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Neurologic Recovery After Cardiac Arrest: a Multifaceted Puzzle Requiring Comprehensive Coordinated Care

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Opinion statement

Surviving cardiac arrest (CA) requires a longitudinal approach with multiple levels of responsibility, including fostering a culture of action by increasing public awareness and training, optimization of resuscitation measures including frequent updates of guidelines and their timely implementation into practice, and optimization of post-CA care. This clearly goes beyond resuscitation and targeted temperature management. Brain-directed physiologic goals should dictate the post-CA management, as accumulating evidence suggests that the degree of hypoxic brain injury is the main determinant of survival, regardless of the etiology of arrest. Early assessment of the need for further hemodynamic and electrophysiologic cardiac interventions, adjusting ventilator settings to avoid hyperoxia/hypoxia while targeting high-normal to mildly elevated $PaCO_2$, maintaining mean arterial blood pressures >65 mmHg, evaluating for and treating seizures, maintaining euglycemia, and aggressively pursuing normothermia are key steps in reducing the bioenergetic failure that underlies secondary brain injury. Accurate neuroprognostication requires a multimodal approach with standardized assessments accounting for confounders while recognizing the importance of a delayed prognostication when there is *any* uncertainty regarding outcome. The concept of a highly specialized post-CA team with expertise in the management of post-CA syndrome (mindful of the brain-directed physiologic goals during the early post-resuscitation phase), TTM, and neuroprognostication, guiding the comprehensive care to the CA survivor, is likely cost-effective and should be

explored by institutions that frequently care for these patients. Finally, providing tailored rehabilitation care with systematic reassessment of the needs and overall goals is key for increasing independence and improving quality-of-life in survivors, thereby also alleviating the burden on families. Emerging evidence from multicenter collaborations advances the field of resuscitation at an incredible pace, challenging previously well-established paradigms. There is no more room for "conventional wisdom" in saving the survivors of cardiac arrest.

Introduction

Approximately 15% of deaths in developed nations are due to sudden cardiac arrest (CA) [1]—a medical event that also carries a high morbidity among survivors. Annual incidences vary significantly across different world regions and range from 66.8 per 100,000 persons in Asia to 113.6 in Australia according to a systematic review performed in 2010 analyzing emergency medical services (EMS)-attended out-of-hospital cardiac arrest (OHCA); survival to discharge ranged from 1.2% in Asia to 12.8% in Australia [2]. Ever since, reports have demonstrated an overall increase in survival and decrease in incidences of OHCA [3]. Scant evidence exists regarding such epidemiologic values for in-hospital cardiac arrest (IHCA), but the incidence is thought to range from 1 to 5 events per 1000 hospital admissions, with survival to hospital discharge varying from 0 to 42% [4]. The overall risk-adjusted survival rate in IHCA was 22.3% in the USA according to the American Heart Association's Get with the Guidelines-Resuscitation (AHA GWTG) registry data analysis. Strategies to improve survival include a longitudinal approach with measures that range from increasing recognition of CA during emergency calls in OHCA [5] and optimizing cardiopulmonary resuscitation (CPR) in IHCA [6] to developing international guidelines in resuscitation and management of post-cardiac arrest syndrome (PCAS) [7]. While the target in most studies is to improve survival, in reality, improving neurologic function is the main goal, as severity of hypoxic-ischemic brain injury is the primary determinant of survival [8]. Death rates associated with withdrawal of life-sustaining therapy (WLST) due to a perceived poor neurologic prognosis may reach 81%, regardless of the etiology of cardiac arrest [9]. Thus, strategies to improve outcome prediction or even delay neuroprognostication when the prognosis is uncertain should also be considered in the chain of survival.

This review will focus on the most recently studied aspects of neurologic recovery, including pathophysiology of ischemia-reperfusion injury, management of post-cardiac arrest syndrome, efforts to develop novel medical therapies, and neuroprognostication in order to guide the clinician in tailoring interventions to meet each unique patient's needs.

Neurologic recovery

The natural history of hypoxic-ischemic encephalopathy (HIE) in the modern era is unknown, as the practice of WLST is common, and neuroprognostic assessments happen relatively early during the first week post-CA. A schematic of the natural history of HIE with the representation of distribution of possible functional outcomes according to the Cerebral Performance Categories (CPC) scale is depicted in Fig. 1. The course of neurologic recovery is likely more complex than the frequently used dichotomy between good and poor outcomes in the initial 2–3 days following CA based on awakening [9–11]. Data available from large trials on post-CA care, such as the Targeted Temperature Management (TTM) trial, demonstrate an overall mortality of approximately 50%, and of survivors, about 40% have a good cerebral performance [12]. Brain death due to diffuse cerebral edema resulting from global hypoperfusion occurs

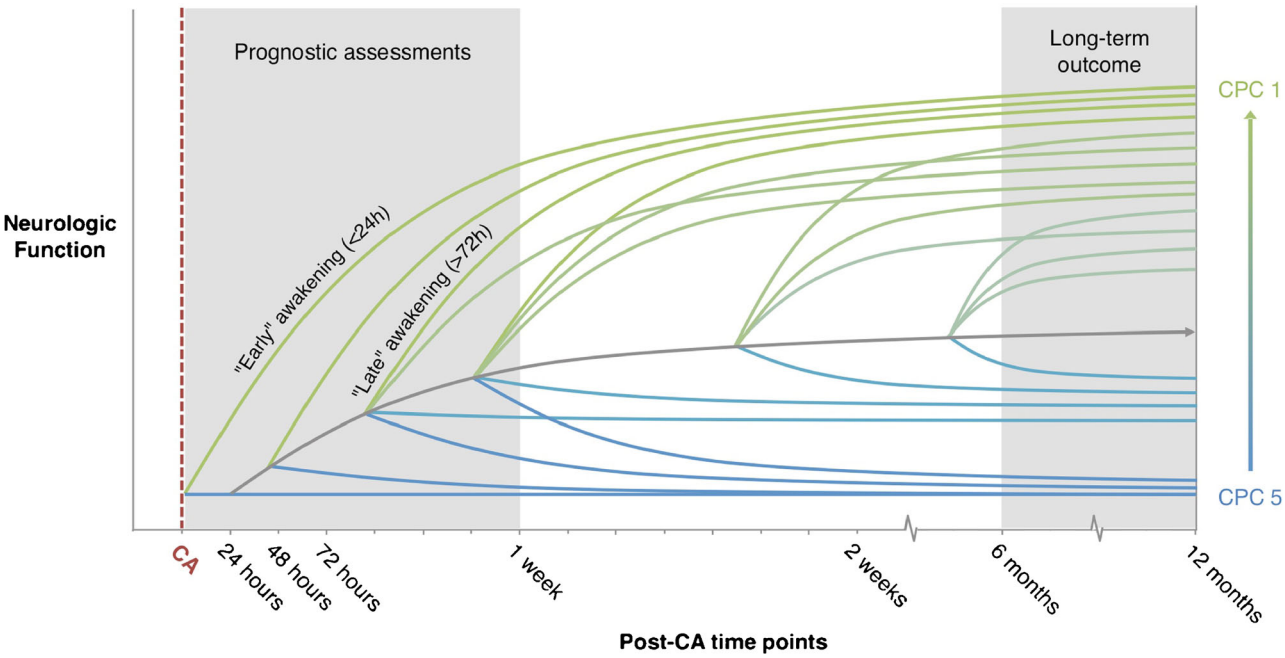

Fig. 1. Schematic of the natural history of hypoxic-ischemic encephalopathy. This is a graphic representation of the distribution of possible functional outcomes in HIE. Individuals who remain comatose after the initial 72 h may still recover and are considered "late" awakeners. The practice of withdrawal of life-sustaining therapies (WLST) excludes the possibility of investigating predictors of late awakening in countries where this practice is common, particularly when WLST occurs soon after cardiac arrest. *CA* cardiac arrest, *CPC* cerebral performance categories score, *HIE* hypoxic-ischemic encephalopathy, *WLST* withdrawal of life-sustaining therapies.

early, usually in the initial 96 h, in approximately 10% of patients that achieve return of spontaneous circulation (ROSC) following conventional CPR [13, 14] and 27.9% in those in whom extracorporeal CPR is performed [14]. Patients at risk for early brain death include those with a neurologic etiology of arrest due to catastrophic brain injury, those with diabetes insipidus, and those with sudden acute cardiocirculatory changes [14]. While premature neuroprognostication is discouraged, recognizing patients in whom the diagnosis of brain death is likely key so that the determination can occur and the potential for organ donation can be ascertained. We usually obtain a non-contrast head computed tomography (CTH) following ROSC, and if there is complete loss of gray-white differentiation and crowding of basilar cisterns in the absence of hypercarbia in a patient with complete brainstem areflexia, we may forego TTM and sedatives; thereby, brain death evaluation can be performed 24 h post-CA if no clinical improvement is seen. Accounting for the patient's temperature, delayed metabolism of sedatives and neuromuscular blockade used during TTM, electrolyte imbalances, cold diuresis, and metabolic derangements due to shock liver and renal failure is important when interpreting the neurologic exam, as all of these factors may act as confounders during brain death determination.

Long-term deficits

The most commonly reported cognitive deficit among HIE patients that regain consciousness is memory loss; delayed recall seems to be particularly impaired [15,

16] in addition to deficits in recognition memory, suggesting a non-selective pattern of brain injury which correlates with diffuse cortical atrophy seen on neuroimaging [16, 17]. Nonetheless, isolated memory loss is uncommon, and the usual pattern of impairment following CA combines memory, subtle motor, and executive function deficits [18].

The pace of cognitive recovery usually reaches a plateau at the 3-month mark following resuscitation [15, 19]; however, prolonged rehabilitation has been shown to improve performance in activities of daily living and should be pursued [20]. Furthermore, comprehensive, well-coordinated care following the hospitalization that includes careful reassessment of patient and support networks in order to identify areas of vulnerability that require further interventions should be the cornerstone of post-CA care.

Returning to work

Post-CA return to work rates vary significantly according to the patient population being studied, but they also depend on the time of evaluation following cardiac arrest: approximately 60–80% previously employed OHCA survivors return to work [21, 22]; in the majority, this happens in the first 6 months. However, long-term follow-up is necessary, since in one quarter of cases, return to work only happened over 1 year later [21]. Importantly, in these cohorts, there was a high proportion of survivors with a CPC of 1 and 2, and these findings should not be extrapolated.

The limitation of currently used outcome scales

Functional status and quality-of-life in survivors depend on many variables not addressed by commonly used outcome scales in neurocritical illness; therefore, interpreting overall outcomes is not a simple task. Among patients with good neurologic recovery following CA, mental and health dimensions of Health-Related Quality-Of-Life (HRQOL) do not significantly differ from the general population matched by age and gender [22–24]. It is noteworthy, however, that even among survivors with a considered good outcome in most studies (CPC 1–2), there is significant granularity regarding quality-of-life [22]. In fact, even among patients with a CPC of 1, quality-of-life may be heterogeneous [22]. Furthermore, in the modern era, approximately one in four long-term survivors report anxiety, and one in seven experience depressive symptoms, both correlating to HRQOL scores [25]. Evidence of depression may be found in almost half of long-term survivors when evaluated by a neuropsychologist [26]. These findings suggest that CPC and HRQOL should be systematically evaluated in CA studies for a more comprehensive understanding of functional outcomes. Recently developed to assess outcome in CA survivors, the Cerebral Performance Categories-Extended (CPC-E) outlines several spectrums of function over 10 domains, each with five levels of severity. CPC-E is quick yet comprehensive and is a promising instrument to provide more detailed aspects of neurologic recovery following CA [27].

The timing of outcome assessment matters

CPC scores at discharge may accurately predict long-term survival [28] but may not be reliable in predicting disability, as 15% of patients assigned to a CPC of 1 at discharge may, in fact, be less independent and have worse cognitive

outcomes when reassessed months later [29]. Moreover, functional status may improve following discharge in patients who survive the first month, and approximately 50% of patients may improve by one point on the modified Rankin Scale between the initial 6 and 12 months post-CA [30]. Telephone interviews evaluating neurocognitive and functional domains are feasible in CA survivors [22, 29]; thus, these assessments are encouraged not only for re-examining long-term outcomes for research purposes but also for screening and tailoring further rehabilitation care to each individual's needs, as, thus far, there is no "best practice" for rehabilitation post-CA [21, 31].

Pathophysiology of hypoxic-brain injury and post-CA syndrome

The exceptional vulnerability of the brain is attributed to its limited tolerance of ischemia and its unique response to reperfusion. The mechanisms of nervous system injury triggered by CA (ischemia) and resuscitation (reperfusion) are complex and multifactorial, and often have a vicious reactivation loop relationship with one another; activation of cell-death signaling pathways leading to neuronal necrosis and apoptosis, excitotoxicity due to a massive glutamatergic state, free radical formation with reactive oxygen and nitrogen species, disrupted calcium homeostasis, activation of pathological protease cascades, and microcirculatory failure all play a role in the pathophysiology of hypoxic-ischemic brain injury [32]. Nonetheless, cerebral microcirculation seems to be preserved in the early phases following ROSC [33]. Brain edema formation is multifaceted, and cytotoxic edema results from ionic homeostasis and cell membrane integrity disruption combined with a disturbance of aquaporin 4 channels [32, 34].

Post-mortem analyses demonstrate a wide range of pathologic changes in the gray matter, which include scattered ischemic eosinophilic neurons, laminar necrosis, and fully developed infarcts with associated microemboli in adjacent leptomeningeal vessels [35]. The overall diffuse gray matter loss has been demonstrated in a magnetic resonance imaging (MRI) study as pronounced atrophy predominantly in the entire cingulate and insular cortex, precuneus, posterior hippocampus, and dorsomedial thalamus [36]. Importantly, the susceptibility of neurons to ischemia and anoxic depolarizations varies substantially; brainstem neurons seem to resist ischemia the most, likely due to their increased pump efficiency during ischemic stress [37]. The white matter is not spared, and non-specific myelin rarefaction and pallor, in addition to vacuole formation, axonal loss, microglial proliferation, and astrocytosis, can be found [35]. Ischemic axonopathies may be immediate, as a direct consequence of ischemia with swelling and dissolution of cytoskeleton, or delayed, following the degeneration of ischemic red neurons; the overall result is a leukoencephalopathy [35].

The inappropriate host response to ischemia-reperfusion: a sepsis-like picture

Post-Cardiac Arrest Syndrome (PCAS) is the result of an unnatural pathophysiologic state caused by reperfusion following whole body ischemia and is characterized by profound endotheliopathy, subsequent capillary leakage, and microcirculatory dysfunction [38]; the inciting step seems to be the

sympathoadrenal hyperactivation resulting from the initial ischemic insult [39]. The sepsis-like inflammatory response due to this endothelial injury affects the CA survivor in his/her entirety, culminating in multisystem organ failure [40, 41]. The nervous system is affected by the influx of inflammatory cells as a consequence of the systemic inflammatory response; this may occur as early as 3 h following ROSC and may endure for the subsequent 3 days [42]. Activation of resident microglia by this cascade may be implicated in the pathophysiology of delayed neuronal death.

Changing the story: targeted temperature management

Several therapies targeting specific mechanisms implicated in the pathophysiology of hypoxic-ischemic brain injury have been tested, unfortunately without a significant impact on outcomes. Temperature modulation following CA has completely changed the scenario as a valuable neuroprotective therapy due to its associated effects in reducing mortality and improving neurologic outcomes in HIE. Since the landmark studies published in 2002 [43, 44], TTM has become standard of care following ROSC for unresponsive OHCA patients presenting with shockable rhythms [45••]; it is also recommended by American Heart Association (AHA) guidelines in IHCA and in non-shockable rhythms due to its favorable risk profile and potential benefits [45••]. The mechanisms by which TTM halts the ischemic injury cascade are varied; this is likely the main reason for its effectiveness. TTM retards destructive enzymatic reactions, suppresses the formation of free-radicals and their reactions, protects the fluidity of lipoprotein membranes, reduces the bioenergetic failure by reducing oxygen demand and improving brain glucose metabolism, tempers intracellular acidosis, decreases endothelial damage, and reduces excitotoxicity by inhibiting the biosynthesis, release, and uptake of excitatory neurotransmitters [46].

Surviving cardiac arrest: resuscitation

There is considerable variation on overall survival for both OHCA and IHCA across different world regions, countries, states, hospitals, and specific locations of CA [2, 47–53]. Not surprisingly, multiple factors can impact outcomes in the resuscitation phase of CA and are included in the chain of survival [3]. Of these, increases in the incidence of bystander CPR and early access to automated external defibrillators in shockable rhythms are the most notable in OHCA. The quality of guideline-based care provided is a significant factor in IHCA survival, as the hospital process composite performance is linearly associated with risk-standardized survival to hospital discharge [54]. Even delays in epinephrine administration for non-shockable IHCA have been associated with lower risk-standardized survival rates [49].

It is important to realize that resuscitation goals and practices are a moving target, given the incredibly fast pace of progress in this field arising from refined and nuanced studies; thus, paradigm shifting concepts quickly arise. From changing "ABC" (airway-breathing-circulation) to "CAB" (circulation-airway-breathing) [55, 56], to emerging provocative evidence suggesting benefits of delaying definitive airway placement [57], to elevating the head-of-bed during CPR [58], to delaying the use of epinephrine in shockable rhythms [59], conventional paradigms are increasingly questioned and modified [60].

Surviving cardiac arrest: post-cardiac arrest care

First and foremost, deciphering the etiology of the arrest is a priority, as this may dictate the pursuit of subsequent treatment avenues. Basic evaluation includes an electrocardiogram (ECG) and often an echocardiogram; non-contrast CTH is important when associated trauma is suspected or to rule out a primary neurologic event.

Notable dissimilarities exist in patient selection criteria for aggressive PCAS care. Age, comorbidities, and details of arrest are appropriately taken into consideration when deciding whether or not further aggressive therapeutic measures should be performed; however, recent observational data also show sex-based disparities in post-CA treatment: women are less likely to undergo TTM and coronary interventions [61]. This disparity in the level of care is translated into outcomes, as the severity of PCAS and the extent of extracerebral organ failure requiring further interventions have a direct association with mortality during hospital admission [62, 63, 64•]. Mortality related to severity of PCAS is attributed to refractory shock, recurrent CAs, decisions to not escalate care (e.g., not offering renal replacement therapy in severe renal failure), or WLST. Not surprisingly, certain patients benefit most from transferring to a cardiac care center for timely hemodynamic and electrophysiologic interventions based on the etiology of CA [65]. However, as outcomes appear to be directly associated with aggressive management in PCAS [66], the positive impact of highly specialized care post-CA likely supports the routine transfer of patients to tertiary centers. Importantly, even patients with CA characteristics suggesting poor prognosis (i.e. longer time-to-ROSC, non-shockable rhythm, unwitnessed arrest) may benefit from being transferred to a regional cardiac resuscitation center [67]. Alternatively, implementing a post-CA consult team seems to be feasible and useful in delaying neuroprognostication beyond the initial 72 h [68]. Ideally, a highly specialized post-CA team should have expertise in the management of PCAS (mindful of the brain-directed physiologic goals during the early post-resuscitation phase, see Table 1), TTM, and neuroprognostication to guide the comprehensive care of the CA survivor. This could even be accomplished remotely by telemedicine [73, 74].

Myocardial injury and cardiac care

Ischemic and non-ischemic cardiac diseases are the main etiology of OHCA; prompt recognition of the underlying pathologic process is imperative to avoiding recurrent arrests and improving outcomes [75, 76]. Patient selection for emergent coronary artery angiography is usually based on the presence of ST elevations on post-ROSC ECG; however, recent evidence suggests that patients without obvious ischemic changes on initial ECG may still have significant coronary lesions [77]. Further studies aiming at improving prediction of coronaropathy and patient selection for further interventions are needed.

Although its true incidence remains unknown, post-arrest myocardial dysfunction (cardiac stunning) is estimated to occur in up to two-thirds of CA survivors [78]. Echocardiography should be obtained routinely following ROSC for the diagnosis of pump failure; shock and vasopressor dependence may result from vasoplegia and are not reliable indicators. Restoration of

Table 1. Neurologic-geared goals in the management of post-cardiac arrest syndrome

Parameter	Goal
Ventilator settings	Titrate oxygenation for O_2 saturation ~95%, PaO_2 80–100 mmHg is reasonable TV 6–8 ml/Kg IBW, titrate MV for $PaCO_2 > 35$ mmHg[a]
Hemodynamic support	Titrate interventions for MAP >65 mmHg
Glucose	Avoid hypoglycemia. Consider insulin for glucose levels >180 mg/dL in non-diabetics[b]
Temperature	Maintain 32–36 °C for initial 24 h, slow rewarming Actively prevent hyperthermia for at least 3 subsequent days

Adapted from [45••, 69–71]. This table also contains authors' opinions
IBW ideal body weight, *MV* minute ventilation, *TV* tidal volume
[a]The precise range of $PaCO_2$ that should be targeted remains unknown. Hypocarbia should be avoided due to impaired cerebral autoregulation and microcirculatory failure post-CA, which may all culminate in cerebral oligemia and secondary brain injury. The TAME trial is a randomized controlled trial evaluating the effect of mild hypercarbia during post-CA period based on promising preliminary results from the CCC trial [72]
[b]The glycemic threshold for insulin may be higher in diabetic patients, and emerging evidence suggests worse outcomes with tighter glucose management

preload and arterial pressure, in addition to providing support of tissue perfusion by inotropes or mechanically in refractory cases, remains the foundation of cardiac-centered post-CA care.

Acute kidney injury

This common complication usually occurs in the initial 3 days following ROSC, affecting over 40% of CA survivors, and of these, over one quarter will eventually undergo renal replacement therapy [79]. Patients at risk are older, have chronic renal disease, experience shock during their ICU stay and require higher doses of epinephrine, have a low creatinine clearance on admission, and have a high cumulative fluid balance at 48 h [79]. In a multicenter cohort, renal failure on admission was the only noncerebral organ dysfunction that had an independent impact on mortality during ICU stay, [62] but had no effect on neurologic recovery in survivors in a smaller study [79].

Temperature modulation

TTM is the cornerstone of brain resuscitation during post-CA care, conferring a 30% survival benefit [80]. Unfortunately, significant variability exists in how TTM is performed, including patient selection criteria, contraindications, duration of cooling, methods for induction and maintenance, and speed of rewarming [81, 82]. Despite conventional knowledge that earlier cooling conveys increased benefit, the majority of studies analyzing benefits of pre-hospital cooling do not support its routine use [83, 84]. The caveat to that arises from the significant heterogeneous methodology used in these studies and low quality of evidence [83]; the concern with pre-hospital cooling is the increased risk of recurrent CA and lower ROSC rates, particularly if large volumes of cold saline are used. Importantly, rapid cooling strategies achieving a decrease in temperature by ≥3 °C/h when targeting 32–34 °C without the use of cold saline have recently been associated with better outcomes [85]. Endovascular devices with temperature control utilizing loop-feedback mechanisms are associated with

faster induction and less fluctuation of temperatures during maintenance phases than external cooling; however, the improvement in favorable outcomes is not statistically significant, and they have higher rates of deep venous thrombosis [86]. Whether certain CA populations may benefit from lower targeted temperatures remains to be proven; longer times-to-ROSC do not warrant deeper hypothermia [87–89]. The duration of TTM is often extrapolated by landmark validating studies, habitually maintaining target temperature for at least 24 h, also the recommendation of the International Liaison Committee on Resuscitation (ILCOR) [84]. The benefits of a longer hypothermic maintenance phase in certain populations have been raised but remain speculative. The TTH48 study seems promising in potentially answering this question [90]. Similarly, contraindications to TTM are extrapolated from the exclusion criteria in prior studies, and the only absolute one, in our opinion, is a comatose or moribund premorbid state. Milder hypothermia targeting 36 °C has much less impact on the coagulation cascade, causes less electrolyte imbalance due to extra/intracellular shifts and cold diuresis, is less associated with severe cardiac arrhythmias, and has much less impact in delaying the metabolism of sedatives. In fact, it is less associated with shivering and requires less sedating medications during the induction and maintenance phases, which, in turn, may diminish the effect of confounders in neuroprognostic assessments [91]. Moreover, likely due to its increased impact on the immune system, targeting 32–34 °C has been associated with higher rates of pneumonia, with a number needed to harm of 15 [92]. The TTM2 trial has been designed to compare targeted hypothermia to normothermia and should provide more definitive evidence on temperature target selection. TTM targeting 36 °C for 24 h using ice packs in the groin and axilla for quick induction in addition to a loop-feedback controlled method as soon as possible following ROSC regardless of rhythm, location, and duration of arrest, followed by controlled rewarming at 0.15–0.25 °C/h, is our preferred approach. Shivering is counterproductive and should be prevented with buspirone and heating packs in the palms and soles, and treated with meperidine or neuromuscular blockade if necessary. Caution should be used with dexmedetomidine, particularly if lower temperatures are targeted, due to a higher risk of bradyarrhythmias. We advocate for aggressive euthermia following rewarming for at least 72 h with a prophylactic antipyretic agent (around the clock acetaminophen, if not contraindicated) as well as with keeping the device used for induction set at 37.5 °C as the maximum allowed temperature. Tailoring of TTM should be considered pending further studies suggesting benefits of different strategies in specific patient populations.

Seizures and status epilepticus

Seizures, status epilepticus, and status myoclonus are common in the CA survivors. Their true incidences are difficult to ascertain due to heterogeneous definitions, time of monitoring (for nonconvulsive seizures and status epilepticus), and reporting bias. Limitations aside, it is estimated that approximately one quarter of unresponsive CA survivors experience seizures [93, 94] and myoclonus [94]; often, they occur prior to electroencephalogram (EEG) monitoring or to rewarming [93]. They all have been reported to be associated with poor outcomes, with variable and relatively high false positive rates, as these data are heavily contaminated by WLST and the consequent self-fulfilling

prophecy bias [95, 96]. Recently, distinct electrographic patterns of early myoclonic activity were recognized, and approximately half of patients with a continuous EEG background and narrow, vertex spike-wave discharges time-locked with myoclonic jerks survived with good outcomes [97•]. Whether seizure activity represents a threat due to potential risk of secondary brain injury or is a marker of neuronal injury remains to be answered; for now, it is prudent to aggressively treat frank seizures or status epilepticus, even if subclinical. Electroencephalographic status epilepticus may occur in up to one third of patients and is often refractory to multiple lines of therapy [94, 98]. Similarly, the best treatment modality (which includes conservative expectant management) is unknown; the TELSTAR study will randomize patients into aggressive suppression of all seizure activity vs. no treatment and will hopefully elucidate the best course of action in these patients [99].

Surviving cardiac arrest: prognostication

Another major aspect of post-CA care is the art of neuroprognostication. Premature prognostic assessments may trim survival in cardiac arrest and, most importantly, may deprive patients that could have clinically improved enough to walk unassisted if given a chance to recover [11]. Conversely, committing neurologically devastated patients to a severely debilitated existence is not only costly in terms of health care dollars [100], but also emotionally and ethically by promoting undue suffering to patients and families. The clinical practice pertaining to end-of-life care decision-making also displays regional variation; while some institutions have clear protocols for applying neuroprognostic assessments and WLST in a standardized fashion, others have no protocol, or WLST is not performed at all and patients are transferred to an extended care facility [101]. There is a growing interest in investigating the impact of neuroprognostication and WLST in the natural history of HIE. A recent study analyzing the effect of this practice in 26 US centers demonstrated that 43% of patients underwent WLST; they were more likely to be older, have a longer arrest duration, more likely to be female, and less likely to have a witnessed arrest [102]. Time to awakening (following commands purposefully or Glasgow Coma Scale >8) is variable and often longer than 3 days, particularly in patients treated with TTM [103, 104], challenging early prognostic assessments.

Several prognostic parameters have been used to guide neuroprognostication, with variable yields depending on whether TTM was employed or not [95, 96]; all studies assessing their prognostic ability are subject to the self-fulfilling prophecy bias to varying degrees. Table 2 displays the most commonly used tools and the suggested timing of assessments based on treatment with TTM. Guidelines summarizing the prognostic ability of these tools are available [45••, 106–110]; of these, only the American Academy of Neurology guidelines from 2006 does *not* account for the exposure to TTM and has been considered outdated by many experts.

Miraculous recoveries and limitations of current neuroprognostication techniques

Accumulating reports of survival with good neurologic recovery despite low likelihood based on one or multiple prognostic factors challenge current

Table 2. Neuroprognostic assessments in treated and untreated unresponsive cardiac arrest survivors with targeted temperature management

Prognostic tool	Timing of assessment TTM	Timing of assessment No TTM
Biochemical marker NSE[a]	Serial measurements q 24 h 1–5 days post-CA	Serial measurements q 24 h 1–5 days post-CA
Biochemical marker Lactate[b]	Serial measurements q 6–12 h 1–3 days post-CA	Serial measurements q 6–12 h 1–3 days post-CA
Neurophysiology EEG	Continuous long-term monitoring or repeat 1 h recording at 12 h post-CA and during rewarming	Continuous long-term monitoring or repeat 1 h recording at 12 and 24 h post-CA
Neuroradiology CTH	48 h post-CA	48 h post-CA
Neurophysiology SSEP	48–72 h following complete rewarming	48–72 h post-CA
Clinical exam Pupillary and corneal reflexes	72 h following complete rewarming	72 h post-CA
Neuroradiology MRI	3–5 days post-CA	3–5 days post-CA

Adapted from [45••, 105, 106]
CA cardiac arrest, *CTH* computed tomography of the head, *EEG* electroencephalogram, *MRI* magnetic resonance of the brain, *NSE* neuron-specific enolase, *SSEP* somatosensory evoked potentials, *TTM* targeted temperature management
[a]Trend should be obtained even if initial value is <33 ng/mL
[b]If initial value is <2 mm/L and patient has no evidence of shock there is no need to trend values

neuroprognostication practices [111–122]. Recently, even findings considered infallible in predicting poor outcome, such as bilateral absent pupillary light reflexes, corneal reflexes, or N20 peaks on somatosensory evoked potentials (SSEP) have lost their immaculate prognostic ability, although they continue to have very low false positive rates [123]. These findings are certainly thought provoking. The overall message from these data mandates that strategies to improve accuracy in neuroprognostication be taken, while clinicians are urged to base their assessments in a multimodal approach and *never* take a single predictor as "fool proof."

The host

Several characteristics unique to patients have been associated with outcomes. Less favorable outcomes are seen in older patients, with a cumulative effect based on decade of life; comorbidities based on Charlson Comorbidity Index were not independent predictors of poor outcome [124]. Discrepancies in level of care and incidence of shockable rhythms between male and females likely account for reported lower survival in women [61, 125].

Cardiac arrest details

Total downtime (time-to-ROSC) is independently associated with survival regardless of initial rhythm in OHCA [58, 126]; however, shockable rhythms have a less pronounced association of total downtime and poor outcomes, suggesting overall higher resilience to ischemia [58, 126]. Duration of arrest,

although important in guiding termination of resuscitation efforts, should never be used alone to ascertain neurologic prognosis given the lack of a reliable cutoff values, particularly in the setting of other favorable features, such as witnessed arrest and the presence of bystander CPR [127]. Non-shockable rhythms have historically been associated with poor outcomes; however, conversion to shockable rhythms during resuscitation occurs in up to one quarter of patients and is associated with approximately three times higher chance of survival and good outcomes when compared to sustained non-shockable rhythms [128, 129].

Physiologic characteristics in the early post-CA phase

Shivering occurs in the great majority of patients treated with TTM and is associated with good neurologic outcome [130]. Similarly, bradycardia during 32–34 °C TTM is independently associated with neurologic recovery and, if not associated with signs of poor end-organ perfusion, should not be aggressively treated [131, 132].

Clinical exam

After almost four decades of advances in the critical care and resuscitation fields, no predictors have shown to be more reliable than absence of the pupillary light reflex [95, 96, 105, 123]. However, the timing of assessment, the method used and the environmental conditions during testing, and the presence of confounders (such as the effect of sedatives) all matter when examining pupillary reactivity to light. Every effort should be taken to increase its yield: dimming the room's lights, examining no earlier than 72 h post-CA or after complete rewarming in TTM-treated patients, waiting for the effect of drugs to be cleared, using a magnifying glass with bright light/LED technology, or even automated pupillometers. Similarly, bilaterally absent corneal reflexes at 72 h post-CA or after complete rewarming in TTM patients are highly predictable of poor neurologic outcome [95, 96, 105, 123] but are subject to variability in their yield depending on the strength and location of stimulation.

The motor response (extensor posturing or absence of response) should no longer be used for prognostication of poor outcome due to unacceptably high false positive rates [95, 96, 105, 123].

Neurophysiologic tests

The absence of bilateral cortical responses (N20) on somatosensory evoked potentials (SSEP) is strongly associated with a poor neurologic outcome [95, 96, 105, 123]; however, their use is limited by the lack of widespread expertise and equipment availability, and the presence of artifact in the inherently noisy ICU environment.

Several EEG features have been shown to be valuable in outcome prediction post-CA: lack of background reactivity, presence of status epilepticus, identical bursts of epileptiform activity, and suppressed background portend low chances for neurologic recovery with variable false positive rates [133, 134]. However, EEG recordings are susceptible to the effect of drugs, and a significant risk for confounding exists [135]. Lack of standardization of stimulation and high inter-rater variability also limit the generalizability of reactivity for outcome prediction [136]. Moreover, the recording evolves over time following CA

and, in the majority of studies, this was not accounted for. Novel-refined evaluation of quantitative EEG measures is promising to overcome the abovementioned limitations of standard EEG [137, 138].

Lactate and pH

Reflecting capillary perfusion independently of hemodynamic variables, lactate values and the lactate clearance rate are good markers of microcirculation, oxygen delivery, and consumption relation [139]. Several studies congruently demonstrate lactate as a predictor for early and late mortality as well as poor neurologic outcome regardless of treatment with TTM; although there is substantial variability in the timing of sampling (as early as 1 h following ROSC to up to 3 days post-CA) and what is considered an elevated value (2, 5, and 10 mmol/L cutoffs), these seems to follow a stepwise predictive effect, with the higher the values and the longer duration of hyperlactatemia, the greater association with mortality [139–144].

Severe acidemia (pH < 7.2) at initiation of TTM is associated with over 3× increased risk for poor neurologic outcome in survivors of CA with shockable rhythms; no such difference in survival and pH was found in patients with non-shockable rhythms [145].

Biochemical markers of neuronal injury

Having their utility restricted by the limited availability of routine testing, markers of neuronal injury have been studied for decades with mixed results [95, 96, 105, 123, 146]. The most widely used is neuron-specific enolase, which has its usefulness limited by the lack of specificity for irreversible neurologic injury; no absolute cutoff is reliable in predicting poor outcomes, and an overall uptrend in values holds a stronger association with further neuronal injury and with the potential for poor outcomes [147].

Neuroradiologic studies

Neuroimaging is a valuable tool in assisting with outcome prediction following CA. Diffuse loss of gray-white differentiation suggestive of cerebral edema on CTH at any time, in the absence of hypercarbia, is consistently associated with poor outcomes; more recent studies dissecting the gray-white ratio in specific brain regions and the quantification of cortical damage by Hounsfield Unit measurement have not found their place yet in routine clinical practice [148].

Brain MRI is more sensitive in detecting subtle hypoxic ischemic injury, but its yield is highly dependent on the timing of image acquisition in relation to CA [148]. The ideal window remains to be validated in large prospective studies; however, MRI 3–5 days following ROSC seems to be reliable in demonstrating the burden of ischemic injury [149]. Importantly, no definite guidelines for the clinical interpretation of an ischemic burden cutoff as predictive of poor outcome exist, and while highly sensitive, MRI is only modestly specific in predicting poor prognosis [150].

Surviving cardiac arrest: a time to act indeed

Further decline in the incidence of CA is to be expected as advances in preventative medicine and increased access to primary care occur. The scientific

community was recently urged by the Institute of Medicine to act and develop further strategies to improve CA survival—an initiative strongly supported by the AHA [151]. Dedicated funding opportunities should boost even further developments in the field of resuscitation. Recognizing that strategies targeting the minimization of secondary brain injury and the improvement in accuracy of neuroprognostication are crucial to accomplish the goal of surviving cardiac arrest.

Compliance with Ethical Standards

Conflict of Interest

Dr. Carolina B. Maciel receives research grant funding from Swebilius Foundation.
Dr. Mary M. Barden declares no potential conflicts of interest.
Dr. David M. Greer serves as Editor-in-Chief of *Seminars in Neurology* and has received compensation for medico-legal consultation.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of Particular Interest, Published Recently Have Been Highlighted as:

- • Of importance
- •• Of major importance

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