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Reducing Brain Injury After Cardiac Arrest: American Academy of Neurology Practice Guideline

Therapeutic hypothermia (TH) (32-34°C for 24 hours) should be mandatory practice for patients who are comatose after being resuscitated from out-of-hospital cardiac arrest, if the initial cardiac rhythm is either pulseless ventricular tachycardia (VT) or ventricular fibrillation (VF), according to the American Academy of Neurology (AAN)'s newly published practice guideline Reducing brain injury following cardiopulmonary resuscitation.

The guideline, which is endorsed by the Neurocritical Care Society and published online in Neurology, is based on the evidence from studies conducted over the last 50 years on ways to reduce brain injury in people who are comatose after resuscitation from cardiac arrest.

The recommendation for patients who are comatose following resuscitation from cardiac arrest, in whom the initial cardiac rhythm is either VT/VF or asystole/pulseless electrical activity (PEA) after OHCA is for targeted temperature management (36°C for 24 hours, followed by 8 hours of rewarming to 37°C, and temperature maintenance below 37.5°C until 72 hours). The recommendation is Level B "should do", and the guideline notes that it is an acceptable alternative to TH. The guideline also states that there is insufficient evidence to support or refute the use of 32°C vs 34°C.

Lower strength recommendations are for patients who are comatose with an initial rhythm of PEA/asystole, in whom the guideline states that TH possibly improves survival and functional neurologic outcome at discharge vs standard care and may be offered (Level C - "might" be done). Prehospital cooling as an adjunct to TH is not recommended, as the available evidence is strong enough to say that it is highly likely to be ineffective in further improving neurologic outcome and survival. The guideline states that it should not be offered (Level A). In addition, other pharmacologic and nonpharmacologic strategies (applied with or without concomitant TH) are also reviewed.

The guideline recommends that future studies try to find optimal target temperatures and rates of cooling and rewarming the body as well as examining which cooling methods work best.

In an accompanying editorial, Gregory Kapinos, MD, MS, a neurointensivist at North Shore Long Island Jewish Health System and Assistant Professor, Hofstra Northwell School of Medicine and Lance B. Becker, MD, chair and professor of emergency medicine at the Hofstra Northwell School of Medicine, write, "The keen semantic nuances used in these AAN guidelines send the correct message to the neurologic community (Yes we cool!) to prevent ongoing misinterpretation of the study by Nielsen at al. [2013]." They suggest that the guidelines could have been "more precise" on prehospital cooling and should have only recommended against the methods that have been proven to be potentially deleterious: 4°C fluid loads or intranasal cooling, adding that it's "premature to close the door on all methods of preshospital TH induction." They write: "We concur with the AAN experts

that less is not more and cooling should be harder, better, faster, stronger, in the sense that neurologists should be hardliners who embrace cooling as a default mode for nearly all cardiac arrest survivors, making it harder to exclude patients, while using cooling techniques that are the better ones, starting as quickly as possible after ROSC, and that 33°C is stronger than 36°C."

The AAN said that families of patients who have suffered cardiac arrest should ask if their loved one qualifies for therapeutic hypothermia. "People who are in a coma after being resuscitated from cardiac arrest require complex neurologic and medical care and neurologists can play a key role in improving outcomes by providing body cooling," said the chair of the guideline committee, Romergryko G. Geocadin, MD, of Johns Hopkins University School of Medicine in Baltimore, and a Fellow of the American Academy of Neurology. "This guideline recommends that cooling is used more often for patients who qualify."

Geocadin told ICU Management & Practice in an email, "We know that implementation of this therapy is really low (6% to 30% in the USA) despite the strong scientific evidence. Families need to know that they have this option—we are empowering families because cardiac arrest survivors are comatose and could not advocate for themselves."

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The treatment of cardiac arrest has made significant progress over the last 10–15 years. This period marks a significant turning point, because the treatment of out-of-hospital cardiac arrest (OHCA) had often been considered an exercise in futility, with no improvement in outcome for the previous 30 years (Berdowski et al. 2010). In recent years, several investigators have documented marked improvements in survival after OHCA, particularly in those cases with an initial shockable rhythm (ventricular fibrillation (VF) or pulseless ventricular tachycardia (pVT) (Wissenberg et al. 2013; Daya et al. 2015; Chan et al. 2014).

Several interventions are likely responsible for the improving survival rates following OHCA. Bystander cardiopulmonary resuscitation (CPR) is associated with survival rates that are 2–3 times higher than those cases without bystander CPR (Hasselqvist-Ax et al. 2015; Rajan et al. 2016). Emergency medical services dispatchers are now better trained to efficiently ask the right questions to enable prompt recognition of cardiac arrest and then to instruct the caller to perform compression-only CPR (telephone CPR) (Bobrow et al. 2016). For shockable rhythms, reducing the delay to attempted defibrillation also improves outcome. Implementation of public access defibrillation (PAD) programs and dispatch of community first responders trained to use automated external defibrillators (AEDs) will reduce the time to defibrillation (Blom et al. 2014). Text alerts can be used to direct first responders to retrieve the nearest AED and then take it to the scene of a cardiac arrest (Zijlstra et al. 2014).

Once return of spontaneous circulation (ROSC) has been achieved, post-resuscitation management impacts significantly on the ultimate neurological outcome. European guidelines for the management of post-cardiac arrest patients were published in 2015 and describe the interventions that will optimise outcome (Nolan et al. 2015). Those patients who achieve ROSC and have ST-elevation (STE) on their ECG will require urgent coronary catheterisation because most of these will benefit from percutaneous coronary intervention (PCI) to restore coronary perfusion (Dumas et al. 2010). The immediate management of those without an obvious non-cardiac cause and without STE is controversial. Some experts advocate urgent coronary catheterisation in all such patients (Dumas et al. 2016). Current European guidance is that these patients should also be discussed with interventional cardiologists and considered for urgent coronary catheterisation (Nolan et al. 2015). Some centres will immediately catheterise cardiac arrest survivors without STE, but only if they had presented with a shockable rhythm.

> **"immediate management of those without an obvious non-cardiac cause and without STE is controversial"**

Cerebral autoregulation is disturbed in 35% of post-cardiac arrest patients and is particularly associated with pre-arrest hypertension (Ameloot et al. 2015a). The optimal target mean arterial pressure (MAP) post cardiac arrest is likely to vary between patients, but to avoid secondary brain ischaemia it has been suggested that the optimal MAP is likely to be in the range 85–105 mmHg, which is somewhat higher than the 65–70 mmHg that is widely used (Ameloot et al. 2015b).

Until recently, in the immediate period after ROSC (certainly prehospital and often in the emergency department) it has been common practice to ventilate the lungs of comatose post-cardiac arrest patients with 100% oxygen. This not unreasonably reflected concerns about harm from hypoxaemia and lack of awareness of harm from high-concentration oxygen. Animal studies have documented worse neurological outcome from the use of 100% oxygen immediately after ROSC, particularly during the first hour (Balan et al. 2006), and some observational studies using data from intensive care unit (ICU) registries have documented an association between hyperoxaemia and worse outcome among post-cardiac arrest patients. In a randomised controlled trial (RCT) the use of routine supplemental oxygen among patients with STE myocardial infarction (but not cardiac arrest), resulted in an increase in size of myocardial infarction compared with patients given oxygen only if hypoxaemic (Stub et al. 2015). A RCT of oxygen titrated to 90–94% versus 98–100% as soon as possible after ROSC and continued until ICU admission (EXACT phase 3 trial) will inform the optimal oxygenation strategy after ROSC (Nolan et al 2017). European guidelines recommend the use of a protective lung ventilation strategy in post-cardiac arrest patients, but this was based mainly on data extrapolated from patients with acute respiratory distress syndrome (Nolan et al. 2015). However, a recent observational study of OHCA patients using propensity matching has documented an association between the use of time-weighted average tidal volumes of < 8 mL kg^{-1} predicted body weight and better neurological outcome (Beitler et al. 2017). Mild hypercapnia may also be associated with better neurological outcome in post-cardiac arrest patients, possibly because it may increase blood flow to ischaemic brain. A phase 2 study comparing mild hypercapnia with normocapnia in 50 post-cardiac arrest patients documented a lesser increase in neuron-specific enolase (NSE)

values in the hypercapnia group (Eastwood et al. 2016). A RCT comparing post-cardiac arrest patients ventilated to either normocapnia or mild hypercapnia (6.6–7.3 kPa) starts recruiting soon (Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest (TAME) [clinicaltrials.gov/ct2/show/NCT03114033]).

Mild hypothermia has been shown to improve neurological outcome from OHCA presenting with a shockable rhythm, but the two prospective studies documenting this are now considered to be of moderate to low quality (Bernard et al. 2002; Hypothermia After Cardiac Arrest Study Group 2002). The targeted temperature management (TTM) study showed no difference in neurological outcome between all-rhythm OHCA patients with ROSC who had their temperature controlled for 24 h at 33°C versus 36°C (Nielsen et al. 2013). Temperature control for comatose survivors of OHCA is still important, but within the range of 32–34°C there is no consensus on the optimal target temperature (Donnino et al. 2016). The Hypothermia or Normothermia-Targeted Temperature Management After Out-of-hospital Cardiac Arrest-trial (TTM-2 [clinicaltrials.gov/ct2/show/NCT02908308]) study will start recruiting soon and will randomise comatose OHCA survivors to temperature control at 33°C versus prevention of fever, with temperature control to a target of 37.5°C initiated only if the patient's temperature reaches 37.8°C.

The commonest mode of death in post-cardiac arrest patients who are admitted to ICU but do not survive is withdrawal of life-sustaining therapy (WLST) following determination of a poor neurological prognosis. We now recognise that in many cases these WLST decisions have been premature and that prognostic tests previously thought to be reliable are associated with unacceptably high false positive rates (Elmer et al. 2014; Cronberg et al. 2017). European guidelines for prognostication in comatose post-cardiac arrest patients advocate a multimodal approach that is delayed until at least 3 days after cardiac arrest (Sandroni et al. 2014). Those ICUs experienced in the management of post-cardiac arrest patients should have easy access to electroencephalography, including somatosensory evoked potentials, and to neurologists who can interpret the findings.

In some countries, regionalisation of post-cardiac arrest treatment has resulted in cardiac arrest centres with availability of 24/7 coronary catheterisation laboratories, intensive care teams experienced in post-resuscitation care and neurologists that can help in the interpretation of neuroprognostic tests (Spaite et al. 2014). The introduction of cardiac arrest centres where high volumes of post-cardiac arrest patients can be treated is associated with better outcomes, even when patients are transported for greater distances as they bypass local hospitals (Tranberg et al. 2017; Schober et al. 2016; Elmer et al. 2016). Investigators in London, UK are about to start recruiting to a study patients with ROSC after OHCA of likely cardiac cause but without STE on their 12-lead ECG, and will compare the outcome of patients randomised to be transported to the nearest acute hospital with those taken to a regional cardiac arrest centre (Patterson et al. 2017). This study will help to determine if all OHCAs of cardiac cause should be treated in a cardiac arrest centres and not just those patients with STE on their 12-lead ECG.

By strengthening every link in the chain of survival it is likely that survival from cardiac arrest can still be improved considerably. ■

Conflict of Interest

Jerry Nolan is Editor-in-Chief of *Resuscitation*. He has a UK National Institute of Health Research (NIHR) grant for the PARAMEDIC-2 study (adrenaline versus placebo in out of hospital cardiac arrest-OHCA) and for the AIRWAYS-2 study (i-gel versus tracheal intubation in OHCA).

Abbreviations

AED automated external defibrillator
ICU intensive care unit
MAP mean arterial pressure
NSE neuron-specific enolase
OHCA out-of-hospital cardiac arrest
PAD public access defibrillation
PCI percutaneous coronary intervention
pVT pulseless ventricular tachycardia
ROSC return of spontaneous circulation
RCT randomised controlled trial
STE ST-elevation
TTM targeted temperature management
VF ventricular fibrillation
WLST withdrawal of life-sustaining therapy

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Targeted Therapeutic Mild Hypercapnia After Cardiac Arrest

Cardiac arrest (CA) causes ischaemic brain injury and persistent cerebral hypoperfusion and cerebral hypoxia during the early post-resuscitation period. $PaCO_2$ is the major physiological regulator of cerebral blood flow, is a modifiable component of care and mild hypercapnia may lead to improved neurological outcomes for resuscitated CA survivors. In order to evaluate the potential therapeutic role of $PaCO_2$, we will conduct the TAME Cardiac Arrest trial. If TTMH therapy, which is cost free, is shown to be effective, the lives of countless CA survivors will be improved, clinical practice will be transformed, and major financial and human cost savings will be realised.

Out-of-hospital cardiac arrest (OHCA) is a common, catastrophic event that represents a major public health problem around the world. In Australia, estimates of the incidence of OHCA are approximately 1 per 1,000 persons per year (approximately 25,000 individuals in Australia each year), with Australian mortality rates varying between 87 to 94% (Berdowski et al. 2010; Victorian Ambulance Cardiac Arrest Registry 2014). For resuscitated CA patients admitted to the Intensive Care Unit (ICU), devastating neurological injury leading to withdrawal of life support or clinically important neurological impairment are the most common outcomes following CA (Lemiale et al. 2013). Accordingly, while the initial problem is cardiac in nature, after ICU admission the main reason for such dismal outcomes is neurological injury. Thus a better neurological outcome is the logical and dominant therapeutic goal in this population (Schneider et al. 2013). Previously, from a large, multicentre, retrospective observational study we reported the association of early $PaCO_2$ values (first 24 hours) with clinical outcomes in 16,542 CA patients admitted to 125 Australia and New Zealand ICUs between 2000 and 2011 (Schneider et al. 2013). Our findings demonstrated that the occurrence of hypocapnia ($PaCO_2$ <35 mmHg) carried a higher mortality rate and a lower likelihood of discharge home for survivors compared with normocapnia ($PaCO_2$ 35-45 mmHg). In contrast, hypercapnia ($PaCO_2$ >45 mmHg) was independently associated with a 16% increase in the likelihood that a CA survivor would be discharged home, thus suggesting both safety and potential neurological benefit. Other subsequent observational studies involving adult resuscitated CA patients admitted to ICU indicate that hypercapnia is independently associated with improved neurological outcomes among survivors, while hypocapnia is associated with worse neurological outcomes, thus providing further evidence of the likely safety and possible benefit of hypercapnia (Eastwood et al. 2014; Vaahersalo et al. 2014).

Cerebral Perfusion and Arterial Carbon Dioxide Following Cardiac Arrest

It is well understood that CA leads to immediate brain ischaemia and that resuscitation leads to reperfusion injury with acute neuronal damage (Wiklund et al. 2012). What is underappreciated is that a state of sustained cerebral hypoperfusion develops and persists even after successful immediate resuscitation, return of spontaneous circulation (ROSC), and admission to the ICU (Ahn et al. 2014; Buunk et al. 2000; Koch et al. 1984). In this regard, several investigations using technologies like positron emission tomography (Edgren et al. 2003), middle cerebral artery blood flow assessment via Doppler ultrasound (Sundgreen et al. 2001), jugular bulb oxygen saturation (Buunk et al. 1999) and cerebral oximetry (Storm et al. 2014), all consistently show sustained hypoperfusion and cerebral hypoxia. For example, observational studies measuring cerebral tissue oxygen saturation ($SctO_2$) by near-infrared spectroscopy in patients receiving post-resuscitation care have demonstrated persistent cerebral under-oxygenation and a statistically significant association between such lower $SctO_2$ values and higher mortality rates (Ahn et al. 2014).

A likely pathophysiological mechanism responsible for such sustained early hypoperfusion relates to impaired cerebrovascular

auto-regulation (Kock et al 1984; Sundgreen et al. 2001). Such impaired auto-regulation may, in turn, make even a normal arterial carbon dioxide tension ($PaCO_2$) insufficient to achieve and maintain adequate cerebral perfusion and, consequently, cerebral oxygenation. However, $PaCO_2$ is the major determinant of cerebral blood flow in humans (Curley et al. 2010; O'Croinin et al. 2005), and an increase in $PaCO_2$ (hypercapnia) markedly increases cerebral blood flow under normal physiological conditions (Curley et al. 2010). The rapid vasodilatory effect of hypercapnia appears related to changes in arterial pH and cerebral vascular resistance (Koch et al. 1984; Meng & Gelb 2015). Additionally, elevated $PaCO_2$ levels are known to have anti-convulsive, anti-inflammatory and antioxidant properties, which may attenuate the inflammatory component of reperfusion injury (Kavanagh and Laffey, 2006; Tolner et al. 2011). Conversely, hypocapnia is known to increase neuronal excitability, increase cerebral oxygen consumption, reduce cerebral blood flow and, thereby, potentially worsen reperfusion injury.

Crucially, $PaCO_2$ is an easily modifiable variable and therefore a potential therapeutic target for the maintenance of cerebral perfusion and oxygenation in resuscitated CA patients (Schneider et al. 2013).

Cerebral Oxygenation and the Potential Role of Targeted Mild Hypercapnia

Until recently, there was no direct evidence on the effect of targeted hypercapnia on cerebral oxygenation in resuscitated CA patients to provide the additional biological rationale for its therapeutic application. To address this, we investigated the impact of targeted mild hypercapnia on cerebral oxygenation by performing a prospective double crossover physiological clinical study (Eastwood et al. 2016a). We enrolled seven adult resuscitated CA patients within 36 hours of their CA and compared the effect of targeting mild hypercapnia ($PaCO_2$ 50-55 mmHg) to standard care (TN) ($PaCO_2$ 35-45 mmHg) on regional $SctO_2$. With a median time from CA to ROSC of 28 minutes, at a median of 26 hours 30 minutes after CA, during TN (a median $PaCO_2$ of 37 mmHg), the median right and left frontal lobe $SctO_2$ was low with a significant proportion of values clearly below normal. However, during targeted mild hypercapnia (a median $PaCO_2$ of 52 mmHg), the median $SctO_2$ had increased to normal or above normal. Such increases were substantial in magnitude and reliably occurred in every patient every time and were not associated with any adverse events. Such findings provide further evidence for the potential role of targeting mild hypercapnia to safely improve cerebral oxygenation.

Table 1. Participant Eligibility Criteria for the TAME Cardiac Arrest Trial

Eligibility	Specific items
Inclusion criteria	1. Adult (age ≥18 years or older) 2. Comatose non-traumatic out-of-hospital cardiac arrest 3. Presence of return of spontaneous circulation following cardiac arrest 4. Receiving invasive mechanical ventilation 5. Admitted to the ICU 6. Within six hours from the onset of the cardiac arrest 7. The treating clinician believes that the patient is at risk of hypoxic brain damage
Exclusion criteria	1. Female who is known or suspected to be pregnant 2. Not receiving invasive mechanical ventilation 3. Able to follow commands 4. Clinical or radiological suspicion of raised intracranial pressure 5. Clinical or radiological suspicion of an intracranial bleed 6. Severe chronic obstructive pulmonary disease 7. Known or suspected pulmonary hypertension 8. Severe metabolic acidosis (pH <7.1 and base excess <-6 mmol/L) uncorrected within the first six hours of ICU admission 9. Transferred from another healthcare facility 10. Participation declined by the treating clinician 11. Cardiac arrest secondary to asphyxia 12. Death considered imminent

> **$PaCO_2$ is a potential therapeutic target for the maintenance of cerebral perfusion and oxygenation in resuscitated CA patients**

Targeted Therapeutic Mild Hypercapnia After Cardiac Arrest

In late 2015, we completed a randomised, controlled, parallel group, multicentre, phase II trial (Eastwood et al. 2016b). This phase II trial sought to determine the preliminary biological efficacy, feasibility, safety of delivering TTMH to resuscitated CA patients compared to standard care (TN) for the 24 hours following ICU admission. This study allocated patients to either TTMH ($PaCO_2$ 50-55 mmHg) or standard care (TN) ($PaCO_2$ 35-45 mmHg). These targets were deliberately established to avoid episodes of hypocapnia in both arms. In order to achieve a target of 50 patients with full assessment of serum neuron-specific enolase (NSE) levels (baseline, 24 hour, 48 hour and 72 hour), 86 patients were randomised from four ICUs in Australia and New Zealand. NSE is a biomarker of neuronal injury. NSE is released into the bloodstream after injury, with lower concentrations over the first 72 hours following CA indicative of decreased neuronal injury. Thus, lower levels of NSE are associated with improved neurological outcome (Calderon et al. 2014).

The study population had a median age of 61 years (79% male) and the majority were

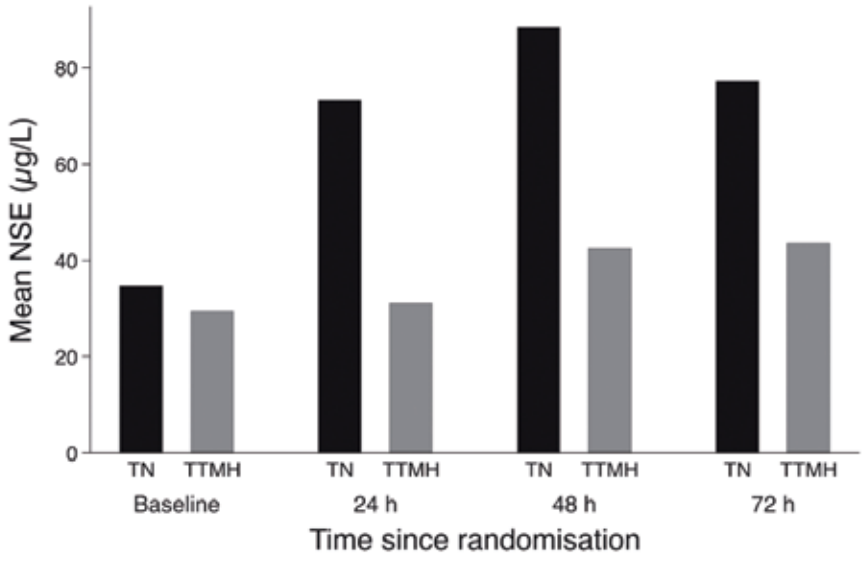

Figure 1. Mean neuron-specific enolase (NSE) concentrations at baseline, 24 hour, 48 hour, and 72 hour for patients allocated to targeted therapeutic mild hypercapnia (TTMH) and standard care (TN) who were enrolled into the CCC trial

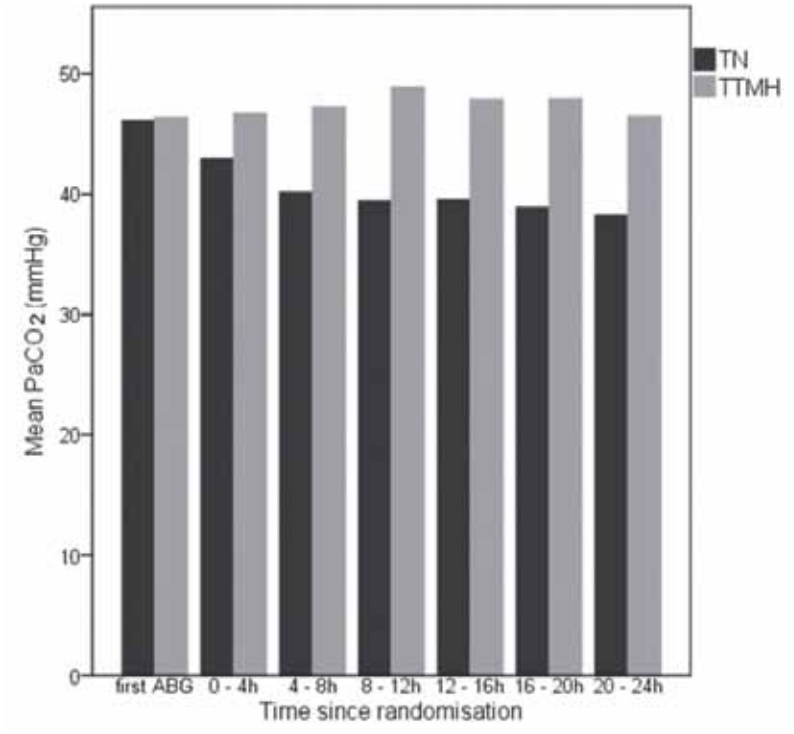

Figure 2. Time course of mean arterial carbon dioxide tension ($PaCO_2$) for patients allocated to targeted therapeutic mild hypercapnia (TTMH) and targeted normocapnia (TN) over the first 24 hours following admission to ICU for patients enrolled into the CCC trial

OHCA (78%). $PaCO_2$ separation was achieved and sustained throughout the first 24 hours following randomisation (**Figure 1**). Overall, we found TTMH significantly attenuated NSE release compared with standard care (TN) over the first 72 hours (**Figure 2**), with an identical pattern for OHCA patients, thus providing a robust signal of biological efficacy for TTMH, without differences in ventilation, temperature, or sedation management. Importantly, patients allocated to either group both avoided episodes of hypocapnia or severe hypercapnia and no clinical adverse events, sudden neurological deterioration, or clinical signs of raised intracranial pressure were reported, supporting the safety of TTMH. Most importantly, at 6 months, overall 23 (59%) TTMH patients had improved neurological outcomes compared with 18 (46%) TN patients (**Figure 3**). In addition, hospital mortality occurred in 11 (26%) TTMH patients compared with 15 (37%) TN patients (p = 0.31) (Eastwood et al. 2016b).

When the OHCA patients (80% of the cohort) were assessed separately, this effect was even stronger, as hospital mortality occurred in 8 (29%) TTMH patients compared with 13 (61%) TN patients. In addition, 20 (65%) TTMH patients had improved neurological outcomes compared with 16 (50%) TN patients (p=0.16). Thus, TTMH was associated with a beneficial biological effect (attenuated NSE levels) and a pattern of improved neurological and clinical outcomes (Eastwood et al. 2016b).

The TAME Cardiac Arrest Trial

There is now compelling epidemiological, biological, physiological, and supportive clinical data suggesting that TTMH can deliver significant outcome improvements in resuscitated CA patients admitted to ICU. In their aggregate, these findings strengthen the need to perform a larger phase III trial to address the question of whether TTMH improves patient-centred outcomes in resuscitated CA patients admitted to the ICU. As such, on behalf of the Australian Resuscitation Outcomes Consortium (Aus-ROC) NHMRC Centre of Research Excellence, the Australian New Zealand Intensive Care Society (ANZICS) Clinical Trials Group, and the Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), the Targeted Therapeutic Mild Hypercapnia After Resuscitated Cardiac Arrest: A Phase III Multi-Centre Randomised Controlled Trial (The TAME Cardiac Arrest Trial) was developed. The primary outcome measure for this study will be the proportion of patients with a favourable neurological outcome at 6 months as assessed using the Glasgow Outcomes Scale Extended (GOSE) (defined as a score ≥5) (Wilson et al. 1998).

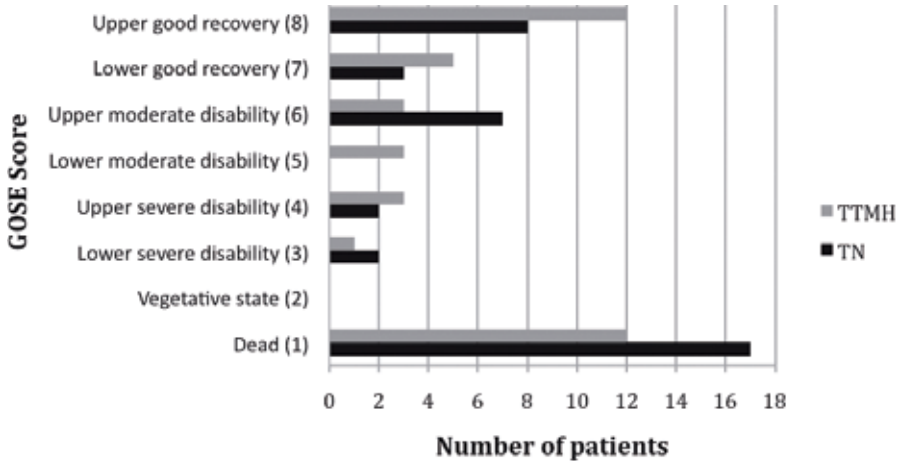

Figure 3. Glasgow outcome score extended (GOSE) assessment of patients allocated to targeted therapeutic mild hypercapnia (TTMH) and targeted normocapnia (TN) at 6 months following randomisation; with a score of >5 considered a favourable outcome for patients enrolled into the CCC trial

Five key secondary outcomes include mortality, functional recovery, cognitive functional recovery, quality of life and a health economic evaluation.

Briefly, the TAME Cardiac arrest trial will recruit 1,700 adult resuscitated OHCA patients from 30 ANZICS Clinical Trials Group member ICUs. All participating ICUs, stratified by site, will randomise patients via a website-enabled computer-generated code with permuted blocks. Eligibility criteria are shown in **Table 1**. Patients allocated to the TTMH protocol will be sedated to achieve moderate to deep sedation (a target Richmond Agitation Scale Score of –3 to –4). Arterial blood gases and end-tidal carbon dioxide levels will be measured at baseline and then used to guide respiratory rate adjustments of minute ventilation to remain within the target $PaCO_2$ range of 50-55 mmHg. Arterial blood gases will be repeated every 4 hours for 24 hours following randomisation or if end-tidal carbon dioxide values change >5 mmHg. While patients allocated to the TN protocol will be managed according to current practice in Australia and New Zealand (Schneider et al. 2013) and in accordance with ILCOR guidelines, which recommend maintaining normocapnia in these patients (Neumar et al. 2010). For both groups, ventilation management for all patients will be guided by arterial blood gas data assessed after adjustment to 37°C (alpha-stat) (standard care) (Eastwood et al. 2015) and, to ensure safety, the treating ICU physician can modify patient management, including the use of sedative agents, muscle relaxants and paralysis, as clinically indicated throughout the 24-hour intervention period. Importantly, all pre-hospital and pre-ICU care will be performed in accordance with state/territory best practice guidelines and existing local protocols. In addition, all post-ICU patient management will be at the discretion of the patient's ward-based treating physicians. ■

Conflict of interest

Glenn M. Eastwood declares that he has no conflict of interest. Rinaldo Bellomo declares that he has no conflict of interest.

Abbreviations

CA cardiac arrest
ICU intensive care unit
ILCOR International Liaison Committee on Resuscitation
NSE neuron-specific enolase
OHCA out-of-hospital cardiac arrest
$PaCO_2$ arterial carbon dioxide tension
ROSC return of spontaneous circulation
$SctO_2$ cerebral tissue oxygen saturation
TN targeted normocapnia
TTMH target therapeutic mild hypercapnia

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Prognostication Following Out-of-Hospital Cardiac Arrest

This article reviews the current evidence on prognostication after cardiac arrest.

Post-resuscitation care has developed and evolved significantly since 2003, following recommendations by the Advanced Life Support task force of the International Liaison Committee on Resuscitation to implement therapeutic hypothermia (TH) in unconscious survivors following out-of-hospital cardiac arrest (OHCA) (Nolan et al. 2003). The 2015 European Resuscitation Council (ERC) and European Society of Intensive Care Medicine (ESICM) guidelines on post-resuscitation care made strong recommendations to avoid severe hyperoxia (large amounts of oxygen) for patients following cardiac arrest (CA). This was primarily based on the evidence that severe hyperoxia is associated with increased in-hospital mortality (Kilgannon et al. 2011) and decreased survival to discharge (Elmer et al. 2015). Supplemental oxygen in absence of hypoxia is also associated with increased early myocardial injury and a large myocardial infarct size assessed at six months (Stub et al. 2015). The ERC-ESICM guidance also recommended emergency cardiac catheterisation and immediate percutaneous coronary intervention for adult patients with return of spontaneous circulation (ROSC) after OHCA of suspected cardiac origin and ST segment elevation on the electrocardiogram (ECG) (Nolan et al. 2015). A large randomised control trial demonstrated no additional benefit in survival following TH at 33˚C to targeted temperature management (TTM) of 36˚C following CA (Nielsen et al. 2013). However, the current ERC-ESIM guidance strongly recommends temperature management between 32˚C-36˚C. These recommendations were reinforced to decrease the pathological and clinical impact caused by CA, known as 'Post-Cardiac Arrest Syndrome' (Nolan et al. 2008).

> "essential that rapport and a good relationship is established with the next of kin"

The four key components of Post-Cardiac Arrest Syndrome were identified as:

I. Post-cardiac arrest brain injury;
II. Post-cardiac arrest myocardial dysfunction;
III. Systemic ischaemic / reperfusion injury;
IV. Persisting precipitating pathology.

Despite advances in post-resuscitation care management, about 50% of resuscitated patients from CA die or have a poor neurological prognosis. One of the major causes of mortality following CA is severe neurological damage due to post-anoxic brain injury (Sandroni and Nolan et al. 2015;). It is therefore essential to have a prognostication model that can predict poor neurological outcome and enable physicians to consider early withdrawal of life supporting treatment.

The Quality Standards Subcommittee of the American Academy of Neurology published a review in 2006 on prediction of neurological outcome in the comatose patient following CA (Wijdicks et al. 2006). However, the patients included in this review did not undergo TH or TTM, which was recommended subsequently. In 2015, ERC-ESICM recommended a multimodal prognostication approach for comatose survivors following CA (Sandroni et al. 2014).

Prognostication Strategy

At the recently concluded annual 37th International Symposium on Intensive Care and Emergency Medicine (ISICEM), Brussels, experts, who presented and published original studies on post-resuscitation care, explained their strategies in the workshop, *Prognostication in post-anoxic brain damage: my strategy* (37th ISICEM)

The key principles to follow are:

- early communication with the family
- delay prognostication
- multimodal evaluation, and
- be patient.

Early Communication

It is essential that rapport and a good relationship is established with the next of kin or family members at the earliest opportunity. There should be attempts to provide meaningful information and for them to be made aware of the critical nature of the patient's medical condition. This will also aid physicians to understand the expectations and goals of family members or patients. There should be regular interaction and it is vital for the family to understand that physicians will make the decision.

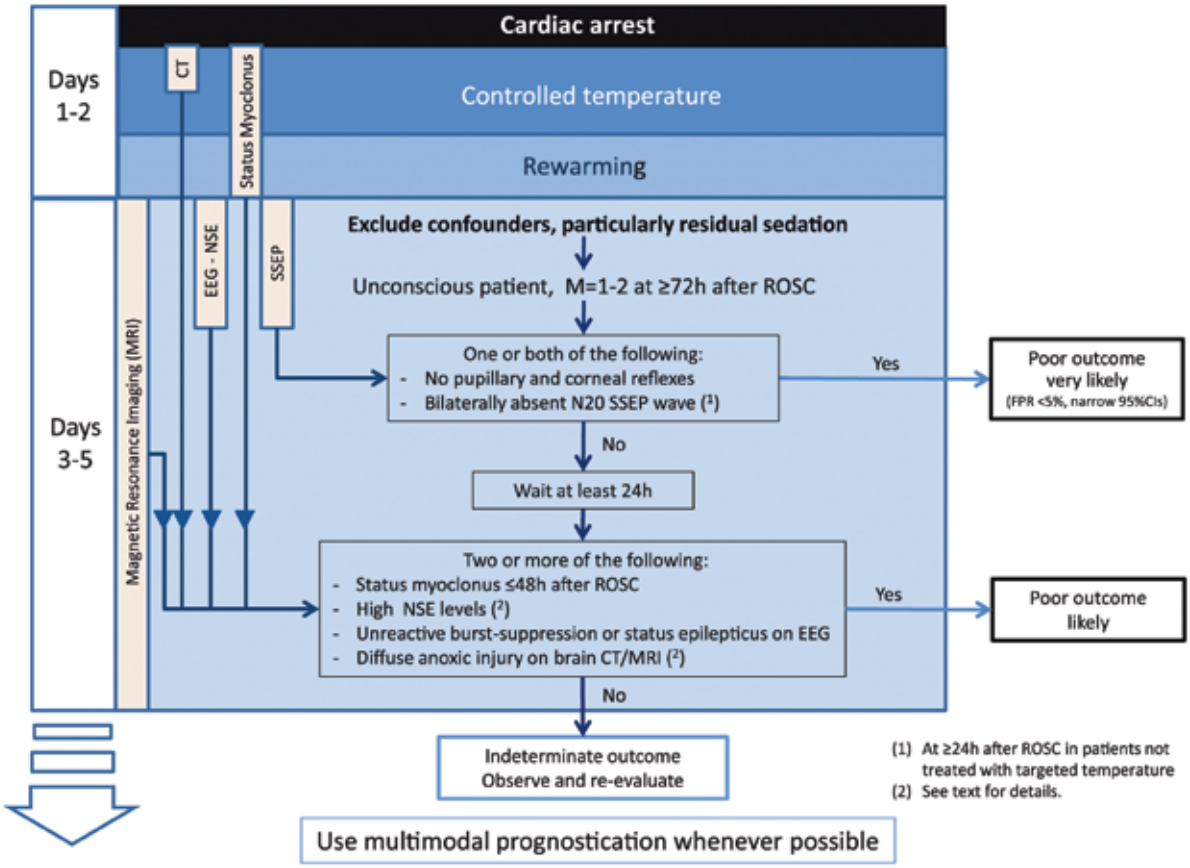

Figure 1. Suggested Prognostication Algorithm
The algorithm is entered ≥72 h after ROSC if, after the exclusion of confounders (particularly residual sedation), the patient remains unconscious with a Glasgow Motor Score of 1 or 2. The absence of pupillary and corneal reflexes, and/or bilaterally absent N20 SSEP wave, indicates a poor outcome is very likely. If neither of the features is present, wait at least 24 h before reassessing. At this stage, two or more of the following indicate that a poor outcome is likely: status myoclonus ≤48 h; high neuron-specific enolase values; unreactive EEG with burst suppression or status epilepticus; diffuse anoxic injury on brain CT and/or MRI. If none of these criteria are met consider continue to observe and re-evaluate. Source: Sandroni et al. 2014

Delay Prognostication

The current evidence supports the practice of first assessment after 72 or 24 hours, depending on whether patients received or did not receive temperature control management, respectively. This will help guide further management, and further prognostication can be carried out 24-48 hours later. However, the phenomenon of 'late awakening' has been described; there is a small subset of patients who will defy the 5-7 day recovery period and may wake up late and will have full neurological recovery. This is where the experience of the treating physician comes into action.

Multimodal Evaluation

The modalities for evaluation were described in the 2013 review (Sandroni et al. 2013) and are as follows:

I. Clinical examination (brainstem reflex, motor response, myoclonus);
II. Electrophysiology (burst suppression, seizures, flat or low amplitude electroencephalogram (EEG), non-reactive EEG, EEG grading, somato-sensory evoked potential (SSEP));
III. Biochemical markers (neuron-specific enolase (NSE), S-100B);
IV. Brain imaging (computed tomography (CT), magnetic resonance imaging (MRI)). It will be even more effective if this is performed by an intensivist alongside a neurologist.

Be Patient

This attribute is key and it is important to have a process. The process involves looking at all the previously described pre-, peri- and post-arrest factors, and continuous delivery of timely optimal care. It is therefore vital to be patient and to follow this process over a period of a week, even if there is no obvious visual recovery in the patient.

In 2014, an advisory statement on prognostication in comatose survivors following CA was published by the ERC and the ESICM (Sandroni et al. 2014). This statement updated and summarised the available evidence on this topic including that of TH-treated patients. The robust analysis of evidence provided practical recommendations on the most reliable prognostication strategies, and formed the basis of the ERC guidelines on resuscitation published in 2015.

The key recommendations are summarised below:

1. Clinical examination

- Using the bilateral pupillary and corneal reflexes at 72 h or more from ROSC to

predict poor outcome in comatose survivors from cardiac arrest, either TH or non-TH treated patients;
- Prolonging observation of clinical signs beyond 72 h when interference from residual sedation or paralysis is suspected, so that the possibility of obtaining false positive results is minimised;
- Not to use absent or extensor motor response to pain (M ≤ 2) alone to predict poor outcome as it has a high false-positive rate; it should be used in combination with other robust predictors.

2. Myoclonus and status myoclonus
- Using the term status myoclonus to indicate a continuous and generalised myoclonus persisting > 30 mins in comatose survivors of CA;
- Using the presence of a status myoclonus within 48 h from ROSC in combination with other predictors to predict poor outcome in comatose survivors of CA, either TH or non-TH treated;
- Evaluate patients with post-arrest status myoclonus off sedation whenever possible.

3. Bilateral absence of SSEP N20 wave
- Using bilateral absence of SSEP N20 wave at ≥72 h from ROSC to predict outcome in comatose survivors following CA treated with controlled temperature;
- There was suggestion to use SSEP at ≥ 24 h from ROSC to predict outcome in comatose survivors following CA not treated with controlled temperature.

4. Electroencephalogram (EEG)
- Absence of EEG reactivity to external stimuli, presence of burst suppression or status epilepticus at ≥ 72 h after ROSC to predict poor outcome in comatose survivors from CA;
- They should be used in combination along with other predictors as this criteria lacks standardisation and does not have very strong evidence.

5. Biomarkers

There is suggestion to use high NSE at 48-72 h from ROSC in combination with other predictors for prognosticating a poor neurological outcome in comatose survivors following CA, either TH or non-TH treated. However, no threshold enabling prediction with zero false-postive results can be recommended. Utmost care and preferably multiple sampling should be employed to avoid false positive results due to haemolysis.

6. Imaging

Using the presence of a marked reduction in grey matter/white matter ratio or sulcal effacement on brain CT within 24 hours after ROSC or presence of the extensive reduction in diffusion on brain MRI at 2-5 days after ROSC to predict a poor outcome in comatose survivors following CA both TH or non-TH treated. The brain CT or MRI should be used in combination with other predictors and only at centres where specific experience is available.

Figure 1 (Sandroni et al. 2014) suggests a prognostication algorithm approach.

Point-of-Care Focused Echocardiography

In a recent systematic review (Tsou et al. 2017), a total of 1695 patients in CA had point-of-care (POC) focused echocardiography performed during resuscitation. The study concluded POC focused echocardiography can be used to identify reversible causes and predict short-term outcome in patients with CA. In patients with a low pretest probability for ROSC, absence of spontaneous cardiac movement on echocardiography can predict a low likelihood of survival and guide the decision of resuscitation termination. It is very early to consider focused echocardiography, and it is currently not a part of prognostication strategies.

Conclusion

The current evidence suggests a delayed (post 72 h), multimodal prognostication approach for unconscious survivors who receive post-resuscitation care following cardiac arrest. ■

Conflict of Interest

Mena Farag declares that he has no conflict of interest. Shashank Patil declares that he has no conflict of interest.

Abbreviations

CA cardiac arrest
ECG electrocardiogram
EEG electroencephalogram
ERC European Resuscitation Council
ESCIM European Society of Intensive Care Medicine
NSE neuron-specific enolase
OHCA out-of-hospital cardiac arrest
ROSC return of spontaneous circulation
SSEP somatosensory evoked potential
TH therapeutic hypothermia
TTM targeted temperature management

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