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Postresuscitation Care after Out-of-hospital Cardiac Arrest

Clinical Update and Focus on Targeted Temperature Management

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ABSTRACT

Out-of-hospital cardiac arrest is a major cause of mortality and morbidity worldwide. With the introduction of targeted temperature management more than a decade ago, postresuscitation care has attracted increased attention. In the present review, we discuss best practice hospital management of unconscious out-of-hospital cardiac arrest patients with a special focus on targeted temperature management. What is termed post–cardiac arrest syndrome strikes all organs and mandates access to specialized intensive care. All patients need a secured airway, and most patients need hemodynamic support with fluids and/or vasopressors. Furthermore, immediate coronary angiography and percutaneous coronary intervention, when indicated, has become an essential part of the postresuscitation treatment. Targeted temperature management with controlled sedation and mechanical ventilation is the most important neuroprotective strategy to take. Targeted temperature management should be initiated as quickly as possible, and according to international guidelines, it should be maintained at 32° to 36°C for at least 24 h, whereas rewarming should not increase more than 0.5°C per hour. However, uncertainty remains regarding targeted temperature management components, warranting further research into the optimal cooling rate, target temperature, duration of cooling, and the rewarming rate. Moreover, targeted temperature management is linked to some adverse effects. The risk of infection and bleeding is moderately increased, as is the risk of hypokalemia and magnesemia. Circulation needs to be monitored invasively and any deviances corrected in a timely fashion. Outcome prediction in the individual patient is challenging, and a self-fulfilling prophecy poses a real threat to early prognostication based on clinical assessment alone. Therefore, delayed and multimodal prognostication is now considered a key element of postresuscitation care. Finally, modern postresuscitation care can produce good outcomes in the majority of patients but requires major diagnostic and therapeutic resources and specific training. Hence, recent international guidelines strongly recommend the implementation of regional prehospital resuscitation systems with integrated and specialized cardiac arrest centers.

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Every year, out-of-hospital cardiac arrest causes millions of premature deaths worldwide. Large survival differences between countries, regions, and rescue systems have been reported.[1–8] Further, recent studies have found an overall increase in survival when there are ongoing quality improvement programs present.[9–13] Patient-related factors, such as age and comorbidities, and etiologic factors, such as the cause of arrest and the initial rhythm, significantly affect survival but are not modifiable by medical interventions. However, factors like bystander cardiopulmonary resuscitation rates, a rapid emergency medical service response time, high-quality cardiopulmonary resuscitation, and reduced time to defibrillation are modifiable factors shown to improve patient outcomes.[4,7,13–16] Some experienced resuscitation systems now report overall survival rates above 50% in out-of-hospital cardiac arrest patients who have shockable rhythms (*i.e.*, ventricular fibrillation and tachycardia), and good functional outcome is observed in most survivors.[9,12,15]

More than 50 yr ago, Peter Safar, M.D., a trained anesthesiologist and one of the pioneers of resuscitation medicine, highlighted the importance of good postresuscitation care to further increase the probability of neurologic recovery in cardiac arrest survivors.[17] Nevertheless, in the decades after Safar's discovery, enthusiasm for post–cardiac arrest therapies dropped as different interventions, including deep hypothermia and experimental drugs (*i.e.*, calcium antagonists, magnesium, and barbiturates), were unable to improve the dismal survival rate observed in these patients.[18] However, the publication of two controlled studies in 2002, which independently showed a significant increase in the survival and neurologic outcomes of moderate hypothermia in unconscious out-of-hospital cardiac arrest patients, renewed interest in targeted therapies that focus on both heart and brain protection and resuscitation.[18–21]

The introduction of therapeutic hypothermia (cooling) has emphasized the importance of the in-hospital therapeutic phase and the need for optimized postresuscitation care in all centers taking care of out-of-hospital cardiac

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arrest patients. In the current review, with a special focus on targeted temperature management, we will discuss the concept of high-quality postresuscitation care and how it may have a critical impact on outcomes in out-of-hospital cardiac arrest patients. First, we discuss post–cardiac arrest syndrome and immediate hospital treatment followed by an overview of all aspects of targeted temperature management, including its impact on organ functions and organ support. Finally, we review the important aspect of neuroprognostication and the logistics of postresuscitation care. Indeed, with good outcomes now being reported, there is no excuse for therapeutic nihilism or downgrading hospital care for this fragile patient group.[20,22–26]

Post–cardiac Arrest Syndrome

Post–cardiac arrest syndrome constitutes a unique and complex pathophysiologic process that is caused by whole-body ischemia followed by reperfusion.[18] Patients with a very short cardiac arrest generally do not often develop post–cardiac arrest syndrome, and effective cardiopulmonary resuscitation may turn the no-flow to a low-flow state, thereby alleviating the magnitude of the injury. After return of spontaneous circulation, the reperfusion injury develops and induces multiple organ dysfunction, which is characterized by postanoxic brain injury, cardiovascular impairment, and a systemic inflammatory response that involves features similar to those observed during sepsis (*i.e.*, an increased systemic level of cytokines and endotoxins and elevated markers of inflammation; fig. 1).[27–29] The magnitude of the inflammatory response is also closely related to the severity of the circulatory and cardiac dysfunction.[30] Post–cardiac arrest shock is the main cause of early death in approximately 23% of out-of-hospital cardiac arrest patients, whereas irreversible neurologic damage is identified later during the hospital course of care and results in the withdrawal of life-sustaining therapies in the cases of most of nonsurvivors.[31] Most of the individual components of post–cardiac arrest syndrome are reversible and possibly amenable with treatment. It is important to support vital functions to both avoid new injuries and allow organ recovery.

Immediate Hospital Management

Unconscious out-of-hospital cardiac arrest patients constitute a heterogeneous group in which patient age, sex, and comorbidity, type of cardiac arrest (witnessed, cause), and system factors (alarm and dispatch and basic and advanced life support, including postresuscitation care) interact in numerous ways. Consequently, each patient will need an individual treatment approach. Upon arrival in the emergency department or intensive care unit, the patient should be assessed with an airway, breathing, circulation, and disability approach (table 1) and targeted temperature management initiated, while prehospital personnel will provide relevant information that must be documented. The cause of out-of-hospital cardiac arrest varies, but there is often a

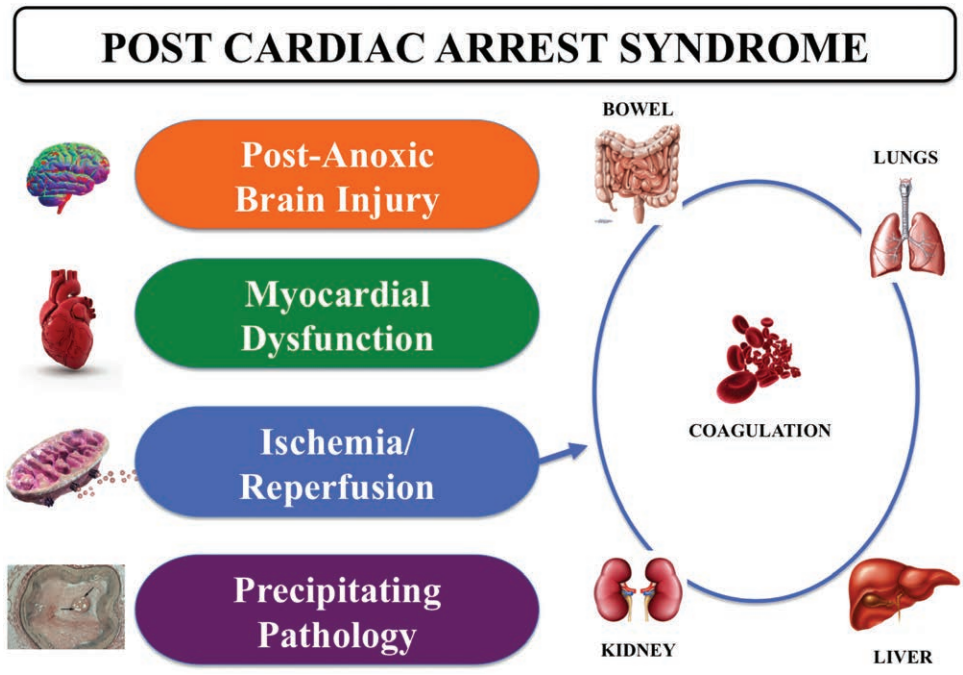

Fig. 1. The four elements of the post–cardiac arrest syndrome.

Table 1. Immediate Assessment of the Post–Cardiac Arrest Patient According to an ABCD Approach

	Relevance Regarding the Cardiac Arrest Patient	Management
A – Airway	The use of supraglottic airways are common in the out-of-hospital setting, and intubation is needed unless the patient is conscious (GCS > 12).	If not secured, secure the airway with an ETT. If the patient has an ETT, verify placement with continuous $ETCO_2$ monitoring. Check the depth of the tube and that the cuff is inflated.
B – Breathing	Assisted ventilation is needed for at least 24 to 48 h. Avoid extreme hyperoxemia and hypocapnia.	Use volume control. Adjust the FIO_2 avoid 100% unless documented hypoxia. Ventilate with 6–8 ml/kg 12 times a min.
C – Circulation	Re-arrest may occur during the first 20 min.	Monitor blood pressure invasively. A sudden drop in $ETCO_2$ suggests re-arrest and mandates CPR. Monitor ECG.
D – Disability	Assess GCS before administering sedative drugs.	Extubation is generally not indicated early after cardiac arrest. Administer sedative drugs such as opiates and hypnotics.
E – Examinations	Immediate examination may reveal clues regarding the cause of the arrest.	Auscultate the heart and lungs. Check the pupils for size, symmetry, and reactivity to light. If possible, obtain an ABG, ECG, ECHO, and chest X-ray.
F – Further aspects	Identify immediately the required life-saving interventions and organize further care.	Transportation to a unit capable of supplying PRC, such as an ICU or a cardiac arrest center.

ABG, arterial blood gas; CPR, cardiopulmonary resuscitation; FIO_2, fraction of inspired oxygen; ECG, electrocardiogram; ECHO, echocardiography; ETT, endotracheal tube; $ETCO_2$, end-tidal carbon dioxide; GCS, Glasgow coma scale; ICU, intensive care unit; PRC, postresuscitation care.

cardiac etiology (*i.e.*, coronary occlusion and/or arrhythmias). Hence, in the absence of other obvious causes (*i.e.*, drowning, electrocution, and drug intoxication), many researchers now promote the use of coronary angiography (table 2). Many patients with an out-of-hospital-cardiac arrest of presumed cardiac origin will show signs of an acute coronary lesion (*i.e.*, ST segment elevation on the electrocardiogram).[32] The current guidelines recommend an immediate coronary angiography in patients with ST segment elevation and, if indicated, a subsequent percutaneous intervention.[33,34] Whether a coronary angiography should also be performed in out-of-hospital cardiac arrest patients without ST elevation is still debated. A prospective registry study demonstrated that in 301 patients without ST elevation, 176 (58%) had at least one significant stenosis, and percutaneous intervention was successfully performed on 78 patients.[35] In the same study, successful coronary angioplasty was an independent prognosticator of survival after hospital discharge *per se*. However, in female and young patients without previous cardiac history, chest pain and ST elevation on electrocardiogram, or those with a high cardiac arrest hospital prognosis score, coronary angiography would show the presence of a culprit lesion in few patients and have a less relevant effect on survival.[36] It is also debatable whether cardiac procedures should be performed on unstable patients, but the coronary angiography/percutaneous intervention might be seen as a part of the resuscitation process, and should be provided as soon as possible in such patients because percutaneous intervention may also contribute to the improvement in cardiac function and shock resolution. Furthermore, a new technique with rapid endovascular core cooling before percutaneous coronary intervention has been shown to be feasible and a reduction in infarct size/myocardium at risk ratio was demonstrated; however, the reduction was not statistically significant.[37] Still, in some institutions, out-of-hospital cardiac arrest patients with a presumed cardiac origin may undergo an immediate coronary angiography and parallel cooling. If the coronary angiography is negative and coronary ischemia is the most likely precipitating factor, the patient then undergoes a cerebral computed tomography scan to rule out major cerebral pathology and a chest computed tomography scan to identify a potential pulmonary embolism.

Targeted Temperature Management and Neuroprotection

Brain protection strategies should be effective to attenuate the progression of cerebral cell injury or to prevent the occurrence of secondary brain damage. However, the complex pathogenesis of postanoxic brain injury, such as endothelial damage, tissue hypoxia, neuroinflammation, impaired mitochondrial function, intracellular calcium overload, and excitotoxicity, is a major limitation to the effectiveness of neuroprotective strategies.[38] Indeed, drug targets are too specific, making drug administration unable to block most of these pathologic mechanisms. Moreover, drug cerebral penetration is unpredictable because very few pharmacokinetics data are available on humans. In addition, many therapeutic agents have been shown to be effective in experimental models, but these findings are not easily translated to a human setting. This is because of the absence of comorbid diseases and/or the need for anesthetics in animal studies, the different timing of administration (*i.e.*, often a pretreatment approach in the experimental setting), and the lack of validation studies in large animal cohorts or in different animal species.

Among all the various treatments, targeted temperature management (*i.e.*, lowering core body temperature to 32 to 36°C and avoiding fever for at least 72 h) is the most

Table 2. Identifying the Cause of the Cardiac Arrest and Tailoring Investigations and Immediate Management Accordingly

Cardiac Arrest Cause	Diagnostic Possibilities	Management Immediately after ROSC	Management Priorities during the Following 24–48 h
Myocardial infarction	12-lead ECG and continuous ECG monitoring, coronary angiography, serial cardiac enzymes, and cardiac ECHO.	Avoid extreme hyperoxemia, avoid hypotension and target a MAP of at least 70 mmHg, and organize immediate coronary angiography.	Use anticoagulation and antithrombotic medication, avoid extreme hyperoxemia, avoid hypotension, and target MAP greater than 70 mmHg.
Cardiac arrhythmia	12-lead ECG and continuous ECG monitoring, coronary angiography, serial cardiac enzymes, and cardiac ECHO. Electrolytes.	Correct any electrolyte abnormalities, consider amiodarone infusion, and consider β-blocking agents.	Avoid and treat arrhythmias, consider and plan the need for ECHO and need for invasive cardiac examinations (electro physiologic testing or MRI).
Cardiogenic shock	Echocardiogram, 12-lead ECG, cardiac enzyme, and BNP.	Initiate inotrope, consider VA ECMO and consider coronary angiogram and the need for an IABP.	If using TTM, consider targeting at 36°C. Stabilize and monitor cardiac function. Initiate medical treatment for myocardial insufficiency.
Asphyxia related to drugs	Small pupils in opiate overdoses and arterial blood gas analysis.	Ventilation targeting normoxia (SpO_2 94–98%), PaO_2 80–100 mmHg.	Aim to alleviate hypoxic brain injury with TTM.
Pulmonary embolism	Echocardiography of the heart; computed tomography can be done with intravenous contrast; d-dimer in out-of-hospital cardiac arrest.	Consider thrombolysis or surgical embolectomy, anticoagulation, and extracorporeal membrane oxygenation.	Anticoagulation with low-molecular-weight heparin or heparin with monitoring the effect. Consider an ultrasound of the lower limbs. Initiate a plan to ascertain the reasons for increased thrombosis risk.
Bleeding, trauma, or related to other causes	Hemoglobin level, coagulation status, focused assessment with "sonography" for trauma (FAST), whole-body computed tomography temperature, arterial blood gases, and electrolytes.	Identify the site of active bleeding and aim for bleeding control. Correct coagulation profile, consider transfusions, warm the patient, and correct acid–base and electrolyte disorders throughout surgery or radiological intervention.	Keep the patients stable and identify possible re-bleeding. Manage coagulation and venous thrombo-embolism prophylaxis.
Intracranial bleeding	Pupillary status and computed tomography of the brain with or without angiography.	Neurosurgical consult regarding possibilities for surgery or coiling.	Stabilize. Control CT brain. Treat with TTM but avoid targeting at 33°C. In case of a dismal prognosis, identify the possibility of organ donation.
Sepsis	Blood, sputum, and urinary cultures, cerebrospinal fluid in specific cases, chest radiography, and targeted computed tomography scan.	Use antibiotics.	Use antibiotics and obtain a source control.

The causes are listed based on approximate incidences in out-of-hospital and in-hospital cardiac arrest patients. BNP, brain natriuretic peptide; CT, computed tomography; ECG, electrocardiogram; ECHO, echocardiography; IABP intra-aortic balloon pump; MAP, mean arterial pressure; MRI, magnetic resonance imaging; Pa_{O_2}, arterial oxygen tension; ROSC, return of spontaneous circulation; Sp_{O_2}, oxygen saturation measured by pulse oximetry; TTM, targeted temperature management; VA-ECMO, veno-arterial extra corporeal membrane oxygenation.

effective neuroprotective strategy available for patients experiencing postanoxic brain injury. Together with many observational studies indicating a better neurologic recovery when targeted temperature management was applied in heterogeneous populations of cardiac arrest patients, two randomized clinical trials showed that targeted temperature management was associated with improved neurologic outcomes in witnessed ventricular fibrillation survivors.[19,21] As such, international guidelines have advocated for the use of targeted temperature management as a neuroprotective intervention in this setting, but also after in-hospital or nonventricular fibrillation cardiac arrest; however, only nonrandomized studies have reported the controversial benefits of targeted temperature management in these conditions.[34] Moreover, the level of evidence supporting these statements remains low, and many relevant questions remain to be answered.

There has been considerable debate surrounding the optimal temperature target since the publication of the target temperature management after out-of-hospital cardiac arrest trial (TTM trial, 2013), which showed similar intact neurologic outcomes and survival with two controlled temperature strategies, that is, 33°C *versus* 36°C.[39] Although many physicians misinterpreted these results as supporting the conclusion that targeted temperature management should be abandoned in cardiac arrest survivors, the trial actually showed that the target temperature during targeted temperature management could be set between 32°C and 36°C, which is definitely not "normothermia," using an active targeted temperature management device or interventions to keep the core temperature below normal values. Whether targeted temperature management is more effective than just avoiding fever will be investigated in the Targeted Temperature Management after Cardiac Arrest 2 study (NCT02908308), which has recently started.

Although a number of centers changed their target temperature to 36°C, claiming that this was closer to normal, was less invasive, and could reduce the potential known and

unknown risks of targeted temperature management, no subsequent substudy has shown any evident benefits of following this 36°C strategy when compared with the 33°C target. In a recent study, the target temperature of post–cardiac arrest patients in the first 24 h after admission significantly rose after the publication of the targeted temperature management trial and was associated with an increased risk of post–targeted temperature management fever.[40] This change was associated with an increased frequency of fever not seen in the targeted temperature management trial. Moreover, when low compliance with the 36°C target was observed, a trend toward a higher occurrence of early fever and clinical worsening in patient outcomes was observed.[41]

Other important unanswered questions are whether targeted temperature management is effective for in-hospital cardiac arrest and for nonshockable rhythms and whether to start targeted temperature management as soon as possible after the initial anoxic injury. Randomized trials using targeted temperature management in out-of-hospital cardiac arrest compared the initiation of cooling procedures by paramedics before hospital admission with the standard targeted temperature management administered after hospital or intensive care unit admission. Despite several methodologic issues, none of these studies could show any benefit from early targeted temperature management *versus* the conventional therapy. If anything, the studies indicated an increased risk of re-arrest or pulmonary edema on admission in patients receiving prehospital cooling, in particular when cold intravenous fluids were used.[42,43] An even more rapid targeted temperature management delivery, that is, during cardiopulmonary resuscitation with transnasal evaporative cooling devices, is under evaluation in a large controlled trial.[44] The ideal duration of targeted temperature management, as well as the ideal technique to provide targeted temperature management, are also unknown. The international guidelines recommend to cool patients for at least 24 h and avoid fever for a total of 72 h after cardiac arrest; nevertheless, several randomized clinical trials have shown that newborn asphyxial arrests had a significant increase in both short-term and long-term neurologic recovery when targeted temperature management was applied for 72 h at 33°C.[34,45] A recent randomized, controlled trial in adult out-of-hospital cardiac arrest patients showed a nonsignificant increase in the survival rate of nearly 7% of patients receiving targeted temperature management for 48 h when compared with those treated for 24 h.[26] Most observational and randomized controlled trials comparing an older and poorer-performing targeted temperature management system to last-generation targeted temperature management devices (*i.e.*, high accuracy feedback temperature control and low variation of target temperature) also showed a trend toward better outcomes for the latter.[46,47] Finally, we have no high-quality data suggesting the best rewarming rate after targeted temperature management as well as for the control of fever and/or shivering. Although experimental studies suggest a very slow rewarming time (*i.e.*, 0.1° to 0.2°C per hour), one clinical study showed that cardiac arrest patients with a rewarming rate exceeding 0.5°C per hour had a higher probability of a poor outcome when compared with those with lower rewarming rates (71% *vs.* 52%).[48] Similarly, several studies have associated post–cardiac arrest fever with poor outcomes; however, the cut-off of fever having the highest risk of causing brain damage, the optimal physical and/or pharmacologic intervention to control fever, and the duration of fever control (*i.e.*, days or weeks) remain largely unknown.[49] The occurrence of shivering during the induction phase of targeted temperature management remains a therapeutic challenge as it may delay achieving the target temperature and increase brain oxygen consumption, potentially harming neuronal recovery. Risk factors for shivering in this setting are low or high body weight, age greater than 65 yr, and short duration of cardiac arrest, patients with these characteristics should be accurately monitored for early recognition of shivering.[50] Although clinical scales have been developed to detect shivering, surface electromyography may be more accurate and effective than clinical assessment and result in more rapid interventions in this setting,[51] although the optimal management of such a complication (*i.e.*, opiates, high-dose sedatives, α2-antagonists, or neuromuscular blocking agents) remains poorly characterized. Thus, although effective, the characteristics of the optimal targeted temperature management after cardiac arrest, the best candidates for the treatment, and the correct timing and device with which to initiate targeted temperature management urgently need more research to inform clinicians how to implement targeted temperature management in this setting. In the absence of high-quality evidence, we recommend initiating targeted temperature management as quickly as possible in all patients admitted to the intensive care unit after cardiac arrest, provided that there are no contraindications and limitation of care has not already been decided (*i.e.*, in the case of terminal disease).

There are no effective alternative strategies to targeted temperature management to promote brain protection in cardiac arrest survivors. Among the tested interventions, noble gases, in particular xenon, can attenuate glutamate-induced cerebral damage after anoxic injury. In a small study, Arola *et al.*[52] showed that patients surviving out-of-hospital cardiac arrest who received inhaled xenon and targeted temperature management at 33°C had better cardiovascular function without significant adverse effects than those treated with targeted temperature management alone. More recently, 110 comatose patients who had experienced out-of-hospital cardiac arrest were randomly assigned to receive inhaled xenon combined with targeted temperature management at 33°C for 24 h or targeted temperature management alone. Cerebral white matter damage, which was evaluated by fractional anisotropy from diffusion

tensor magnetic resonance imaging, was lower in the xenon group, although no significant differences in the clinical neurologic outcomes were observed.[53]

Similar to noble gases, glucagon-like peptide-1 analogs may provide large organ-protective effects after ischemia and reperfusion injury. In a recent randomized, controlled trial, 120 consecutive comatose patients resuscitated from out-of-hospital cardiac arrest randomly received targeted temperature management combined with either one of the analogs exenatide or a placebo. Despite no significant effects regarding the concentrations of neuron-specific enolase levels over time between the two groups, survival rates increased by almost 10% at 3 months, and no significant side effects were observed in the exenatide group.[54] These promising findings require further confirmation in large phase III randomized, controlled trials. Other drugs, such as cyclosporine or erythropoietin, have not shown any beneficial effect on either organ dysfunction or neurologic outcome in out-of-hospital cardiac arrest patients.[55,56] Future studies combining several drugs with targeted temperature management are urgently needed to optimize neuroprotective strategies in this setting.

Respiratory Management

Oxygenation

Titrating oxygenation by adjusting the inspired fraction of oxygen (F_{IO_2}) is a key feature of the immediate management of cardiac arrest patients. International guidelines recommend ventilation with 100% F_{IO_2} during cardiopulmonary resuscitation; however, upon the return of spontaneous circulation, the F_{IO_2} should be titrated to target an arterial oxygen saturation of 94% to 98%.[33] Monitoring peripheral oxygen saturation is, in some cases, difficult because of severe vasoconstriction, and an arterial blood gas (ABG) sample should be obtained and analyzed as soon as possible.[57] The optimal arterial oxygen tension (P_{aO_2}) is unknown, but cooling procedures may decrease metabolism and oxygen consumption.[58,59] However, there is little evidence on whether oxygenation and ventilation targets should be modified in patients treated with targeted temperature management, yet extreme hyperoxia is associated with poor neurologic outcome, and hypoxia (*i.e.*, P_{aO_2} less than 60 mmHg) appears harmful; both should be avoided, regardless of the use of targeted temperature management.[60–63] Extreme hyperoxia is often related to prolonged and uncontrolled ventilation with a 100% F_{IO_2} during patient transport, which in most cases is not required.[64] As such, F_{IO_2} should rapidly be individualized and guided by saturation and ABG, whereas positive end-expiratory pressure should be set at a level of 6 to 8 mmHg to avoid atelectasis and allow for a lung ventilation strategy. During intensive care unit treatment, the optimal P_{aO_2} target should be adjusted according to what is frequently done in the management of other forms of brain injury, such as traumatic brain injury, where a range of 80 to 100 mmHg is generally maintained to avoid the risk of tissue hypoxia (table 3). Patients with cardiac arrest that is related to a respiratory cause or complicated by aspiration may remain hypoxic, and fiber optic bronchoscopy to remove gastric contents, careful lung recruitment with a moderate level of positive end-expiratory pressure, and the use of muscle relaxants are likely to be beneficial.

Table 3. Suggested Physiologic Targets during ICU Care in PRC Patients

Variable	Target	Relevance to the PRC Patients
Ventilation		
Oxygen	PaO_2 80–100 mmHg SaO_2 94–98%	Hypoxia and hyperoxia are harmful and should be avoided.
Carbon dioxide	38–45 mmHg	Hypocapnia is common during TTM and causes brain ischemia.
Circulation		
Mean arterial blood pressure	> 65–70 mmHg	Avoid MAP below 65–70 mmHg with fluids and norepinephrine. In patients with chronic hypertension, a higher target may be considered.
Lactate	< 2 mM	Commonly elevated in the beginning but should decrease during the first 24 h.
Electrolytes		
Glucose	6–10 mM	Avoid glucose-containing solutions unless the patients has hypoglycemia.
Sodium	140–145 mM	Hyponatremia may aggravate cerebral edema.
Potassium	3.5–4.5 mM	Hypokalemia is commonly related to a rapid correction of the acidosis, the use a sodium bicarbonate and TTM. May increase the risk of arrhythmia.
Temperature		
TTM	32°–36°C	Use a feedback device to achieve and remain at the set target temperature for at least 24 h.
Rewarming	0.25°–0.5°C per hour until a target of 36.5°–37°C is reached	Rewarm the patient using a feedback device.

ICU, intensive care unit; MAP, mean arterial pressure; Pa_{O_2}, arterial oxygen tension; PRC, postresuscitation care; Sa_{O_2}, arterial oxygen saturation; TTM, targeted temperature management.

Ventilation and Carbon Dioxide Targets

Diligent management and monitoring of ventilation is paramount in targeted temperature management patients as dyscarbia is a frequent occurrence.[65] Initially after cardiac arrest, ventilation may be adjusted to achieve arterial carbon dioxide tension of around 38 to 45 mmHg (table 3) using a tidal volume of 6 to 8 ml/kg and a frequency of 12 breaths per minute. There is no definitive evidence regarding lung-protective ventilation in cardiac arrest, but given the risk of pneumonia and the inflammatory response after cardiac arrest, it seems reasonable to ventilate with a tidal volume of 6 to 8 ml/kg (ideal body weight).[66] Hypocapnia commonly occurs during the initial postresuscitation phase, especially in patients treated with targeted temperature management at 33°C, because of the decreased metabolism and carbon dioxide production, which is also induced by the concomitant use of sedatives.[65] Hypocapnia causes cerebral vasoconstriction and decreased oxygen delivery and should be avoided.[67] There is currently no role for hyperventilation as a means to control intracranial pressure in almost any cardiac arrest patients. In general, the limited data available using invasive intracranial pressure monitoring indicates that intracranial hypertension is uncommon during the first 24 to 48 h in those treated with targeted temperature management.[68] Because there are no noninvasive means to monitor arterial carbon dioxide tension, the frequent measurement of ABG samples is the only way to avoid hypo- and hypercapnia during intensive care unit treatment. The continuous monitoring of end-tidal carbon dioxide may be one means of preventing hypocapnia, but it cannot be used as a surrogate for ABGs. Moreover, there is considerable controversy regarding the use of the "alpha stat" approach (*i.e.*, ABG values not corrected for temperature) or "pH stat" (*i.e.*, ABG values corrected for temperature) in targeted temperature management patients. It appears that when targeting strict normoventilation, the alpha stat approach has resulted in an increased cerebral oxygen extraction and jugular vein desaturation with lower cerebral flow velocities when compared with the hydrogen ion concentration approach.[69] However, there is inconclusive evidence on whether one of the two strategies influences the outcome in cardiac arrest patients.[70] There is some evidence suggesting a potential beneficial role for moderate (*i.e.,* 55 to 65 mmHg) hypercapnia in such patients,[71] with a large randomized clinical trial currently ongoing (Targeted Therapeutic Mild Hypercapnia after Resuscitated Cardiac Arrest: A phase III multicenter randomized controlled trial [TAME], Clinicaltrials.gov NCT03114033) which will yield interesting findings on ventilation management in this setting.

Circulatory Management

Post–cardiac arrest syndrome heavily influences hemodynamics in resuscitated out-of-hospital cardiac arrest patients (fig. 1).[29] The more unstable the patient is, the more invasive monitoring is needed. However, the use of an invasive blood pressure measurement is needed for all patients. Routine use of pulmonary artery catheters is not recommended, but repeated cardiac ultrasonography or minimally invasive estimation of cardiac output for the assessment of cardiac function appears useful.[72] Shock occurring after out-of-hospital cardiac arrest often results from postarrest myocardial dysfunction. One study reported low cardiac index (less than $1.5\,L \cdot min^{-1} \cdot m^{-2}$) in 66% of patients during the first 12 h after return of spontaneous circulation, with nadir cardiac index values at 6 h.[73] Partial recovery over the next 48 to 72 h was observed in the survivors, predominantly in patients with a good prognosis.[74–76] Arterial hypotension is a common finding, and a systolic blood pressure less than 90 mmHg or a mean arterial pressure (MAP) less than 65 mmHg was reported in 47% to 73% of patients.[28,74,77,78] Hypotension and the need for vasopressor support after return of spontaneous circulation correlates with poor overall outcome.[74,77–81] An optimal blood pressure target has not been defined in out-of-hospital cardiac arrest patients. However, several studies have shown increased mortality and likelihood of a poor outcome in patients with a MAP of less than 65 to 70 mmHg, especially during the first 48 h (table 3). Some patients may benefit from having an even higher blood pressure, especially those with chronic hypertension. More individualized approaches to identify the optimal MAP are currently under investigation, but conclusive evidence is lacking. Thus, setting a target above 65 to 70 mmHg is a reasonable general goal for out-of-hospital cardiac arrest patients.

Vasopressors are needed in 55% of patients and for up to 72 h after the cardiac arrest, despite the normalization of cardiac index, emphasizing the dissociation between left ventricular systolic function and systemic hemodynamics.[28] Treatment of postarrest myocardial dysfunction and shock include optimizing preload, restoring blood pressure, and securing organ perfusion.[29,33,34] Because of capillary leak and vasoplegia, high doses of crystalloids are often needed. Initial resuscitation with 1 to 2 l of isotonic crystalloids in hypotensive patients after return of spontaneous circulation is regularly used. Among vasopressors, norepinephrine is recommended as the first choice; the secondary choice can be vasopressin or epinephrine, whereas dopamine does not seem to have a beneficial effect.[82] Low cardiac output, with signs of insufficient organ perfusion, low urine output, and lactic acidosis may need inotropes. The first choice is dobutamine, but other drugs (epinephrine, milrinone, and dopamine) may be used as well.[83]

Other hemodynamic variables, such as central venous oxygen saturation, lactate clearance, and microcirculation, could be an alternative to MAP to optimize hemodynamics in cardiac arrest patients.[84–86] However, there is a lack of clear target thresholds to be used in clinical practice for all of these variables and a lack of well-conducted studies

showing that therapeutic strategies based on such values may improve organ function and patient outcome.

In selected patients with circulatory failure or refractory cardiac arrest, treatment with assist devices, such as Impella or veno-arterial extracorporeal membrane oxygenator pumps, is rapidly entering clinical practice and becoming more commonly used.[87] Data show that selected patients with refractory out-of-hospital cardiac arrest can stabilize and recover with the use of these devices.[88] Another supportive device, the intra-aortic balloon pump, is used less frequently in most institutions, and outcome data on the use of intra-aortic balloon pump after cardiogenic shock attributable to coronary lesions remain disappointing.[89,90]

The influence of mild hypothermia on hemodynamics is well described. Vasoconstriction is the primary cold effector response, which is partly triggered by increased norepinephrine concentration. Blood is displaced to the core, and together with norepinephrine it increases blood pressure, cardiac output, and stroke volume, but with a side effect of reduced heart rate.[91] Whether targeted temperature management has a positive or negative effect on hemodynamics in patients experiencing cardiogenic shock has for a while been a topic of discussion. The physiologic changes after mild hypothermia support a beneficial effect, and a series of small studies have demonstrated that targeted temperature management significantly improves cardiac output and reduces the need for a vasopressor requirement.[92–95] However, a *post hoc* study of the targeted temperature management trial comparing 33°C with 36°C showed a lower hart rate, elevated levels of lactate, and increased vasopressor support in the 33°C group; blood pressure was the same for both groups.[74] Thus, the evidence is insufficient to make a firm recommendation for targeted temperature management treatment in out-of-hospital cardiac arrest patients with cardiogenic shock. Bradycardia seen in patients treated with targeted temperature management can be a result of sedation or the precipitating disease, but from time to time we encounter profound bradycardia attributable to the cooling itself; the patient may then be rewarmed to 36°C but, if this does not help, a pacemaker treatment or further rewarming should be considered.

Cerebral Management

Analgosedation

Although no definitive evidence exists regarding the best analgosedation regimen or optimal duration in cardiac arrest patients, some trends have emerged.[33] When targeted temperature management is applied, patients have been deeply sedated with a mixture of hypnotics and opioids, which is often combined with neuromuscular blocking drugs to prevent shivering and facilitate cooling and mechanical ventilation.[96] Although neuromuscular blocking agents are used to a lesser extent now, they still are valuable treatment options because they allow for lower doses of hypnotics and opioids in case of shivering or myoclonus, with some retrospective studies suggesting that their use may even improve outcome.[97,98] However, the use of neuromuscular blocking agents mandates a simultaneous and appropriate monitoring of analgesia, sedation, and neuromuscular function, which remain very complex in post–cardiac arrest patients. There is no proven role for sedation breaks during the first 24 h because in most cases the results will not affect treatment decisions. However, if mechanical ventilation is prolonged in patients having shown neurologic recovery, daily sedation breaks are likely to be useful, even after out-of-hospital cardiac arrest. It is important to recognize that the metabolism of some sedative drugs, especially propofol, fentanyl, and morphine, is prolonged during hypothermia, and dosing may need to be reduced depending on the chosen target temperature.[99] In general, the dosing of sedation agents can be reduced during rewarming (and for those not treated with targeted temperature management) after 24 to 36 h. Drugs that have been used safely include a continuous infusion of propofol or midazolam combined with fentanyl or remifentanil. When compared with a combination of midazolam and fentanyl, propofol and remifentanil result in a shorter time to extubation in those without more severe brain injury.[100] Delayed awakening also appears more commonly in patients treated with midazolam and fentanyl compared with patients treated with propofol and remifentanil.[101] Delayed awakening may be partially related to the sedation regimen and is more common in the elderly and those with renal insufficiency and severe circulatory shock.[102] On the other hand, in the hemodynamically unstable patient, midazolam is generally preferred as opposed to propofol, given its association with hypotension and its effect on cardiac function.[101] There are preliminary data on the use of inhalation agents for sedating patients, but so far the experience is limited, and it is unknown whether their use improves outcome.[103,104]

Seizure Treatment

Abnormal electro encephalogram activity occurs in up to 30% of cardiac arrest patients, and this activity is commonly related to more severe hypoxic ischemic encephalopathy and may be worsened by hypotension and cerebral hypoperfusion.[105] During deep sedation, clinical seizure may go unnoticed unless the electroencephalogram is monitored.[33,106,107] Ideally, the electroencephalogram should be monitored continuously, but intermittent electroencephalogram is an option in symptomatic patients if continuous electroencephalogram is not available.[105] Moreover, continuous electroencephalogram facilitates early detection of epileptic activity and may also be helpful for prognostication. Current guidelines recommend continuous electroencephalogram over intermittent electroencephalogram even though there is no definitive evidence supporting this practice. Some forms of epileptic activity seen in cardiac

arrest patients are different from what is seen in patients with epilepsy and status epilepticus.[33,108]

In general, malignant epileptic electroencephalogram activity is associated with a worse prognosis than in patients with a normal electroencephalogram.[108] Routine seizure prophylaxis is not recommended in cardiac arrest patients.[33] However, in patients with observed epileptic activity, a treatment attempt with sodium valproate, levetiracetam, phenytoin, lorazepam, or propofol appear justified given the pathophysiologic rationale, in particular when seizure develops in the context of a continuous and reactive electroencephalogram background or in the absence of other neurologic predictors of poor outcome.[33,109] There is also inconclusive evidence regarding which drug is the most effective.[110] One benefit of using valproate is the possibility to monitor blood levels. In more severe cases, treatment with either midazolam or propofol that targets burst suppression, followed by a gradual decrease in dosing, is a commonly applied approach. Myoclonus is the most serious form, which in general is resistant to treatment and commonly results in a poor outcome.[111] Clonazepam may be used as symptomatic treatment.

Glucose Control

Hyperglycemia is commonly seen in cardiac arrest patients after the return of spontaneous circulation,[112,113] and it may be related to both delayed return of spontaneous circulation and the intra-arrest use of epinephrine. Persistent hyperglycemia is most likely to worsen secondary brain injury and should be treated with an intravenous infusion of insulin.[33] Few studies have addressed glucose control, specifically in cardiac arrest patients, but a glucose target of 1.08 to 1.80 g/dl (6 to 10 mM) is generally recommended in general intensive care unit patients (table 3).[114,115,116] Targeting a tight glucose control (0.72 to 1.08 g/dl [4 to 6 mM]) may increase the incidence of hypoglycemia without providing a clear benefit.[117] Patients undergoing targeted temperature management targeting 33°C are likely to exhibit greater variation in glucose levels and require more insulin.[115,117] In these patients, extra attention to glucose management is justified.[115] Hypoglycemia should be avoided because it increases mortality in the critically ill. In general, infusion of hypotonic glucose-containing solutions should be avoided.[118]

Electrolyte Management

Because of changes in acid–base status, hypoxia, and high catecholamine levels, deviations in potassium concentration are common during and directly after resuscitation. However, this usually does not require specific treatment.[119] The optimal serum potassium concentration in out-of-hospital cardiac arrest patients is not known, but in patients with acute myocardial infarction the lowest mortality was seen in patients with a serum potassium of 3.5 to 4.5 mM (table 3) when compared with those with higher or lower levels.[120] It is well known that serum potassium concentration drops parallel to a decline in body temperature, and potassium shifts into the cells or is lost because of renal dysfunction and cold diuresis.[121–123] It is therefore important to monitor potassium levels during cooling to avoid hypokalaemia (*i.e.*, less than 3 mM). A recent study on cardiac arrest patients diagnosed 207 (86%) and 77 (32%) of the patients with hypokalemia and hyperkalemia, respectively.[121] Neither hypo- nor hyperkalemia was associated with poor neurologic outcome (Cerebral Performance Category 3 to 5) or ventricular arrhythmia. Another study also found no difference in potassium levels between patients with and without ventricular arrhythmias.[122] However, the link between serum potassium disturbances and arrhythmias remains unclear, because a third study found a significant association between ventricular arrhythmias and hypokalemia.[123]

In such cases, different repletion policies are applied. One early study recommended only replacing measured losses.[124] This policy is supported by an animal study that demonstrated that the potassium concentration causing cardiac toxicity diminishes with progressive hypothermia, indicating that the potassium compensation may not be as aggressive as in normothermic patients.[125] In a study that demonstrated a relationship between potassium concentration and ventricular arrhythmias, the authors recommended maintaining potassium at 3.0 mM.[123] We recommend a potassium infusion to keep serum potassium between 3.5 and 4.5 mM (table 3). However, in general, potassium repletion should be conservative, closely monitored, and likely stopped as rewarming begins because of potassium shifting back out of cells. If hyperkalemia is encountered, rewarming might be extended, allowing the kidney to excrete extra potassium.

Regarding sodium, there is limited evidence on optimal targets. However, because cerebral edema is a possibility, it appears justified to target 140 to 145 mM. Concerning the other electrolytes magnesium, phosphate, and (to a certain extent) calcium, their serum concentrations also drop during hypothermia.[126,127] There is not much information on the repletion treatment in patients treated with targeted temperature management, but because hypomagnesaemia, hypophosphatemia, and hypocalcemia all are linked to adverse events or bad outcomes, we recommend the serum concentration to be within or close to what is a normal serum concentration.

Infection Prevention

The overall risk of infection in postresuscitation patients is high. Both post–cardiac arrest syndrome and targeted temperature management *per se* impair the body's general resistance to infections. Occurring in up to 65% of cases, pneumonia constitutes the main clinical challenge.[128] This is primarily attributable to pulmonary aspiration during

the cardiac arrest event, which is further augmented by breast compression injuries, endotracheal intubation, and mechanical ventilation. The incidence of bacteremia is also high, and gram-negative bacteria and staphylococcus aureus are commonly isolated pathogens.[129,130] One retrospective study demonstrated that prophylactic antibiotic is associated with a reduction in pneumonia.[131] However, functional outcomes or mortality did not change in this study or in another big retrospective cohort study.[132] In general, studies on targeted temperature management indicate a tendency toward more pneumonia in patients exposed to a larger dose of cooling (*i.e.*, lower temperatures or prolonged cooling),[26,39] but, importantly, this tendency was not linked to overall outcomes, such as survival.[21,26,39,133] There might be subgroups of patients, such as those treated with extracorporeal membrane oxygenator, in whom prophylactic antibiotic could be indicated,[132] but overall the evidence supporting prophylactic antibiotic is of limited quality and there is no consensus recommending. Despite this limited evidence, many centers, including ours, use prophylactic antibiotics.

Extracerebral Organ Dysfunction Management

Gastrointestinal Function

Intestinal ischemia occurs during cardiac arrest and can lead to translocation of bacteria and endotoxins. Moreover, there is concern that enteral nutrition in shock further compromises splanchnic perfusion, and it is also presumed that targeted temperature management decreases gut motility and delays gastric emptying.[134,135] Thus, despite the general consensus that early enteral nutrition helps to maintain the gut barrier, whether enteral feeding is feasible and safe in patients on vasopressors and during targeted temperature management after out-of-hospital cardiac arrest has been debated. However, one observational study on hemodynamically stable patients receiving at least one vasopressor demonstrated that early enteral nutrition was associated with reduced mortality compared with late enteral nutrition.[136] Furthermore, in a prospective observational study in comatose out-of-hospital cardiac arrest patients treated with targeted temperature management, it was demonstrated that enteral feeding is feasible in small amounts (10 ml/h) that were well tolerated during hypothermia, and increasing the amounts during rewarming was possible. When normothermia is reached, the feeding rate can be further increased.[2,137] Accordingly, a recent consensus endorsed by the European Society of Intensive Care Medicine recommended starting early enteral nutrition as soon as shock is controlled with fluids and vasopressors, and starting low-dose enteral nutrition early in patients receiving therapeutic hypothermia.[138] We recommend giving 10 ml/h for the first 24 h; thereafter, the rate can be increased if the patient is not going to be extubated. Still, we do not know whether the feed is actually absorbed, and several pharmacokinetic studies indicate very low absorption during targeted temperature management.

More recently, some interesting clinical data have supported the finding that cardiac arrest triggers the occurrence of severe mesenteric ischemia. In one retrospective study, enterocyte lesions, suggesting tissue hypoxia (*i.e.*, gastrointestinal bleeding or necrotic lesions), were observed in all patients presenting early signs of gut dysfunction, such as gastric distension, lack of motility, and feeding intolerance, who underwent gut endoscopies.[139] In another study, the urinary intestinal fatty acid-binding protein, which marks intestinal permeability, was extremely high on admission and normalized by the third day after admission; high endotoxin levels in these patients were positively correlated with the highest intestinal fatty acid–binding protein level.[140] A high level of endotoxemia is an independent predictor of the occurrence of shock and the intensity of vasopressor administration. Thus, post–cardiac arrest gut dysfunction may significantly contribute to the occurrence of cardiovascular dysfunction, and monitoring gut integrity can contribute to a better understanding of the pathophysiology of extracerebral organ failure in this setting.[141]

Concerning stress ulcus prophylaxis, there are no data on out-of-hospital cardiac arrest patients treated with targeted temperature management. However, they are considered high-risk intensive care unit patients. The evidence for ulcus prophylaxis in this patient group is weak, but presumably most intensive care units (including ours) use stress ulcus prophylaxis in out-of-hospital cardiac arrest patients.[142–144]

Coagulation Management

Coagulation abnormalities are common in patients who are resuscitated from out-of-hospital cardiac arrest.[145,146] Furthermore, these abnormalities are more severe in patients who die within the first day or are in shock, corresponding to a more severe post–cardiac arrest syndrome. Metabolic acidosis from cardiac arrest and cardiac failure also affect a patient's coagulation status.[145,147] More important is the wide variety of antithrombotic drugs used in post–cardiac arrest syndrome patients undergoing coronary angiography and percutaneous intervention.[148] Coagulopathy might also occur because of a dilution effect as therapeutic targeted temperature management often is induced by the infusion of 1 to 2 l of cold crystalloids. Moreover, post–cardiac arrest syndrome implies decreased peripheral resistance, as in sepsis, and intensive care unit treatment often includes a large amount of intravenous crystalloids. In general, cooling is associated with prolonged time to form clots, but it has no effect on clot strength.[147,149] However, augmenting the cooling dose does not have a big impact on hemostasis. Prolonged targeted temperature management treatment does not affect platelet aggregation further, but it impairs thrombin generation.[150,151] Likewise, targeted temperature management at 33°C is not associated with impaired hemostasis compared to 36°C.[152] Thrombelostometry and

platelet aggregation analyses should be performed at 37°C, irrespective of whether the body temperature is 33°C or 37°C.[153]

Bleeding concerns have been considered a relative contraindication to targeted temperature management.[154] However, experience from controlled clinical trials indicates that bleeding is not a major problem in out-of-hospital cardiac arrest patients undergoing targeted temperature management.[19,21,152,155] Still, in most of these studies patients with severe coagulopathies are excluded, so we still do not know how this patient category reacts to targeted temperature management. Consequently, targeted temperature management should be used with caution in these patients. Likewise, patients with ongoing bleeding, for example, from a trauma related to the cardiac arrest, should be treated with caution. Hypothermia is known to induce coagulopathy in trauma patients, and bleeding should be controlled before targeted temperature management is induced, with 36°C the initial target temperature.[156] Altogether, bleeding concerns are not contraindications for targeted temperature management except for active bleeding trauma or surgical patients.

As for bleeding, venous thromboembolism may also pose a challenge in out-of-hospital cardiac arrest patients.[157,158] After resuscitation, patients experience a brief hypercoagulable state[145] followed by a prolonged coagulable state with a deranged coagulation system and with risk of thrombus formation.[145,159] The situation may to some extent be balanced by anticoagulation treatment and targeted temperature management. However, in the face of a severe reperfusion injury, together with all the other factors affecting coagulation, disseminated intravascular coagulation may occur and the situation may become somewhat unpredictable and difficult to treat.[157,158,160] Unfortunately, information on this subject is scarce and no guidelines are available. Our recommendation is therefore to follow the patient's clinical and coagulation status closely and individualize treatment.

Renal and Liver Function

There is a paucity of data on the relationship between renal and liver failure and outcomes in postresuscitation patients. Recent studies indicate that the incidence of acute kidney injury is around 40% among cardiac arrest survivors; however, the criteria used to define acute kidney injury significantly differ among various studies.[161] In some studies, the use of renal replacement therapy was quite high (33% of acute kidney injury patients).[162] A longer duration of arrest, an initial nonshockable rhythm, the presence of shock, and higher creatinine or lactate levels on admission were independent predictors of acute kidney injury.[161] Also, hospital mortality was significantly higher in acute kidney injury *versus* nonacute kidney injury patients. In a recent study, nonsurvivors of cardiac arrest had a higher incidence of renal failure on admission and during the intensive care unit stay than survivors. In a multivariable analysis, independent predictors of intensive care unit mortality were renal failure on admission, a high simplified acute physiology score II at admission, high maximum serum lactate levels within the first 24 h after intensive care unit admission, and the development of sepsis.[163] No protective effects of targeted temperature management have been described in post–cardiac arrest acute kidney injury patients when compared with the use of normothermia.

There are almost no data on liver dysfunction after cardiac arrest. In a recent study, Champigneulle *et al.*[164] reported that hypoxic hepatitis occurred in 11% of patients resuscitated after an out-of-hospital cardiac arrest, and in a multivariate analysis, this was significantly associated with intensive care unit mortality.

Neuroprognostication

The overall prognosis for at least two-thirds of out-of-hospital cardiac arrest patients depends on the severity of postanoxic brain injury; therefore, accurate neuroprognostication is mandatory to identify patients who have the potential for brain recovery and to avoid aggressive and intensive therapies in those who have irreversible brain damage.[165] Clinical examination is the cornerstone of neuroprognostication in these out-of-hospital cardiac arrest patients; nevertheless, the need for sedatives and analgesic drugs during targeted temperature management may delay the accuracy of neurologic examination to provide a prognosis and could lead to the inappropriate prediction of a poor outcome in the early phase of therapy in almost one-third of patients.[166] Moreover, up to 30% of patients treated with targeted temperature management will regain consciousness 4 to 10 days after arrest, particularly if they are cooled at lower target temperatures (32° to 33°C), are older, have renal failure, and had experienced postresuscitation shock.[102]

Thus, in the early phase after arrest, important findings on brain function can be obtained using additional predictive tools, such as a cerebral computed tomography scan, measurements of neuron-specific enolase, and electroencephalogram.[167] Several studies have shown that the loss of differentiation between gray and white matter, which is quantified by calculating the ratio in Houndsfield units of gray over white matter, on an early (fewer than 24 h from arrest) computed tomography scan was associated with poor neurologic outcome.[168] Debate regarding the regions of interest where gray over white matter should be measured, the optimal gray over white matter cut-off, and whether the use of targeted temperature management may influence the predictive value of an early computed tomography scan is ongoing.

Nevertheless, neuron-specific enolase remains the most studied biomarker of brain injury in comatose survivors of cardiac arrest. Although nonsurvivors have significantly higher neuron-specific enolase values than survivors, no clear cut-off can be identified, and international guidelines

consider "high neuron-specific enolase levels" to have limited predictive value in this setting.[169] In a recent study, neuron-specific enolase values above 66, 48, and 38 μg/l at 24, 48, and 72 h, respectively, from arrest predicted poor neurologic outcomes with less than a 2% error rate.[170] In another large study, neuron-specific enolase concentrations greater than 90 μg/l predicted poor outcomes with a positive predictive value of 99% and a false positive rate of 0.5%. In addition, neuron-specific enolase levels of less than or equal to 17 μg/l excluded the occurrence of poor neurologic outcomes, here with a negative predictive value of 92%.[171] Importantly, neuron-specific enolase should not be used in isolation to predict outcomes because several pitfalls exist (*i.e.*, hemolysis, cancers, and handling of blood samples). Concerning electroencephalogram, it should be initiated as soon as possible after hospital admission, either with continuous monitoring or intermittent repeated tracings, because most predictive electroencephalogram findings occur in the first 12 to 24 h after arrest.[172] In particular, the so-called highly malignant electroencephalogram patterns (*i.e.*, burst-suppression, generalized periodic discharges on a suppressed background, and suppressed background) are very predictive of a poor outcome.[173] All other patterns of intermediate malignancy (*i.e.*, low-voltage, discontinuous background, and presence of periodic, rhythmic, and epileptiform discharges on a normal voltage background) are less reliable, whereas a continuous electroencephalogram background can predict neurologic recovery in 60% to 80% of patients.[174]

Postanoxic status epilepticus is associated with poor outcomes in most cases, although a late onset, if associated with other favorable prognostic markers or a continuous electroencephalogram background, can result in a good neurologic outcome if aggressively treated, in some cases.[175] Assessment of electroencephalogram reactivity, that is, changes in electroencephalogram background in response to several noxious and nonnoxious stimuli using a standardized protocol, can provide significant information regarding the extent of the postanoxic cerebral injury.[176] However, low interobserver agreement still limits the use of such an approach in most centers admitting cardiac arrest patients.

After targeted temperature management and sedative discontinuation, clinical examination should be performed at least daily. Recovery of a motor response, at least localizing pain (Glasgow coma score – motor response at or above 5) after discontinuation of sedation, is a sign of a favorable prognosis. For those patients still unresponsive, absent motor responses or extensor posturing (Glasgow coma score – motor response below 2) to external stimuli that are associated with the bilateral absence of pupillary light reflex or corneal reflexes at 72 h after arrest is a strong predictor of a poor prognosis and has a risk of misclassification of less than 5%.[169] Another important clinical predictor of poor outcomes is the presence of status myoclonus, in particular when axial, synchronous, and stereotyped or when associated with a burst suppression or subcortical origin on the electroencephalogram.[177,178]

In the absence of any of these predictive factors, bilateral absence of cortical N20 responses on somatosensory evoked potentials after 72 h from arrest, in particular when the examination is adequately performed and the tracing is of high quality, predict a poor neurologic outcome, with a misclassification rate of less than 1%.[169] Finally, bilateral ischemic lesions, in particular of basal ganglia and thalami, on diffusion-weighted imaging of magnetic resonance imaging were associated with poor outcomes, although study cohorts have been relatively small and used very select patient populations.[179] In a recent multicenter study, whole-brain white matter fractional anisotropy measured by diffusion tensor imaging between 7 to 28 days after cardiac arrest was also highly predictive of a patient's long-term neurologic outcome.[180]

Taken together, these findings indicate the need for a multimodal approach to assess neurologic prognosis in comatose cardiac arrest survivors. After hospital admission, continuous or repeated electroencephalogram monitoring should be initiated, even during sedation and targeted temperature management; the presence of highly malignant patterns, of a continuous electroencephalogram background, of status epilepticus, or of electroencephalogram reactivity should be used as prognostic factors (fig. 2). Early brain computed tomography scans showing a low gray over white matter or neuron specific enolase assessment any time from 24 to 72 h after arrest above 70 mg/l can also be used as indicators of a poor prognosis. Upon discontinuation of targeted temperature management and sedation, repeated neurologic examination, including motor response, brainstem reflexes, and the presence of status myoclonus, can be important to assess the outcome in this setting. In patients who remain comatose, somatosensory-evoked potential measurement should be performed at 72 h after arrest, and if bilateral absence of N20 potentials is found, a poor neurologic outcome can be anticipated. If all these tests show no predictive findings, prognostication becomes more difficult, and should include magnetic resonance imaging, and no final decisions of withdrawal of life-sustaining therapies should be made before a prolonged observation period (1 to 2 weeks) is achieved.

Logistics of Postresuscitation Care

Current international guidelines provide support for taking an active approach to postresuscitation care patients. Still, recent surveys indicate a large gap between published guidelines and the actual care provided.[181,182] To remedy this situation, authorities such as the American Heart Association and the European Resuscitation Council now strongly recommend the implementation of emergency medical service resuscitation systems with integrated specialized cardiac arrest centers that are providing comprehensive postresuscitation care.[34,183]

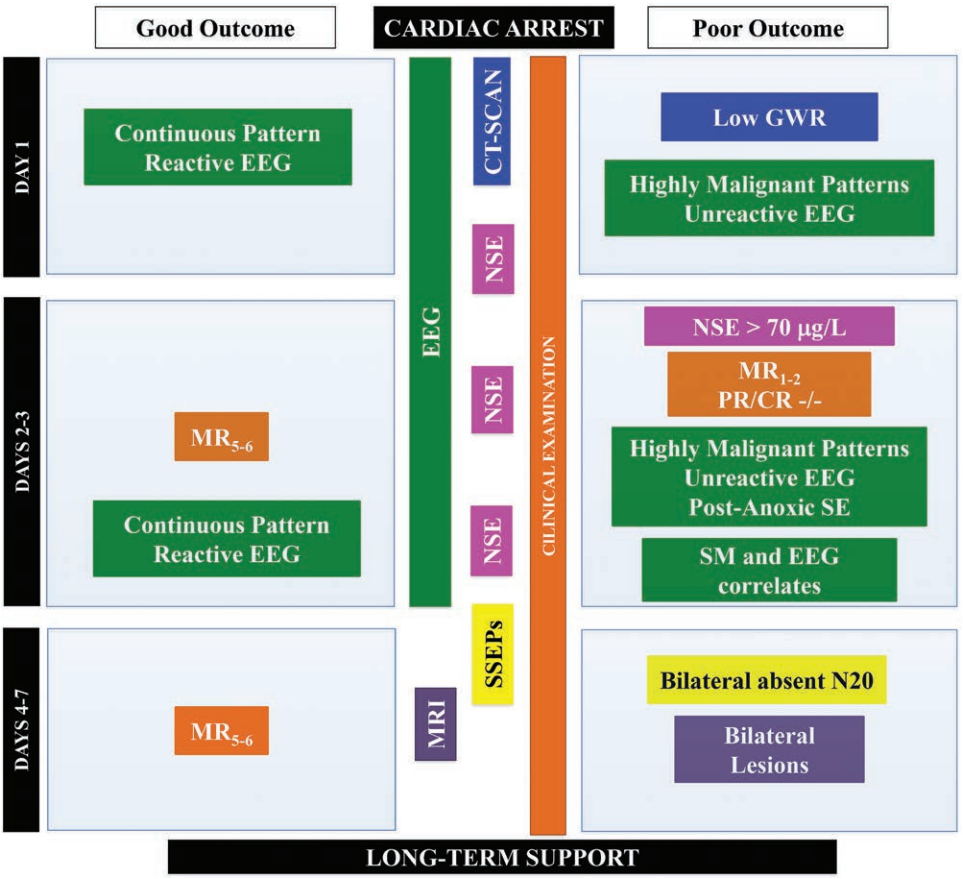

Fig. 2. Multimodal approach for the prognostication of a neurologic outcome after cardiac arrest. CR, corneal reflexes; CT, computed tomography; EEG, electroencephalogram; GWR, gray to white matter ratio; MR, motor response; MRI, magnetic resonance imaging; MR_{1-2}, absent or posturing motor response; MR_{5-6}, localizing pain at stimuli or obeying orders; N20, cortical responses during SSEPs; NSE, neuron-specific enolase; PR, pupillary reflexes; SE, status epilepticus; SM, status myoclonus; SSEPs, somato-sensory-evoked potentials.

Admission to these cardiac arrest centers has been associated with better outcomes.[25,184–187] Added transport times do not seem to constitute a problem.[25,188,189] The key services that a cardiac arrest center must provide include: (1) coronary angiography/percutaneous intervention, echocardiography, extracorporeal membrane oxygenator availability 24/7, and availability of invasive electrophysiologic testing; (2) specialized critical care with intensivist presence 24/7; (3) targeted temperature management; (4) multimodal prognostication to determine neurologic outcome; and (5) rehabilitation.[183,185,190] Patient volume may also be an issue, even though patient volume is just one of many quality factors to consider.[183] Commitment to this group of patients, ongoing research, and a focus on innovation may be equally important. Establishing community-based resuscitation systems with integrated cardiac arrest centers should be regarded as a continuous quality improvement process.[14,22,34,183] Using cardiac arrest registry data to monitor out-of-hospital cardiac arrest outcomes will allow for the benchmarking of centers to ensure good outcomes.[24,25,185–187]

Conclusions

Out-of-hospital cardiac arrest is a major cause of mortality and morbidity worldwide. The present review discusses hospital management of unconscious survivors of out-of-hospital cardiac arrest best practice with a special focus on targeted temperature management. The post–cardiac arrest syndrome affects all organs and requires specialized intensive care 24/7. Immediate and continued hemodynamic support and cardiac intervention are treatment cornerstones. Targeted temperature management remains the most important neuroprotective strategy. Targeted temperature management should be started as soon as possible and maintained for at least 24 h at a temperature of 32° to 36°C, and rewarming should not exceed 0.5°C per hour. However, the optimal cooling

rate, target temperature, and length of cooling has yet to be determined. Outcome prediction in individual patients is challenging, and delayed multimodal prognostication has therefore become an integral part of postresuscitation care. Key elements of multimodal neuroprognostication are clinical examination, electroencephalogram, somatosensory evoked potentials, biomarkers like neuron-specific enolase, and neuroimaging (computed tomography and magnetic resonance imaging). Postresuscitation care requires highly specialized resources 24/7. Accordingly, international guidelines recommend the implementation of regional prehospital resuscitation systems with integrated and specialized cardiac arrest centers.

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Competing Interests

Dr. Taccone reports receiving lecture fees from Bard Medical (Covington, Georgia) and Dr. Skrifvars reports receiving lecture fees from Covidien (Dublin, Ireland), Medtronic (Minneapolis, Minnesota), and Bard. The other authors declare no competing interests.

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