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Dion Stub, Stephen Bernard, Stephen J. Duffy and David M. Kaye

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Post Cardiac Arrest Syndrome
A Review of Therapeutic Strategies

Dion Stub, MBBS; Stephen Bernard, MBBS, MD; Stephen J. Duffy, MBBS, PhD; David M. Kaye, MBBS, PhD

Out-of-hospital cardiac arrest (OHCA) is a common initial presentation of cardiovascular disease, affecting up to 325 000 people in the United States each year.[1] In a recent meta-analysis of >140 000 patients with OHCA, survival to hospital admission was 23.8%, and survival to hospital discharge was only 7.6%.[2] In patients who initially achieve return of spontaneous circulation (ROSC) after OHCA, the significant subsequent morbidity and mortality are due largely to the cerebral and cardiac dysfunction that accompanies prolonged whole-body ischemia. This syndrome, called the post cardiac arrest syndrome, comprises anoxic brain injury, post cardiac arrest myocardial dysfunction, systemic ischemia/reperfusion response, and persistent precipitating pathology[3,4] (Table 1). The contribution of each of these components in an individual patient depends on various factors, including prearrest comorbidities, duration of the ischemic insult, and cause of the cardiac arrest. This review focuses on therapeutic strategies and recent developments in managing patients who are initially resuscitated from cardiac arrest.

There are 3 major aspects that require consideration in the management of the post cardiac arrest patient. After resuscitation, a decision must be made in relation to the appropriate triage of the OHCA patient. The next phase of management concerns the in-hospital treatment, which must address each component of the postarrest syndrome as appropriate for the individual patient. Finally, there are issues relating to prognostication and the deployment of various secondary prevention measures. Our recommended treatment algorithm is summarized in the Figure. This ideally follows from the implementation of basic and advanced life support measures, including effective cardiopulmonary resuscitation and defibrillation when appropriate, which are major determinants of outcome.[2] Such an approach to care may be further modified according to the presence of other comorbidities and precipitating factors, which should be assessed in as much detail as possible.

Regional Systems of Care

The treatment of the patient with ROSC after OHCA requires a multidisciplinary team with significant experience and expertise in the management of these patients. Regional systems of care are well established by other time-critical interventions in patients after trauma,[5] stroke,[6] and ST-elevation myocardial infarction (STEMI).[7]

In a similar manner, data are emerging to suggest that the development of cardiac arrest treatment centers may provide improved outcomes for the OHCA patient. A Japanese cardiac arrest register showed that OHCA patients transported to critical cardiac care hospitals had improved survival compared with patients transported to hospitals without specialized cardiac facilities (odds ratio, 3.39; $P<0.001$).[8] In a Swedish study of almost 4000 OHCA patients, there was marked variability in hospital outcomes after adjustment for prehospital factors, with survival varying from 14% to 42% in different centers.[9] A US cross-sectional study of 109 739 patients indicated that hospital factors, including teaching status, size, and urban location, were associated with outcome in patients resuscitated from cardiac arrest[10]; a separate study designed to optimize all facets of cardiac arrest care showed that transport to dedicated cardiac arrest centers was also associated with an improvement in outcomes.[11] Conversely, the recent study by the Resuscitation Outcomes Consortium Investigators of 4087 patients with OHCA found increased rates of survival in patients after OHCA who were treated at larger hospitals capable of invasive cardiac procedures, but this was not an independent association when adjusted for prehospital factors.[12]

One concern regarding the establishment of regional systems of care for post cardiac arrest management is the potential for longer transport times to hospital. However, recent data indicate that increasing transport time is not associated with adverse patient outcomes.[13] Further research into the safety of bypassing the nearest hospital to facilitate transfer to a cardiac center is needed.

The data supporting implementation of systems of care approach for OHCA are preliminary and limited. The American Heart Association, however, has recommended that patients with OHCA in whom the initial cardiac rhythm is ventricular fibrillation (VF) or OHCA with ST-segment elevation be transported directly to centers with expertise and facilities in the management of acute coronary syndromes.[14,15]

Initial Management

It is important that a comprehensive management algorithm is applied to the post cardiac arrest patient. This model is

From the Baker IDI Heart Diabetes Institute (D.S., S.J.D., D.M.K.); Alfred Hospital Heart Centre (D.S., S.J.D., D.M.K.); and Alfred Hospital Intensive Care Unit (S.B.), Melbourne, Australia.

Correspondence to Dr Dion Stub, Heart Centre, Alfred Hospital Commercial Rd, Melbourne, Australia 3004. E-mail d.stub@alfred.org.au

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Table 1. Post Cardiac Arrest Syndrome: Pathophysiology and Potential Treatment Strategies

Post Cardiac Arrest Syndrome	Anoxic Brain Injury	Arrest-Related Myocardial Dysfunction	Systemic Ischemic/ Reperfusion Response	Persistent Precipitating Pathology
Pathophysiology	Disrupted calcium homeostasis Free radical formation Cell death signaling pathways Reperfusion injury No reflow Additional insults: pyrexia, hyperglycemia, hyperoxygenation	Stunning phenomenon Global hypokinesis Elevated LVEDP Preserved coronary blood flow (excluding patients with ACS)	Intra-arrest global tissue hypotension Reperfusion injury Endothelial activation Systemic inflammation Activation of clotting cascades Intravascular volume depletion Disturbed vasoregulation Risk of infection	ACS plaque rupture/thrombus formation Chronic ischemic myocardial scar Pulmonary embolism Cardiomyopathies: dilated, restrictive, hypertrophic, genetic, channelopathy, congenital
Potential therapeutic approaches	Therapeutic hypothermia Early hemodynamic optimization Ventilation and airway protection Seizure control Controlled oxygenation	Systems of care Revascularization Intravenous fluid Inotropes IABP ECMO LVAD	Goal-directed therapy Intravenous fluids Vasopressors Glucose control Hemofiltration Antimicrobials	Address disease specific origin

ACS indicates acute coronary syndrome; LVEDP, left ventricular end diastolic pressure; IABP, intra-aortic balloon pump; ECMO, extracorporeal membrane oxygenation; and LVAD, left ventricular assist device.

consistent with care in other emergent situations, such as early goal-directed therapy in patients with severe sepsis.[16] In patients with OHCA, goal-directed therapy protocols have been introduced as part of a package of postresuscitative care to improve survival.[17,18] Interventions include focusing on ensuring adequate oxygenation and ventilation, support of the circulation, timely institution of therapeutic hypothermia (TH), consideration of coronary angiography, and general critical care measures, such as blood glucose control.

Oxygenation and Ventilation

Although 100% oxygen is commonly used during initial resuscitation, both animal models and observational studies highlight the potential harm of oxygen toxicity.[19,20] In a multicenter cohort study of 6326 patients admitted to intensive care after OHCA, arterial hyperoxia (Pao_2 >300 mm Hg) was independently associated with increased in-hospital mortality compared with patients with normoxia or hypoxia.[20] Accordingly, until there are further data from prospective, controlled clinical trials, it seems reasonable to recommend that both hyperoxia and hypoxia after ROSC be avoided. In conjunction, careful control of Pco_2 is also critical because hypocarbia causes cerebral vasoconstriction and hyperventilation decreases cardiac output.

Circulatory Support

Hemodynamic instability is common after cardiac arrest, and may be associated with poorer prognosis. Stabilization of the circulation involves fluid therapy, vasoactive drug therapy, and consideration of mechanical support. Early echocardiography provides information on the extent of myocardial dysfunction and may assist in guiding treatment.[21]

The optimal hemodynamic targets in the postresuscitative period remain unclear. In a single-center study using a postresuscitative care treatment algorithm, there was a non-statistically significant 28% improvement in mortality in 20 patients compared with historical controls.[18] In that study, key aspects of therapy were the early initiation of TH, maintenance of a relatively elevated mean arterial pressure (80 to 100 mm Hg), use of a pulmonary artery catheter in cases of worsening cardiogenic shock, and early determination of left ventricular ejection fraction with echocardiography used to guide inotropic drug therapy. Another study used TH, urgent coronary reperfusion, and goal-directed therapy in 61 patients, and compared this strategy with historical controls.[17] There was a 30% improvement in favorable neurological outcome. Interestingly, this study had a target mean arterial pressure of 65 to 70 mm Hg. On the basis of the available evidence, it is reasonable to target a mean arterial pressure of 65 to 100 mm Hg, taking into consideration the patient's normal blood pressure and severity of myocardial dysfunction.

If adequate circulatory stability is not achievable with the use of fluid therapy and modest inotropic drug therapy, the use of mechanical support should be considered. There is some clinical evidence of benefit with the use of the intra-aortic balloon pump in acute coronary syndrome complicated by cardiogenic shock[22]; however, a recent review indicated no overall benefit in patients with STEMI and cardiogenic shock.[23] Intra-aortic balloon pumps have been used to various degrees in observational series in cardiac arrest, with insertion rates of 22% to 46% of patients.[24–26]

Given that the level of circulatory support provided by the intra-aortic balloon pump may be inadequate in the setting of severe ventricular dysfunction, alternative devices that provide greater degrees of cardiac support may be considered. Percutaneous cardiopulmonary bypass with extracorporeal membrane oxygenation is one such option, with the additional benefits of possibly aiding resuscitation in prolonged arrest.[27–29] In a recent systematic review of extracorporeal

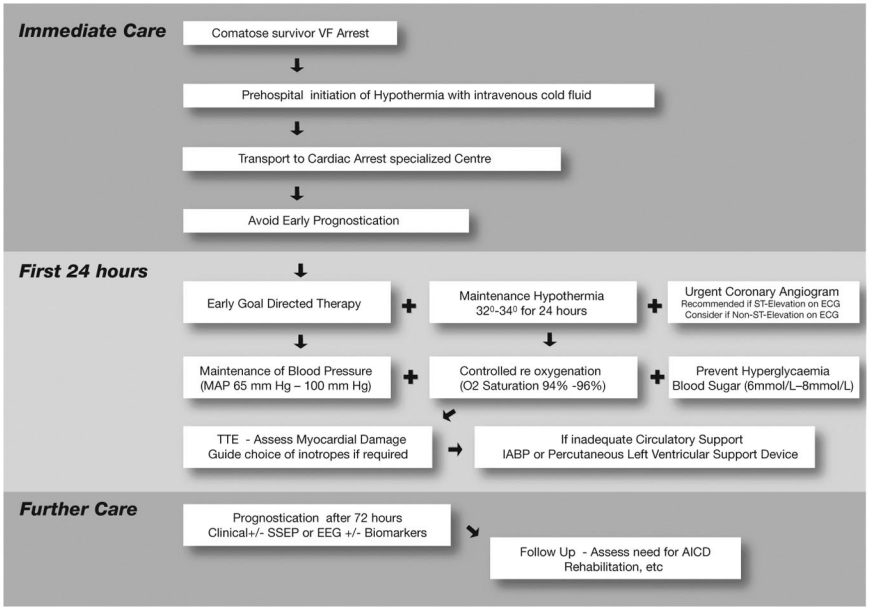

Figure. Post cardiac arrest treatment algorithm. MAP indicates mean arterial blood pressure; TTE, transthoracic echocardiogram; IABP, intra-aortic balloon pump; SSEP, somatosensory evoked potentials; EEG, electroencephalography; and AICD, automated internal cardioverter-defibrillator.

membrane oxygenation initiated during cardiac arrest, an overall in-hospital survival rate of 45% was found.[30] There is also interest in other percutaneous left ventricular assist devices that have hemodynamic profiles superior to the intra-aortic balloon pump that, if available, should be considered.[31,32]

Neuroprotection: Therapeutic Hypothermia

Post cardiac arrest anoxic brain injury is a major cause of morbidity and mortality, and is responsible for approximately two thirds of the deaths in the post cardiac arrest period.[33] One important advance in post-ROSC management is the use of TH to treat comatose survivors of OHCA. Two randomized, controlled trials have clearly confirmed the benefit of TH after cardiac arrest.[34,35] Both studies investigated mild TH in comatose adult patients after OHCA secondary to VF.

The first trial, the European Multicenter Trial, conducted by the Hypothermia After Cardiac Arrest Study group, enrolled 275 patients.[34] At 6 months, 55% of the cooled patients had a good outcome compared with 39% of normothermic control subjects. The second study, from Australia, enrolled 77 patients who were resuscitated from OHCA with an initial cardiac rhythm of VF.[35] At hospital discharge, 49% of patients who were cooled to 33°C for 12 hours had good neurological outcomes compared with 26% of the control group. A subsequent individual patient data meta-analysis indicated that the number needed to treat to provide a favorable neurological outcome is 6.[36] As a result of these trials, TH is now recommended in the management of anoxic neurological injury after cardiac arrest[3,4] (Table 2).

There is uncertainty regarding the applicability of TH to patients in cardiac arrest in whom the initial cardiac rhythm is asystole or pulseless electric activity.[40] These patients have significantly poorer outcomes compared with patients with an initial cardiac rhythm of VF/ventricular tachycardia.[2,4] There is some evidence, however, that TH will benefit patients with an initial rhythm of asystole or pulseless electric activity.[36,41] The most recent International Liaison Committee on Resuscitation guidelines recommend using hypothermia after cardiac arrest if the initial rhythm is ventricular tachycardia or VF and consideration of its use for other rhythm disturbances.[3,4]

The physiological benefits of TH are thought to be multifactorial, including decreases in cerebral oxygen demand and direct cellular effects and a reduction in reactive oxygen species generation.[42] Despite the recommendation that hypothermia should be initiated as soon as possible after cardiac arrest, the method, timing, and duration of hypothermia treatment have yet to be comprehensively studied. Hypothermia can be induced by a variety of different methods,

Table 2. Select Randomized Controlled Studies of Therapeutic Hypothermia in Out-of-Hospital Cardiac Arrest

Reference	n	Target Temperature, °C	Cooling Duration, h	Initial Rhythm	Target MAP, mm Hg	Survival, %	Good Neurological Recovery, %
Hachimi-Idrissi et al,[37] 2001	30	34	4	Asystole/PEA	>60	19 vs 7	13 vs 0
HACA Group,[34] 2002	275	32–34	24	VF/VT	>60	59 vs 45	55 vs 39
Bernard et al,[35] 2002	77	33	12	VF/VT	90–100	49 vs 32	49 vs 26
Bernard et al,[38] 2010	234	33	24	VF/VT	100	50*	49
Castren et al,[39] 2010	200	34	24	All rhythms	. . .	36*	27

MAP indicates mean arterial blood pressure; PEA, pulseless electric activity; HACA, Hypothermia After Cardiac Arrest Study; VF, ventricular fibrillation; and VT, ventricular tachycardia.

*Randomized study of prehospital vs in-hospital initiation of hypothermia (all patients cooled).

including surface cooling, ice-cold infusions, evaporative transnasal cooling, and endovascular cooling catheters.[37,39,43] Although studies have examined cooling efficacy and time to target temperature, no available studies have compared different cooling devices with respect to the key clinical end points of mortality and morbidity.

Given that animal models of early initiation of hypothermia lead to improved neurological outcomes, the prehospital induction of TH has been proposed.[44] Two randomized, controlled trials of paramedic administration of ice-cold fluids to induce TH have indicated that this is a safe and effective means of induction of cooling. These trials, however, have not shown clinical benefit compared with cooling patients on arrival to hospital.[38,45]

The rewarming phase can be regulated with external or internal devices used for cooling or by other heating systems. The optimal rate of rewarming is not known, but a current recommendation is to rewarm at ≈0.25°C/h to 0.5°C/h.[46] Care should be taken during the induction and rewarming phases to monitor electrolyte and hemodynamic changes carefully.

Therapeutic hypothermia decreases heart rate and increases systemic vascular resistance.[47] There is also evidence that TH may be beneficial to the heart in the postarrest period. Animal studies have shown improvement in myocardial function, myocardial salvage, and reduced infarct size in the setting of cardiac arrest or acute myocardial infarction with the use of TH.[48] Early studies of the use of TH, before cardiac magnetic resonance imaging, revealed a trend toward a reduction in infarct size.[43,49] In the setting of acute myocardial infarction and cardiac arrest, observational trials have also shown a nonsignificant reduction in infarct size with hypothermia.[50] A recent study of 20 patients with STEMI revealed a significant increase in myocardial salvage on cardiac magnetic resonance imaging in those patients who received TH before reperfusion.[51]

Possible adverse effects of hypothermia include electrolyte and intravascular volume changes, cardiac arrhythmias, immunological impairment, and altered coagulation profile. These complications, however, usually can be easily managed in an intensive care environment. Clinical trials have not found any significant increase in severe complications of TH compared with patients treated with normothermia.[34,35,38,46]

Overall, TH is an important intervention after cardiac arrest and resuscitation. Issues relating to the method and timing of cooling, use in non–VF/ventricular tachycardia, and use in patients with in-hospital cardiac arrest require further clinical trials.

Other Neuroprotective Strategies

Seizures increase the cerebral metabolic rate, and may accentuate neurological injury after OHCA. Phenytoin is used for seizure treatment, and, in a rat model of cardiac arrest, reduced brain edema by attenuating intracellular salt and water.[52] Although thiopentone is neuroprotective in animal models,[53] a large clinical trial showed no benefit.[54] Other neuroprotective agents, such as magnesium and calcium channel inhibition, have undergone prospective clinical trials with no improvement in outcomes.[55,56]

Management of Acute Coronary Syndrome in the OHCA Patient

Coronary artery disease is a major cause of OHCA, commonly related to the development of acute coronary syndrome or ventricular arrhythmia resulting from previous scar formation. Together, these account for 40% to 90% of cases.[57] Rarer causes of cardiac-related arrhythmias are dilated and hypertrophic cardiomyopathies, channelopathies, and pulmonary embolism.

Patients with OHCA have been excluded from most large, randomized trials that focus on the management of acute coronary syndrome, which makes decision making regarding the role of primary percutaneous coronary intervention (PCI) in this group of patients difficult. Observational data are strongest in the setting of OHCA and STEMI. The initial ECG shows ST elevation in 30% to 60% of patients with ROSC after OHCA.[25,58–60] In a multicenter French study of 186 patients with OHCA and STEMI, primary PCI was performed routinely, with stents inserted in 90% of patients. Survival at 6 months was 54%, with 46% of patients free of neurological impairment.[25] A number of other observational series have indicated high procedural success rates and in-hospital survival rates between 60% and 78%, with early coronary angiography for patients with STEMI after OHCA.[24,26,61,62]

Although an urgent interventional approach for OHCA with STEMI is recommended, the role of urgent coronary angiography in patients with OHCA and non-STEMI is uncertain. Many clinicians may advocate waiting to assess neurological recovery before proceeding to angiography.[63] Proponents of an early interventional approach suggest that 40% of cardiac arrests caused by unstable coronary plaques may be missed if decision making is based on ECG criteria alone[58,60] (Table 3). A recent study of cardiac arrest patients undergoing coronary angiography found that significant coronary lesions occur in up to 66% of patients without ST elevation.[59] The largest series in coronary intervention and OHCA has found that primary PCI was an independent predictor of survival regardless of initial ECG findings (odds ratio, 2.06; $P=0.013$).[60]

Given the available data, combined with the difficulties of early prognostication with TH, current guidelines suggest that it is reasonable to consider all survivors of OHCA of suspected cardiac origin for primary PCI.[14] When emergent coronary intervention is unavailable, treatment with thrombolytic drugs may be considered. The use of prehospital thrombolysis for cardiac arrest has been studied, but has not shown significant benefit compared with placebo.[64,65] If no facilities are available for immediate PCI, thrombolysis should be considered for patients with STEMI after OHCA.[66,67] The potential interaction between thrombolysis and TH has not been well studied, with possible issues of efficacy of thrombolysis and increased risk of hemorrhage.

Combining Hypothermia and Coronary Intervention

Combining TH with primary PCI is emerging as a new approach to further improve outcomes. Table 4 highlights recent observational studies in which, collectively, TH was used in 86% of patients and PCI in just under half, with a

Table 3. Select Studies of Coronary Angiogram After Resuscitation From Cardiac Arrest

Reference	Trial Details	n	STEMI, %	PCI, %	IABP, %	Survival, %	Good Neurological Recovery, %
Spaulding et al,[58] 1997	Prospective observational study; VF and non-VF arrest	84	42	44	11	38	36
Garot et al,[25] 2007	Retrospective observational study; STEMI after VF/VT	186	100	87	43	54	46
Gorjup et al,[61] 2007	Retrospective observational study; VF and non-VF arrest	135	100	80	16	69	55
Hosmane et al,[62] 2009	Retrospective observational study; STEMI after VF/VT	98	100	79	NA	64	59
Anyfantakis et al,[63] 2009	Retrospective observational study; VF and non-VF arrest	72	32	33	22	49	46
Lettieri et al,[26] 2009	Retrospective observational study; VF and non-VF arrest	99	100	90	22	78	68

STEMI indicates ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; IABP, intra-aortic balloon pump; VF, ventricular fibrillation; and VT, ventricular tachycardia.

cumulative survival of 47%.[24,50,60,68,69] These nonrandomized trials have revealed the combination of TH and PCI to be safe, feasible, and possibly more efficacious in comatose survivors of OHCA than either therapy alone.

Prognostication

Despite the advances in postresuscitative care, a significant proportion of patients will have a poor neurological outcome. The need for prolonged intensive care in patients with severe neurological impairment and little hope for recovery is devastating for families. This also consumes considerable resources. There is a need, therefore, for accurate and timely neurological prognosticating in comatose survivors of cardiac arrest. It is also important to avoid withdrawal of active management in patients who may make a meaningful recovery.

A number of prearrest factors, such as patient comorbidities, are associated with poorer survival.[70] Intra-arrest details, such as initial cardiac rhythm, time to ROSC, absence of bystander cardiopulmonary resuscitation, and maximal end-tidal CO_2, are also associated with patient outcome.[2] However, no factors are sufficiently reliable to conclude that continued care is futile.

An evidence-based approach to prognostication based on postarrest factors has been proposed by the American Academy of Neurology, including key clinical, biochemical, and neurophysiological parameters.[71] The role of neurological imaging at present is largely limited to the exclusion of intracranial pathologies, such as hemorrhage or stroke. These guidelines, however, are based on evidence that predates the widespread introduction of TH, which raises concern regarding the ongoing validity of this approach. Hypothermia may delay the clearance of sedation and mask return of neurological function.[72]

Clinical Examination

The most reliable predictor of neurological outcome in the prehypothermia era was the neurological examination.[71] A recent study examined the validity of clinical findings in patients who had received hypothermia. In a retrospective review of 36 patients, the authors found that the absence of motor responses better than extensor posturing on day 3 may not be reliable, whereas absent papillary and corneal reflexes at day 3 remained accurate at predicting hopeless prognosis in the hypothermia setting.[73]

Table 4. Select Studies of Combination Therapies for Out-of-Hospital Cardiac Arrest

Reference	Trial Details	n	Cooling, %	PCI, %	BSL, mmol/L	MAP, mm Hg	Survival, %	Good Neurological Recovery, %
Hovdenes et al,[24] 2007	Retrospective observational study after VF arrest	50	100	72	4–7	NA	82	68
Knafelj et al,[68] 2007	Retrospective observational study; STEMI after VF/VT arrest	40	100	90	NA	NA	75	55
Sunde et al,[17] 2007	Prospective observational study; VF and non-VF arrest	61	77	49	5–8	>65–70	56	56
Gaieski et al,[18] 2009	Prospective observational study; VF and non-VF arrest	18	100	39	<8.5	80–100	50	44
Dumas et al,[60] 2010	Prospective observational study; VF and non-VF arrest	435	86	41	NA	NA	40	37
Stub et al,[69] 2011	Retrospective observational study after VF arrest	81	75	38	NA	NA	64	57

PCI indicates percutaneous coronary intervention; BSL, blood sugar level; MAP, mean arterial blood pressure; VF, ventricular fibrillation; STEMI, ST-elevation myocardial infarction; and VT, ventricular tachycardia.

Neurophysiological Tests

The assessment of somatosensory evoked potentials is a commonly performed neurophysiological test of the integrity of central pathways. The absence of early cortical somatosensory evoked potentials has been shown to be a reliable predictor of poor outcome[74]; conversely, the presence of somatosensory evoked potentials does not necessarily guarantee good neurological outcomes.[75,76]

Electroencephalography has been used to evaluate the depth of coma and extent of damage after cardiac arrest. However, the predictive value of individual patterns is poor. A meta-analysis before the use of TH concluded that electroencephalography was strongly associated with poor outcome, but not invariably linked with futility, with a small false-positive rate of 3%.[71] A recent prospective study of prognostication in 111 patients receiving TH indicated that electroencephalography in this setting may be better than previously reported, but also suggested that clinical findings in patients who receive TH may be unreliable.[77]

Biochemical Markers

Biochemical markers in peripheral blood, such as neuron-specific enolase and S100β, have been used to prognosticate functional outcome after cardiac arrest.[78] Although a recommendation has been made on the use of biochemical markers as predictors of poor outcome,[71] care must be taken because of the lack of standardization of measurement techniques.[4] As with neurophysiological tests, there are conflicting data on whether there is decreased accuracy in the use of biochemical markers after the use of TH.[76,79]

The current evidence suggests that there is uncertainty in the prognostication of patients with coma after OHCA who have been treated with TH. The recovery period after hypothermia therapy has not been defined clearly, and early withdrawal of life-sustaining treatment may not be justified. Until more is known about the impact of TH, prognostication should probably be delayed until day 3 after rewarming from TH[3,4] and should use multiple modalities.

Further Care

The recovery of patients after cardiac arrest requires input from a multidisciplinary team with expertise in assessment for rehabilitation, neuropsychological assessment, if appropriate, and discharge planning. The decision regarding further therapy such as the need and timing of an automated implantable cardioverter-defibrillator is also important.[80]

Conclusions

In patients who achieve ROSC after OHCA, morbidity and mortality remain significant in part because of the development of a specific post cardiac arrest syndrome. To achieve improved survival and improved neurological outcomes, it will be necessary to develop and adopt a systematic approach to all elements of the pathophysiological process. Treatment strategies focusing on both prehospital and postresuscitative care are vital to improving patient outcomes, and may be further optimized with the development of regional systems of care. Specifically, emphasis should be placed on the development of specialist centers that offer goal-directed therapies, including TH, early coronary angiography, and temporary circulatory support when appropriate, together with comprehensive neurological assessment and therapy.

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Disclosures

None.

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KEY WORDS: heart arrest ■ cardiopulmonary resuscitation ■ hypothermia ■ myocardial infarction ■ revascularization