndrome.

A high probability exists of identifying an ACS in the patient who is resuscitated from cardiac arrest. In out-of-hospital cardiac arrest studies, acute myocardial infarction has been documented in $\approx 50\%$ of adult patients.^{13,121,122} An acute coronary occlusion was found in 40 (48%) of 84 consecutive patients who had no obvious noncardiac cause 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 hours after ROSC from out-of-hospital cardiac arrest, troponin T has been reported to be 96% sensitive and 80% specific for diagnosis of acute myocardial infarction, whereas creatine kinase-MB is 96% sensitive and 73% specific.¹²⁵ In the NRCPR registry, only 11% of adult in-hospital arrests were attributed to myocardial infarction or acute ischemia.⁵ The proportion of in-hospital patients who achieve 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% to 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.

Hemorrhagic 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 hemorrhagic cardiac arrest should be considered a separate clinical syndrome.

Primary pulmonary disease such as chronic obstructive pulmonary disease, 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 edema 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 edema is more common after cardiac arrest caused by asphyxia.⁶⁰ It is possible that perfusion with hypoxic blood during asphyxia preceding complete circulatory collapse is harmful.

Sepsis is a cause of cardiac arrest, acute respiratory distress syndrome, and multiple organ failure. Thus, a predisposition for exacerbation of post-cardiac arrest syndrome exists 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.

V. Therapeutic Strategies

Care of the post-cardiac arrest patient is time-sensitive, occurs both in and out of the hospital, and is provided sequentially 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, hemodynamically 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 compared with historical controls.^{12,13,132}

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 hemodynamic monitoring, and cerebral monitoring. Gen-

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 hemodynamic monitoring
Echocardiography
Cardiac output monitoring (either noninvasive or PA catheter)
3. Cerebral monitoring
EEG (on indication/continuously): early seizure detection and treatment
CT/MRI

CVP indicates central venous pressure; ScvO₂, central venous oxygen saturation; CBC, complete blood count; PA, pulmonary artery; EEG, electroencephalogram; and CT/MRI, computed tomography/magnetic resonance imaging.

eral 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 validated prospectively.

Early Hemodynamic Optimization

Early hemodynamic optimization or early goal-directed therapy 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 utilization. Early goal-directed therapy 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 a central venous pressure of 8 to 12 mm Hg, MAP of 65 to 90 mm Hg, ScvO₂ >70%, hematocrit >30% or hemoglobin >8 g/dL, lactate ≤2 mmol/L, 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 early goal-directed therapy include modulation of inflammation, reduction of organ dysfunction, and reduction of healthcare resource consumption.^{133–135} In severe sepsis, early goal-directed therapy has also been shown to reduce mortality.¹³³

The systemic ischemia/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 hemodynamic 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 the 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 posts ischemic brain adequately without putting unnecessary strain on the posts ischemic 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 1 human study, hypertension (MAP >100 mm Hg) during the first 5 minutes after ROSC was not associated with improved neurological outcome⁵⁰; however, MAP during the first 2 hours 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 to 75 mm Hg¹³ or as high as 90 to 100 mm Hg^{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 minutes of untreated cardiac arrest.^{42,43,136} At the opposite end of the spectrum, a patient with an evolving acute myocardial infarction or severe myocardial dysfunction might benefit from the lowest target MAP that will ensure adequate cerebral oxygen delivery.

The optimal central venous pressure goal for post-cardiac arrest patients has not been defined by prospective clinical trials, but a range of 8 to 12 mm Hg has been used in most published studies. An important consideration is the potential for persistent precipitating pathology that could cause elevated central venous pressure independent of volume status, such as cardiac tamponade, right-sided acute myocardial infarction, pulmonary embolism, and tension pneumothorax or any disease that impairs myocardial compliance. A risk also exists of precipitating pulmonary edema in the presence of post-cardiac arrest myocardial dysfunction. The post-cardiac arrest ischemia/reperfusion response causes intravascular volume depletion relatively soon after the heart is restarted, and volume expansion is usually required. No evidence is available to indicate an advantage for any specific type of fluid (crystalloid or colloid) in the post-cardiac arrest phase. Some animal data are available indicating that hypertonic saline may improve myocardial and cerebral blood flow when given during CPR,^{137,138} but no clinical data 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 utilization caused by microcirculatory failure or mitochondrial failure.

Additional surrogates for oxygen delivery include urine output and lactate clearance. Two of the randomized prospective trials of early goal-directed therapy described above used a urine output target of $\geq 0.5 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$.^{133,135} A higher urine output goal of $>1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ is reasonable in postarrest patients treated with therapeutic hypothermia, given the higher urine production during hypothermia¹³; 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 ischemia of cardiac arrest. This limits the usefulness of a single measurement during early hemodynamic 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 hemoglobin concentration in the post-cardiac arrest phase has not been defined. The original study of early goal-directed therapy in sepsis 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 hemoglobin concentration was maintained at 10 to 12 g/dL compared with 7 to 9 g/dL.¹⁴² A post-cardiac arrest care protocol published by a group from Norway included a hemoglobin target of 9 to 10 g/dL.¹³

In summary, the value of hemodynamic optimization or early goal-directed therapy in post-cardiac arrest care has yet to be demonstrated in randomized prospective clinical trials, and little evidence is available 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 to 100 mm Hg (taking into consideration the patient’s normal blood pressure, cause of arrest, and severity of any myocardial dysfunction), central venous pressure of 8 to 12 mm Hg, $ScvO_2 >70\%$, urine output $>1 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$, and a normal or decreasing serum or blood lactate level. Goals for hemoglobin concentration during post-cardiac arrest care remain to be defined.

Oxygenation

Existing guidelines emphasize the use of a fraction of inspired oxygen (FiO_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 postschemic 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 than immediate adjustment of the FiO_2 to produce an arterial oxygen saturation of 94% to 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 FiO_2 to produce an arterial oxygen saturation of 94% to 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 appears to be preserved.^{53,55,146,147} Cerebrovascular resistance may be elevated for at least 24 hours in comatose survivors of cardiac arrest.⁵⁵ No data exist to support the targeting of a specific $Paco_2$ after resuscitation from cardiac arrest; however, extrapolation of data from studies of other cohorts suggests ventilation to normocarbina is appropriate. Studies in brain-injured patients have shown that the cerebral vasoconstriction caused by hyperventilation may produce potentially harmful cerebral ischemia.^{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 biotrauma¹⁵⁴ in patients with acute lung injury. The Surviving Sepsis Campaign recommends the use of a tidal volume of 6 mL/kg (predicted) body weight and a plateau pressure of ≤ 30 cm H_2O during mechanical ventilation of patients with sepsis-induced acute lung injury or acute respiratory distress syndrome.¹⁵⁵ However, no data are available to support the 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 $>6 \text{ mL/kg}$ to prevent hypercapnia. When therapeutic hypothermia is being induced, 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. No evidence exists 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 normocarbida and should be monitored by regular measurement of arterial blood gas values.

Circulatory Support

Hemodynamic 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 maintenance of normal electrolyte concentrations and use of standard drug and electrical therapies. No evidence exists to support the prophylactic use of antiarrhythmic drugs after cardiac arrest. Dysrhythmias are commonly caused by focal cardiac ischemia, and early reperfusion treatment is probably the best antiarrhythmic therapy. Ultimately, survivors of cardiac arrest attributed to a primary dysrhythmia should be evaluated for placement of a pacemaker or an implantable cardioverter-defibrillator.

The first-line intervention for hypotension is to optimize right-heart filling pressures by use of intravenous fluids. In 1 study, 3.5 to 6.5 L of intravenous crystalloid was required in the first 24 hours after ROSC after out-of-hospital cardiac arrest to maintain right atrial pressures in the range of 8 to 13 mm Hg.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 hours, with a central venous pressure goal of 8 to 12 mm Hg.¹³

Inotropes and vasopressors should be considered if hemodynamic 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 hours 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 arrest cardiovascular dysfunction. Despite improving hemodynamic 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 ischemia 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 ScvO₂, lactate clearance, and urine output. If a pulmonary artery catheter or some form of noninvasive cardiac output monitor is being used, therapy can be further guided by cardiac index and systemic vascular

resistance. No evidence exists that the use of a pulmonary artery catheter or noninvasive cardiac output monitoring improves outcome after cardiac arrest.

If volume expansion and treatment with vasoactive and inotropic drugs do not restore adequate organ perfusion, mechanical circulatory assistance should be considered.^{158,159} This treatment can support circulation in the period of transient severe myocardial dysfunction that often occurs for 24 to 48 hours after ROSC.⁹⁷ The intra-aortic balloon pump 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 documented recently in some studies.^{13,160} If additional cardiac support is needed, more invasive treatments such as percutaneous cardiopulmonary bypass, 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 percutaneous cardiopulmonary bypass 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 ACS

CAD is present in the majority of out-of-hospital cardiac arrest patients,^{163–165} and acute myocardial infarction 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 ischemic heart disease within 6 hours 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% to 86% of cardiac arrest survivors and in 15% to 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 are 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 focuses on early primary PCI in post-cardiac arrest patients with ST-elevation myocardial infarction.^{14,168–171} Although inclusion criteria and the outcomes reported were variable, average intervals from symptom onset or CPR to balloon inflation ranged from 2 to 5 hours, 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 ST-elevation myocardial infarction who received early coronary angiography/PCI and mild therapeutic hypothermia compared with a 66% in-hospital mortality rate for matched historical control subjects who underwent PCI without therapeutic hypothermia.¹⁴ In this study, 21 (78%) of 27 hypothermia-treated 6-month survivors had a good neurological 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 ST-elevation myocardial infarction) have also shown promising results. In 1 such study, 77% of all survivors of out-of-hospital cardiac arrest with presumed cardiac origin underwent immediate coronary angiography, which revealed CAD in 97%; of these, >80% had total occlusion of a major coronary artery.¹³ Nearly half of these patients underwent reperfusion interventions, with the majority by PCI and a minority by coronary artery bypass graft. Among patients admitted after ROSC, the overall in-hospital mortality rate 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 whether 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 no facilities are available 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 of thrombolytic therapy have been well characterized in post-cardiac arrest patients,^{174–176} the potential interaction of mild therapeutic hypothermia and thrombolytic therapy has not been studied formally. Theoretical considerations include a possible impact on the efficacy of thrombolysis and the risk of hemorrhage. Coronary artery bypass graft 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 who have electrocardiographic criteria for ST-elevation myocardial infarction 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 electrocardiography-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 ST-elevation myocardial infarction. 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, hypoxemia, hypovolemia, hypokalemia, hyperkalemia, metabolic disorders, accidental hypothermia, tension pneumothorax, cardiac tamponade, toxins, intoxication, and 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 standardized 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°C to 34°C for 12 to 24 hours. 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 arrest¹⁸⁰ and all rhythm arrests.^{12,13,132} Other observational studies provide evidence of a 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 minutes of ROSC when cooling is maintained for only a short duration (1 to 2 hours).^{183,184} When prolonged cooling is used (>24 hours), however, less is known about the therapeutic window. Equivalent neuroprotection was produced in a rat model of cardiac arrest when a 24-hour period of cooling was either initiated at the time of ROSC or delayed by 1 hour.¹⁸⁵ In a gerbil forebrain ischemia model, sustained neuroprotection was achieved when hypothermia was initiated at 1, 6, or 12 hours after reperfusion and maintained for 48 hours¹⁸⁶; however, neuroprotection did decrease when the start of therapy was delayed. The median time to achieve target temperature in the HACA trial was 8 hours (interquartile range 6 to 26 hours),⁸ whereas in a study by Bernard et al,⁹ average core temperature was reported to be 33.5°C within 2 hours of ROSC. 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 (saline 0.9% or Ringer's lactate, 30 mL/kg)^{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 by use of 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 that 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 with 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 approximately 0.25°C to 0.5°C per hour.¹⁸¹ Particular care should be taken during the cooling and rewarming phases, because metabolic rate, plasma electrolyte concentrations, and hemodynamic 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 hypovolemia will compound hemodynamic instability. Diuresis may produce electrolyte abnormalities, including hypophosphatemia, hypokalemia, 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 hyperglycemia.⁹ This should be treated with insulin (see "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 difference 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 sulfate, a naturally occurring *N*-methyl-D-aspartate 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 antiarrhythmic properties, and some animal data indicate that magnesium provides added neuroprotection in combination with hypothermia.²⁰² Magnesium sulfate (5 g) can be infused over 5 hours, 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 hours after cardiac arrest.^{63,205,206} The risk of a poor neurological outcome increases for each degree of body temperature above 37°C.⁶⁴

In summary, preclinical and clinical evidence strongly supports 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°C to 34°C for at least 12 to 24 hours.¹⁷⁷ Most experts currently recommend cooling for at least 24 hours. Although data support cooling to 32°C to 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 defined clinically, current consensus 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) 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°C to 0.5°C per hour), although the optimum rate for rewarming has not been defined clinically. If therapeutic hypothermia is not undertaken, pyrexia during the first 72 hours 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 to 10 minutes 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 (eg, the Richmond or Ramsay Scales) may be helpful.^{207,208} Both opioids (analgesia) and hypnotics (eg, 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 is advised for patients during sustained neuromuscular blockade.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 hours after ROSC, no secure data are available 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, myoclonus, or both occur in 5% to 15% of adult patients who achieve ROSC and 10% to 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 postarrest 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 (eg, intracranial hemorrhage, 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 to 6.1 mmol/L or 80 to 110 mg/dL) with insulin reduced hospital mortality rates in critically ill adults in a surgical ICU²²⁰ 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 therapy and control groups.²²² Among the patients with an ICU stay ≥ 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 after cardiac arrest is ≈ 3.4 days.^{6,13}

Hyperglycemia is common after cardiac arrest. Blood glucose concentrations must be monitored frequently in these patients and hyperglycemia 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 (144 mg/dL).^{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 group with a blood glucose target of 4 to 6 mmol/L (72 to 108 mg/dL) and a moderate glucose control group with a blood glucose target of 6 to 8 mmol/L (108 to 144 mg/dL).²²³ Episodes of moderate hypoglycemia (<3.0 mmol/L or 54 mg/dL) occurred in 18% of the strict glucose control group and 2% of the moderate glucose control group ($P=0.008$); however, no episodes of severe hypoglycemia (<2.2 mmol/L or 40 mg/dL) occurred. No difference in mortality was found. A target glucose range with an upper value of 8.0 mmol/L (144 mg/dL) has been suggested by others.^{13,224,225} The lower value of 6.1 mmol/L (110 mg/dL) may not reduce mortality any further but instead may expose patients to the potentially harmful effects of hypoglycemia.²²³ The incidence of hypoglycemia 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 ischemia to study numerous neuroprotective modalities, including anesthetics, anticonvulsants, calcium and sodium channel antagonists, *N*-methyl-D-aspartate-receptor antagonists, immunosuppressants, growth factors, protease inhibitors, magnesium, and γ -aminobutyric acid 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}

Many negative or neutral studies have been published of targeted neuroprotective trials in humans with acute ischemic stroke. Over the past 10 years, the Stroke Therapy Academic Industry Roundtable (STAIR) has made recommendations for preclinical evidence of drug efficacy and enhancement of 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, evidence to recommend any pharmacological neuroprotective strategies to reduce brain injury in post-cardiac arrest patients is inadequate.

Adrenal Dysfunction

Relative adrenal insufficiency occurs frequently after successful resuscitation of out-of-hospital cardiac arrest and is associated with increased mortality (see Section III).^{119,236} One small study 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, no evidence is available 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 (7%) of 72 received hemodialysis, 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} Compared with other intubated critically ill patients, post-cardiac arrest patients are at particularly high risk of developing pneumonia within the first 48 hours of intubation.²⁴¹

Placement of Implantable Cardioverter-Defibrillators

In survivors with good neurological recovery, insertion of an implantable cardioverter-defibrillator 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 implantable cardioverter-defibrillator is strongly recommended if myocardial ischemia was not identified as the single trigger of sudden cardiac death or if it cannot be treated by coronary revascularization. Systematic implementation of implantable

cardioverter-defibrillator 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 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.

VI. Post-Cardiac Arrest Prognostication

With the brain's heightened susceptibility to global ischemia, the majority of cardiac arrest patients who are resuscitated successfully 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 are 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 the 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 classic 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 1 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 mellitus,^{259,264} sepsis,²⁶⁵ metastatic cancer,²⁶⁶ renal failure,²⁶⁷ homebound lifestyle,²⁶⁶ and stroke,²⁶⁷ were associated with outcome, although 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 found 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 (FPRs) make this 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 (ETCO₂) of <10 mm Hg (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 brain-stem 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 provides 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 brain-stem reflexes or a Glasgow Coma Scale motor score of ≤ 2 at 72 hours had an FPR of 0% (95% CI 0% to 3%) for predicting poor outcome.²⁵⁴ In a recent prospective trial, it was reported that absent pupillary or corneal reflexes at 72 hours had a 0% FPR (95% CI 0% to 9%), whereas absent motor response at 72 hours had a 5% FPR (95% CI 2% to 9%) for poor outcome.²¹¹ Poor neurological outcome is expected with these findings because of the extensive brain injury involving the upper brain stem (midbrain), which is the location of the ascending reticular formation (responsible for arousal) and where the pupillary light response and motor response to pain are 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% to 8.8%]),²⁵⁴ it may be misdiagnosed by nonneurologists.

Combinations of neurological findings have been studied in an attempt to find a simple summary scale such as the Glasgow Coma Scale,²⁸⁶ which is based on the patient's best verbal, eye, and motor responses. The Glasgow Coma Scale score—especially a low motor component score—is associated with poor outcome.^{287–289} The importance of brain-stem reflexes in the assessment of brain injury has been incorporated into a Glasgow Coma Scale–style scale called the Full Outline of UnResponsiveness (FOUR) scale; the FOUR score includes the 4 components of eye, motor, and cranial nerve reflexes (ie, 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 (SSEPs) is a neurophysiological test of the integrity of the neuronal pathways from a peripheral nerve, spinal cord, or brain stem 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 (which represents 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 hours to 1 week after ROSC very reliably predicts poor outcome (FPR for poor outcome=0.7%, 95% CI 0.1% to 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 centers. Other evoked potentials, such as brain-stem 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 studied extensively 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 μ V, 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% to 11%).²⁵⁴ The authors concluded that the EEG alone was insufficient to prognosticate futility. Electroencephalography is noninvasive 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 nonneurologists 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 edema characteristics.^{61,305} The acquisition of magnetic resonance imaging 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 magnetic resonance imaging studies in the critically ill are increasingly being undertaken. Some limited

studies have shown that diffuse cortical abnormalities in diffusion-weighted imaging or fluid-attenuated inversion recovery are associated with poor outcome.³⁰⁶ Metabolic abnormalities (ie, increasing lactate) detected in the brain using functional neuroimaging with magnetic resonance spectroscopy³⁰⁷ and positron emission tomography have also been 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 hemorrhage 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 characterize 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 as a guide for treatment.

Biochemical Markers

Biochemical markers derived initially from cerebrospinal fluid (creatine phosphokinase-BB)^{313,314} or peripheral blood (neuron-specific enolase [NSE] and S100 β) have been used to prognosticate functional outcome after cardiac arrest. The ease of obtaining samples has favored blood-based biochemical markers over those in cerebrospinal fluid. 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 μ g/L drawn between 24 and 48 hours after ROSC was required to achieve an FPR of 0% (95% CI 0% to 43%) for predicting poor outcome with a sensitivity of 14%.³¹⁵ Another study showed that serum NSE concentrations >33 μ g/L drawn between 24 and 72 hours after ROSC predicted poor outcome after 1 month, with an FPR of 0% (95% CI 0% to 3%).²¹¹ Numerous other studies show various thresholds from 30 to 65 μ g/L for poor outcome and mortality.^{316–322}

The biochemical marker S100 β is a calcium-binding protein from astroglial and Schwann cells. In cardiac arrest survivors, 1 study showed that an S100 β cutoff of >1.2 μ g/L drawn between 24 and 48 hours after ROSC was required to achieve an FPR of 0% (95% CI 0% to 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 μ g/L, as a predictor of poor outcome,²⁵⁴ care must be taken. This caution is based on problems such as lack of standardization in study design and patient treatment, the 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 standardize 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 prognostication of poor outcome.^{255,293,299,327} No clinical decision rule or multimodal prognostication protocol has been validated prospectively, however.

Prognostication in Hypothermia-Treated Patients

Therapeutic hypothermia improved survival and functional outcome for 1 in every 6 comatose cardiac arrest survivors treated, according to a meta-analysis.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 the 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 some concern exists that seizures may be masked when a neuromuscular-blocking drug is used.²¹⁹

No studies exist that detail 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 to 28 hours after cardiac arrest in 3 of 4 hypothermia-treated patients with permanent coma (FPR 0%, 95% CI 0% to 100%; sensitivity 75%, 95% CI 30% to 95%).³²⁹ An earlier study from the same group found that the 48-hour NSE and S100 values that achieved a 0% FPR for poor outcome were 2 to 3 times higher in patients treated with hypothermia than in the normothermic control group (NSE >25 versus 8.8 $\mu\text{g/L}$; S100 β 0.23 versus 0.12 $\mu\text{g/L}$).³¹⁷

In summary, both theoretical and evidence-based concerns suggest 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 defined clearly, 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 (eg, hypothermia).

VII. Pediatrics: Special Considerations

Pediatric cardiac arrests are typically caused by respiratory failure, circulatory shock, or both. In contrast to adults, children rarely develop sudden arrhythmogenic VF arrests from CAD. Arrhythmogenic VF/ventricular tachycardia arrests occur in 5% to 20% of out-of-hospital pediatric cardiac arrests and \approx 10% of in-hospital pediatric arrests.^{5,20,330–332}

Although clinical data are limited, differences in both the causes of cardiac arrest and developmental status are likely to contribute to differences between adult and pediatric post-cardiac arrest syndrome.^{97,330,333–335} For example, the severity and duration of post-cardiac arrest myocardial stunning in pediatric animal models are substantially less than in adult animals.^{102,336–338}

In terms of treatment, a critical knowledge gap exists 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} On the basis of this extrapolation, close attention to temperature management (avoidance of hyperthermia and consideration of induction of hypothermia), glucose management (control of hyperglycemia and avoidance of hypoglycemia^{347–349}), blood pressure (avoidance of age-adjusted hypotension), ventilation (avoidance of hypercarbia or hypocarbia and avoidance of overventilation), and hemodynamic support (maintenance of adequate cardiac output to meet metabolic demand) is recommended by consensus for children after cardiac arrest, but this is not supported by specific interventional studies in the postarrest 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-ischemic 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-ischemic 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 evaluated adequately in children. Despite this, several centers treat children after cardiac arrest with therapeutic hypothermia based on extrapolation of the adult data.³⁵⁷ Several physical and pharmacological methods are available for temperature control, all feasible in the pediatric intensive care environment, with specific advantages and disadvantages.^{187,189,358–360}

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 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
Economic
Cultural: these may impact the extent of treatment deemed appropriate in the postresuscitation phase
Social

Extracorporeal Membrane Oxygenation

Perhaps the ultimate technology to control postresuscitation temperature and hemodynamic parameters is ECMO. Several studies have shown that placing children on ECMO during prolonged CPR can result in good outcomes. In 1 report, over a 7-year period, 66 children were placed on ECMO during CPR.³⁶¹ The median duration of CPR before establishment of ECMO was 50 minutes, 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 hemodynamic support and temperature control during the postresuscitation phase. According to the Extra-Corporeal Life Support registry, the use of ECMO during prolonged CPR has become one of the most common indications for ECMO therapy over the past few years.

Pediatric Cardiac Arrest Centers

High-quality, multimodal postarrest care improves survival and neurological outcome in adults.¹³ Pediatric post-cardiac arrest care requires specifically adapted equipment and training to deliver critical interventions rapidly and safely to avoid latent errors and preventable morbidity and mortality. Survival of children after in-hospital arrest is greater when they are treated in hospitals that employ specialized pediatric staff.³⁶² These data suggest that development of regionalized pediatric cardiac arrest centers may improve outcomes after pediatric cardiac arrests, similar to improvements seen with the establishment of trauma centers and regionalized neonatal intensive care. For now, stabilization and transfer of pediatric postarrest patients to optimally equipped and staffed specialized pediatric facilities should be encouraged.^{363,364}

VIII. Challenges to Implementation

Publication of clinical guidelines alone is frequently inadequate to change practice. Several barriers to changing clinical practice

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
Conduct a pilot phase

are often present, 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 implementation of 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 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°C to 34°C for 12 to 24 hours. 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 centers, however.^{12–14,132,160,369}

Barriers to Implementation

The numerous barriers to implementation of guidelines have been described recently 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-recognized 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 (eg, time to achieve target temperature when therapeutic hypothermia is used), it is possible to identify which local protocols and practices need modification. Process and clinical factors should be monitored as part of the quality program. The iterative process of conducting a reaudit and making further changes as necessary should enable optimal performance. Ideally, the standards against which local practice is audited are established at the national

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 are the mechanism(s) and time course of post-cardiac arrest coma?

What are the mechanism(s) and time course of post-cardiac arrest delayed neurodegeneration?

What are the mechanism(s) and time course of post-cardiac arrest myocardial dysfunction?

What are the mechanism(s) and time course of impaired oxygen delivery and utilization after cardiac arrest?

What is the role of intravascular coagulation in post-cardiac arrest organ dysfunction and failure?

What are 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 are the optimal target temperature, initiation time, duration, and rewarming rate?
 - c. What is the most effective cooling technique (external vs 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 goal-directed hemodynamic optimization?
6. What are the optimal goals (parameters and target ranges) for early hemodynamic optimization?
 - a. MAP?
 - b. CVP?
 - c. Central or mixed venous oxygen saturation?
 - d. Hemoglobin 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 hemofiltration?
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

1. What is the optimal decision rule for prognostication of futility?
2. What is the impact of therapeutic hypothermia on the reliability of prognostication of futility?

(Continued)

Table 5. Continued**Pediatrics**

1. What is the evidence specific to children for the knowledge gaps listed above?
2. What is the role of ECMO in pediatric cardiac arrest and postarrest support?

Barriers

1. What is the most effective approach to implementation of therapeutic hypothermia and optimization of post-cardiac arrest care?
2. What is the value of regionalization of post-cardiac arrest care to specialized centers?

CVP indicates central venous pressure; ECMO, extracorporeal membrane oxygenation.

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-hour 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. Prehospital treatment by emergency medical services may involve both paramedics and physicians, and continuation of treatment in the hospital will involve emergency physicians and nurses, cardiologists, neurologists, critical care physicians and nurses, and cardiac catheterization laboratory staff. Treatment guidelines will have to be disseminated across all these specialty groups. Implementation in all these environments may also be challenging; for example, maintenance of hypothermia during cardiac catheterization may be problematic.

Therapies such as primary PCI and therapeutic hypothermia may not be available 24 hours a day in many hospitals that admit comatose post-cardiac arrest patients. For this reason, the concept of "regional cardiac arrest centers" (similar in concept to level 1 trauma centers) has been proposed.³⁷² The concentration of post-cardiac arrest patients in regional centers may improve outcome (this is not yet proven) and should help to facilitate research.

IX. Critical Knowledge Gaps

In addition to summarizing what is known about the pathophysiology and management of post-cardiac arrest syndrome, a goal of the present 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.

Disclosures

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Robert W. Neumar	University of Pennsylvania	NIH grant R01 NS29481 (role: Principal Investigator, "Calpain-Mediated Injury in Post-Ischemic Neurons")†; NIH grant R21 NS054654 (role: Principal Investigator, "Optimizing Therapeutic Hypothermia After Cardiac Arrest")†	None	None	None	None	Gaymar Industries, Inc: consultant, advised on surface cooling technology*	None
Jerry P. Nolan	Royal United Hospital, Bath, UK	None	None	None	None	None	None	Speaking fee of \$500 from KCI*
Christophe Adrie	Massachusetts General Hospital	Unrestricted grant for research on brain death from the publicly funded organization Agence of biomedicine, which manages organ donation in France†	None	None	None	None	None	None
Mayuki Aibiki	Ehime University, Japan	None	None	None	None	None	None	None
Robert A. Berg	The University of Arizona College of Medicine	Medtronic: "Mediators of Post-Resuscitation Myocardial Dysfunction in Piglet VF Study"†; Laerdal: Evaluation of a New Device for Directing CPR in Infantile Swine"†; NIH-NHLBI R01HL7169403 "Post-Countershock CPR After Prolonged VF"†	None	None	None	None	None	None
Bernd W. Böttiger	University of Cologne, Germany	None	None	None	None	None	None	Support from Boehringer Ingelheim (reimbursement for executive and steering committee meetings of the Thrombolysis in Cardiac Arrest [TROICA] trial only)*
Clifton Callaway	University of Pittsburgh	NIH grant: Resuscitation Outcomes Consortium (VOI HL077871)†; Hypothermia and Gene Expression After Cardiac Arrest (R01 N5046073)†	Hypothermia equipment donated from Medivance, Inc, to support laboratory research*	None	None	None	None	Patents: VF waveform analysis, licensed to Medtronic ERS, Inc*
Robert S.B. Clark	University of Pittsburgh	NIH grant HD045968: "Gender-Specific Treatment of Pediatric Cardiac Arrest"†	None	None	None	None	None	None

Continued

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Continued

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Christian Spaulding	Cochin Hospital, Paris, France	French government research grant*	None	Cordis*; Abbott*	None	None	None	None
Kjetil Sunde	Institute for Experimental Medical Research, Ullevaal University Hospital	Laerdal Foundation for Acute Medicine†	None	None	None	None	None	None
Terry Vanden Hoek	University of Chicago Hospital	NIH-DOD/Office of Naval Research*; NIH: "Preconditioning Against a Source of Reperfusion Oxidants"*; Philips Medical Systems: "In-Hospital CPR: Improving Quality and Survival"*	Medivance, Inc*	None	None	None	None	Patents: hypothermia induction patents (3 issued, 3 pending)*



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*Modest.

†Significant.

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Gavin Perkins	University of Warwick, UK	None	None	None	None	None	None	None
Jasmeet Soar	Southmead Hospital, North Bristol NHS Trust	None	None	None	None	None	None	Editor, <i>Resuscitation</i> *
Max Harry Weil	Weil Institute of Critical Care Medicine	None	None	None	None	None	None	None

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