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Optimizing brain protection after cardiac arrest: advanced strategies and best practices

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Cardiac arrest (CA) is associated with high incidence and mortality rates. Among patients who survive the acute phase, brain injury stands out as a primary cause of death or disability. Effective intensive care management, including targeted temperature management, seizure treatment and maintenance of normal physiological parameters, plays a crucial role in improving survival and neurological outcomes. Current guidelines advocate for neuroprotective strategies to mitigate secondary brain injury following CA, although certain treatments remain subjects of debate. Clinical examination and neuroimaging studies, both invasive and non-invasive neuromonitoring methods and serum biomarkers are valuable tools for predicting outcomes in comatose resuscitated patients. Neuromonitoring, in particular, provides vital insights for identifying complications, personalizing treatment approaches and forecasting prognosis in patients with brain injury post-CA. In this review, we offer an overview of advanced strategies and best practices aimed at optimizing brain protection after CA.

1. Introduction

The International Liaison Committee on Resuscitation reports an annual incidence of emergency medical service (EMS)-treated out-of-hospital cardiac

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arrest (OHCA) ranging from 30 to 97 individuals per 100 000 population [1,2]. Return of spontaneous circulation (ROSC) is achieved in approximately one-third of patients. A recent meta-analysis from 141 studies observed an incidence of ROSC of 29.7% (95% CI, 27.6–31.7%), with a survival rate to hospital admission of 22% (95% CI, 20.7–23.4%) [3]. The global survival rate remains poor, varying between 3.1% and 20.4% [2,4]. In Europe, the average survival rate is about 8% [5].

Survival rates after OHCA are higher (10.5%; 95% CI, 9.2–11.7%) when collapse is witnessed, compared with non-witnessed events. Early initiation of bystander-provided cardiopulmonary resuscitation (CPR) also leads to improved survival rates (11.3%; 95% CI, 9.3–13.2%) [3].

After ROSC, most comatose patients arriving at the hospital are admitted to intensive care units (ICUs), where they spend on average 3–5 days [6]. However, ICU mortality rate for these patients is high, approximately 70% [7]. Accordingly, a large French retrospective study analysing data from 4445 OHCA survivors reported a 33% survival rate to ICU discharge and a 67% ICU mortality rate [8].

The brain's limited tolerance to ischemia-reperfusion injury is a critical factor, with up to 70% of hospitalized individuals dying from the effects of post-cardiac arrest brain injury (PCABI), even following successful initial resuscitation efforts [9–11]. PCABI is the primary cause of long-term disability among survivors [12], with approximately 19% experiencing moderate-to-severe neurological damage that hinders their ability to return to work and daily activities [2].

In approximately 10% of ICU-admitted patients, the brain injury progresses to brain death [13], occurring in 9–24% of successfully resuscitated OHCA patients [13,14]. The great majority of patients with predicted poor neurological outcome die following withdrawal of life-sustaining treatment (WLST) [15,16].

The consideration of WLST introduces a potential bias in reported outcomes, influenced by varying practices across different political systems. In nations where WLST is usually practised, approximately 80% of post-cardiac arrest survivors have a positive neurological outcome by six months [17,18]. In contrast, a prospective study conducted in Italy, where WLST was not routinely practised, revealed contrasting results: while there was a relatively high survival rate of 60%, 47% of patients experienced an unresponsive wakefulness state, 19% had severe disabilities and only 32% achieved a favourable neurological outcome [19]. This disparity underscores the significant impact of WLST practices on reported neurological outcomes following cardiac arrest (CA), highlighting the need for standardized approaches and clear reporting in clinical studies.

2. Post-resuscitation care

After achieving ROSC following CA, intensive care management becomes essential and significantly influences both survival and neurological outcomes [20]. Current guidelines offer limited strong recommendations on post-CA care, reflecting the uncertainty in available evidence [21,22], which contributes to considerable variability in clinical practices [15,23].

Key recommendations focus on preventing secondary brain injury post-CA, emphasizing temperature control (TC), treatment of seizures, as well as the maintenance of normal physiological parameters [24]. These strategies are pivotal in improving patient outcomes and guiding clinical management following successful resuscitation from CA (figure 1).

2.1. Temperature

While the modern concept of therapeutic hypothermia as a neuroprotective strategy dates back to Fay's study in the 1941s [25], it was only about 20 years ago that international guidelines began recommending TC of 32°C to 34°C as a standard of care in post-resuscitation care of OHCA [26].

In 2002, two randomized clinical trials (RCTs) were published reporting benefits on survival [27] and neurological function [27,28] in patients resuscitated after CA due to ventricular fibrillation treated with moderate hypothermia (32–34°C) for 12–24 h [27,28]. The beneficial effects of hypothermia are attributed to several mechanisms: firstly, it prevents adenosine triphosphate (ATP) depletion by blocking specific intracellular signalling pathways; secondly, it modulates the inflammatory response by promoting the production of anti-apoptotic proteins, decreasing complement activation [29], thereby reducing overall inflammation and excitotoxic neurotransmitter release [30].

Research conducted in animal models indicates that body temperature may affect the extent of brain damage following global ischemia [31–33], particularly highlighting the detrimental effects of hyperthermia [33]. Similar associations between hyperthermia and worse neurological outcomes have been observed in humans experiencing various brain injuries, including CA [34,35]. Conversely, hypothermia has been shown to exert protective effects in numerous animal models [33,36].

Historically, therapeutic hypothermia has been divided into: mild (34.5–36.5°C), moderate (34.5–32°C), marked (28–32°C) and profound hypothermia (<28°C) [37]. Nowadays, the term 'therapeutic hypothermia' has been replaced by TC, which implies a broader range for controlling body temperature [38], reflecting a reevaluation of the target temperature management (TTM) concept.

Recent human studies on TTM have shown contrasting results. On the one hand, the Therapeutic Hypothermia after Cardiac Arrest in No shockable Rhythm (HYPERION) trial randomized 581 patients who had been resuscitated from CA with non-shockable rhythm and compared a TTM of 33°C to a TTM of 37°C. This trial reported that hypothermia at 33°C for 24 h improved neurological outcomes at 90 days (10.2% in hypothermia group versus 5.7% in the normothermia group), while overall mortality was similar between the groups (81.3% in hypothermia group and 83.2% in the normothermia group) [39]. It is worth noting that the potential benefits of TTM at 33°C were predominantly observed in patients with in-hospital CA, whereas the difference between the intervention groups in the OHCA cohort was only 2%. However, the study's data are inconsistent, as evidenced by a fragility index of 1, which indicates a high risk of missing significant outcomes at follow-up [39].

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Furthermore, many studies have failed to demonstrate the beneficial effects of hypothermia. The international TTM trial conducted in 2013 in comatose survivors of CA treated with hypothermia at 33°C compared with controlled temperature at 36°C found no significant differences in outcomes related to survival and neurological function [6].

More recent findings from the TTM2 trial also support this trend, comparing TTM at 33°C with active fever prevention. This trial found no significant differences in mortality or neurological outcomes between patients treated with TTM at 33°C and those receiving active fever control (< 37.5°C). However, it did highlight a notable increase in arrhythmias and haemodynamic instability in the hypothermia group [40].

Furthermore, six RCTs investigating prehospital cooling strategies failed to demonstrate any benefit from early induction of hypothermia [38,41–45].

A recent meta-analysis published in 2022, pooling data from the TTM and TTM2 trials involving 2800 patients, similarly concluded that hypothermia at 33°C did not reduce six month mortality compared with normothermia following OHCA [46].

A recent meta-analysis published in 2024, which analysed data from the TTM2 trial and the HYPERION trials, included 912 survivors from OHCA with initial non-shockable rhythm and divided them into hypothermia and normothermia groups. This analysis reported that hypothermia at 33°C did not significantly improve survival or functional outcomes [47]. Additionally, no difference in mortality at three months (80.1% versus 82.1% risk ratio (RR) with hypothermia: 1.04; 95% CI, 0.89–1.20; $p = 0.63$) or functional outcomes (hypothermia 90% versus normothermia 82.2%, RR with hypothermia: 0.99; 95% CI, 0.87–1.15; $p = 0.97$) between groups was shown [47].

The optimal timing for TC remains uncertain. Simpson *et al*. [48] in a recent *post hoc* analysis of the TTM2 trial, explored different effects between a strategy involving target temperature of 33°C followed by controlled rewarming versus normothermia with a strict fever control. Despite the hypothesis that faster cooling might lead to neuroprotective effects after CA with hypoxic brain injury, the results showed no significant differences in outcomes (mortality or neurological function at six months) between the hypothermia and normothermia groups. Additionally, no superior outcomes were observed in patients who were rapidly cooled compared with those in the normothermia group. Interestingly, a sub-analysis within the hypothermia group revealed higher mortality in patients that were cooled faster.

Based on low-certainty evidence, recent guidelines stress on the importance of fever avoidance and active treatment [21]. The more recent guidelines for comatose patients after CA, co-issued by the European Resuscitation Council (ERC) and the European Society of Intensive Care Medicine (ESICM), mention continuous monitoring of temperature and active prevention of fever, defined as a temperature > 37.7°C, for at least 72 h. However, due to insufficient evidence, no recommendation is made either for or against targeted temperature control within the range of 32–36°C or early induction of cooling after CA. Furthermore, active rewarming to achieve normothermia after mild hypothermia and prehospital cooling with rapid infusion of large volumes of cold intravenous fluids after ROSC are not recommended [49]. Table 1 summarizes the key evidence on TC in post-CA patients.

Extensive research is needed to better understand pros and cons of TTM in comatose patients after CA, including the potential therapeutic window within achieving hypothermic TTM, as well as its integration into a structured neuro-prognostication protocol.

2.2. Sedation and analgesia management

After OHCA, sedation is often required for patients treated with mechanical ventilation (MV) or TTM to provide comfort and optimize ventilator synchrony. Although there are comprehensive guidelines on sedation and pain management for critically ill ICU patients [50,51], specific knowledge to the OHCA population is limited.

Sedation in the OHCA population has unique challenges, including the exclusion from the standard sedation scale as Richmond Agitation Sedation Scale (RASS) because these patients are often brain injured and comatose, making it difficult to differentiate between the sedation dose and the degree of unresponsiveness [52]. In addition, data on sedation in critically ill patients after OHCA are difficult to collect because guidelines for treating pain, sedation and delirium in critically ill patients explicitly exclude brain-injured patients receiving TTM, a common therapeutic strategy to mitigate anoxic brain injury [50].

To achieve analgesia and sedation, opioid analgesics such as fentanyl or remifentanil infusion are considered first-line treatments for patients after CA undergoing MV or TTM [53]. If these are insufficient, sedative-hypnotics with amnestic and antiseizure effects such as propofol or benzodiazepine are commonly used [54], with propofol usually preferred due to its shorter duration of action compared with benzodiazepines.

Recently, new evidence explored the use of volatile anaesthetics for sedation of patients in ICU. A recent study compared a TTM (32–34°C) method with standard intravenous sedation to a modified TTM (34–36°C) method along with sevoflurane sedation. The study found that the incidence of delirium was significantly lower ($p = 0.001$) in OHCA patients treated with sevoflurane and modified TTM (16.1% versus 37.3%). In addition, a shorter duration for MV and ICU length of stay was observed with sevoflurane and modified TTM, though no significant difference in mortality was noted [55].

Ketamine and dexmedetomidine may also be considered. Dexmedetomidine is preferred in the case of light sedation in awake patients, because it does not affect the respiratory drive. Ketamine has varying effects depending on the dose: it provides mild sedation, anti-shivering and analgesic effects at low doses, while higher doses can induce complete sedation or anaesthesia.

As with any pharmacological therapy, side effects especially the haemodynamic and neurological ones, must be considered. Analgesic and sedative drugs in fact often reduce sympathetic tone, resulting in vasodilation, hypotension, bradycardia up to even a low cardiac output state. In cases of haemodynamic instability, ketamine may be a suitable choice because of its sympathomimetic effects. On the contrary, dexmedetomidine may pose a higher risk of hypotension and bradycardia due to

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Table 1. Randomized controlled trials and meta-analysis on temperature control and main results. CA, cardiac arrest; CI, confidence interval; HR, hazard ratio; OHCA, out-of-hospital cardiac arrest; OR, odds ratio; RR, risk ratio; TTM, targeted temperature management.

study title	authors	year	methods	interventions	primary outcome measures	secondary outcome measures	conclusions
randomized controlled trials							
mild therapeutic hypothermia to improve the neurologic outcome after CA [27]	hypothermia after cardiac arrest study group	2002	analysis of neurologic outcome and mortality at six months after CA in patients treated with therapeutic hypothermia over a period of 24 h or to receive standard treatment with normothermia	136 patients (75 patients in the hypothermia group at 32–34°C measured in the bladder versus 54 in the normothermia group)	patients in the hypothermia group had a favourable neurologic outcome in comparison to the normothermia group (RR, 1.40; 95% CI, 1.08–1.81)	mortality at six months was 41% in the hypothermia group versus 55% in the normothermia group (RR, 0.74; 95% CI, 0.58–0.95)	hypothermia increased the rate of a favourable neurologic outcome and reduced mortality
treatment of comatose survivors of OHCA with induced hypothermia [28]	Bernard *et al.*	2002	survival evaluation and neurological outcome of patients after CA treated with hypothermia or normothermia	77 patients (43 patients treated with hypothermia at 33°C for 12 h and 34 patients treated with normothermia)	49% patients treated with hypothermia survived and had a good outcome as compared with 26% treated with normothermia ($p = 0.046$)	good outcome was observed for hypothermia group as compared with normothermia group (OR, 5.25; 95% CI, 1.47–18.76; $p = 0.011$)	hypothermia appears to improve outcomes in patients with coma after resuscitation from OHCA
targeted temperature management at 33°C versus 36°C after cardiac arrest [6]	Nielsen *et al.*	2013	analysis of mortality and neurologic function at 180 days after OHCA in patients treated with TTM at either 33°C or 36°C	939 patients (473 in the 33°C group and 466 in the 36°C group)	at the end of the trial, 50% mortality in the 33°C group versus 48% in the 36°C group (HR, 1.06; 95% CI, 0.89–1.28; $p = 0.51$)	at 180 days, 54% in the 33°C group versus 52% in the 36°C group had died or had poor neurologic function (RR, 1.02; 95% CI, 0.88–1.16; $p = 0.78$)	hypothermia at a targeted temperature of 33°C did not confer a benefit as compared with 36°C
targeted temperature management for cardiac arrest with non-shockable rhythm [38]	Lascarrou *et al.*	2019	evaluation of mortality, safety and neurological outcome of patients after CA treated with hypothermia (33°C for 24 h) or normothermia (37°C)	581 patients (284 in the hypothermia group versus 297 patients in the normothermia group)	at day 90, 10.2% in the hypothermia group versus 5.7% in the normothermia group were alive with a good neurological outcome (difference, 4.5%; 95% CI, 0.1–8.9; $p = 0.04$)	mortality at 90 days did not differ significantly between groups (81.3% in hypothermia versus 83.2% in normothermia; difference, −1.9%; 95% CI, −8.0 to 4.3)	hypothermia at 33°C for 24 h led to a higher percentage of patients who survived with a favourable neurological outcome at day 90 compared with targeted normothermia
hypothermia versus normothermia after OHCA [39]	Dankiewicz *et al.*	2021	analysis of mortality and functional outcome at six months after OHCA in patients treated with targeted hypothermia at	1850 patients (925 in the hypothermia group and 881 in the normothermia group)	at six months, 50% mortality in the hypothermia group versus 48% in the normothermia group (RR, 1.04; 95% CI, 0.94–1.14; $p = 0.37$)	488 of 881 patients (55%) in the hypothermia group and 479 of 866 patients (55%) in the normothermia group had	targeted hypothermia did not reduce the incidence of death by six months compared with targeted normothermia

(*Continued*.)

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Table 1. (*Continued.*)

			33°C, followed by controlled rewarming, or targeted normothermia with early treatment of fever (body temperature, ≥37.8°C)			moderately severe disability (RR, 1.00; 95% CI, 0.92–1.09). Arrhythmia resulting in haemodynamic compromise was more common in the hypothermia group than in the normothermia group (24% versus 17%, $p < 0.001$)	
meta-analysis							
hypothermic versus normothermic temperature control after CA [46]	Holgersson *et al.*	2022	analysis of all-cause mortality and functional outcome at six months in patients after OHCA treated with TTM at 33°C (hypothermia) versus 36°C (normothermia)	2800 patients (1403 assigned to hypothermia and 1397 to normothermia)	death occurred for 49.4% in the hypothermia group and 47.9% in the normothermia group (RR, 1.03; 95% CI, 0.96–1.11; $p = 0.41$)	a poor functional outcome occurred for 54.3% in the hypothermia group and 54.0% in the normothermia group (RR, 1.01; 95% CI, 0.94–1.08; $p = 0.88$)	hypothermia at 33°C did not decrease six month mortality compared with normothermia after OHCA
hypothermia versus normothermia in patients with cardiac arrest and non-shockable rhythm: a meta-analysis [47]	Taccone *et al.*	2023	analysis of mortality at three months and unfavourable functional outcome at 3–6 months in unconscious patients with OHCA and an initial non-shockable rhythm	912 patients (442 assigned to hypothermia (33°C) and 470 to normothermia (36.5–37.7°C))	at three months, 80.1% mortality in the hypothermia group versus 82.1% in the normothermia group (RR, 1.04; 95% CI, 0.89–1.20; $p = 0.63$)	at the last follow-up, 90% of the hypothermia group versus 89.2% of the normothermia group had an unfavourable functional outcome (RR, 0.99; 95% CI, 0.87–1.15; $p = 0.97$)	hypothermia at 33°C did not significantly improve survival or functional outcome

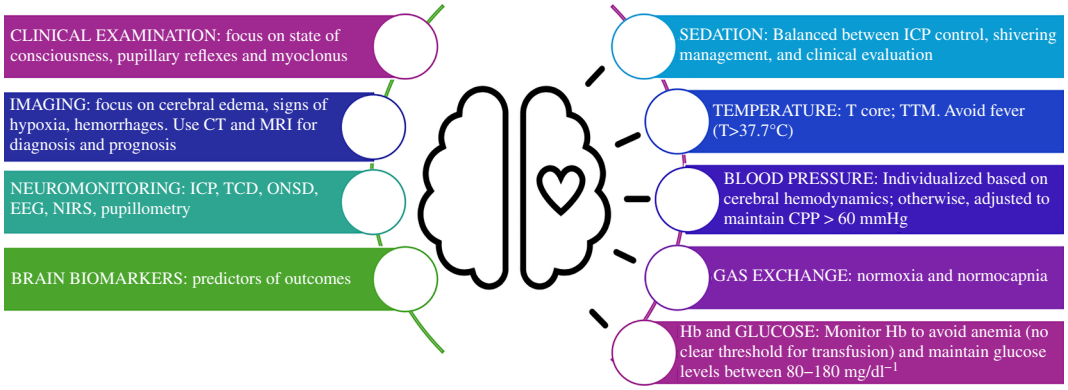

Figure 1. Brain protection after cardiac arrest. CPP, cerebral perfusion pressure; CT, computed tomography; EEG, electroencephalogram, Hb, haemoglobin; ICP, intracranial pressure; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; ONSD, optic nerve sheath diameter; TCD, transcranial Doppler; TTM: temperature target management.

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the anti-adrenergic effects [54]. A small RCT reported the need for higher doses of norepinephrine in OHCA survivors sedated with propofol–remifentanil compared with midazolam–fentanyl [56]. The haemodynamic effects are particularly important in patients with cardiogenic shock, which is not uncommon in OHCA patients. While any sedative can aggravate haemodynamic compromise, propofol and dexmedetomidine have a more pronounced effect [53].

The effects of sedation on cerebral physiology and outcomes after OHCA are yet unknown. In a mouse model of CA, early sedation at ROSC with propofol or dexmedetomidine demonstrated beneficial effects on survival when used in hypothermia-treated mice (propofol (81%) versus no sedation (25%), $p = 0.008$; dexmedetomidine (88%) versus no sedation (25%), $p = 0.002$). In addition, animals not receiving sedation developed worse neurological outcomes, cerebral hyperemia and poorer electroencephalogram (EEG) patterns [57].

In humans, evidence of neurotoxicity and neuroprotection is controversial, particularly for ketamine and propofol [58,59]. Although ketamine and propofol may act at the *N*-methyl-D-aspartate (NMDA) receptors to antagonize neuronal excitotoxicity, the translation of this concept into clinical outcomes has not been established [53].

The relationship between sedation and neuromuscular blockade (NMB) must also be considered. NMB is often used in patients receiving TTM to control shivering, necessitating a high level of sedation and analgesia to avoid awareness [60]. Post-CA patients could also develop seizures that are commonly controlled by sedatives, but sedation and NMB might mask clinical manifestations of seizures, justifying strict EEG monitoring for their detection [61].

In the post-CA population, balancing sedation is crucial. Light sedation can lead to increased intracranial pressure and cerebral oxygen consumption, while deep sedation may be necessary to avoid shivering and pain but carries the risk of complications and precludes clinical assessment. Currently, the STEPCARE trial, an ongoing international study (NCT05564754) started in 2023, aims to analyse the effects of three aspects of standard care (temperature, mean arterial pressure (MAP) and sedation) that might protect against secondary brain damage in survivors of OHCA. Regarding sedation, the trial aims to compare the effects of continuous sedation for 36 h with a RASS target of −4 or −5 versus minimal sedation with a RASS target of −2.

After OHCA, sedation is often needed but the delicate balance between right drugs, timing and dosage is yet uncertain. New knowledge on sedation effects in post-CA patients is thus warranted with also a comparison between the effects of continuous vs minimal sedation.

2.3. Blood pressure management

The 2021 ERC guidelines recommend avoiding a MAP < 65 mmHg in post-CA patients during their ICU stay [21]. This recommendation, adapted from sepsis guidelines, has been questioned due to the unique characteristics of post-CA syndrome. Secondary brain tissue hypoxia occurs after CA [62,63] leading to development of cerebral penumbra, which is at risk for additional ischemic damage in the case of suboptimal perfusion and brain oxygenation [64]. Since MAP is crucial for brain oxygen delivery, influencing cerebral perfusion pressure (CPP), and intracranial pressure (ICP), maintaining an adequate cerebral perfusion is essential for post-CA patients. Mild hypotension can risk brain hypoperfusion, especially in cases of impaired cerebral autoregulation, high ICP, or cerebral oedema [65]—conditions commonly found in post-CA syndrome.

During the first 6–12 h of ICU stay, post-CA patients treated with a target MAP of 65 mmHg experienced a profound decrease in cerebral oxygenation, known as the 'delayed hypoperfusion phase', which can cause additional cerebral damage and worse prognosis [66]. In patients with chronic hypertension, compensatory cerebrovascular autoregulatory responses may be compromised and the lower threshold of cerebrovascular autoregulation may be right-shifted, reducing the range of MAPs in which cerebral blood flow (CBF) remains constant [67], suggesting a potential benefit from higher MAPs to maintain adequate cerebral perfusion [68–70].

Recent studies on blood pressure thresholds during post-OHCA care in the ICU have reported that low MAP is associated with worse outcomes [71,72], while higher MAP values are associated with better neurological outcomes [73]. Laurikkala *et al*. [72] found that in patients with poor neurological outcomes, the lowest MAP during the first 6 h was 58 mmHg (interquartile

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range (IQR), 56–61), compared with 61 mmHg (IQR, 59–63) in those with good outcomes ($p < 0.01$). The lowest MAP was independently associated with poor outcomes (odds ratio (OR), 1.02 per mmHg; 95% CI, 1.00–1.04; $p = 0.03$).

Besides, Russo *et al*. [74] found a significant association between higher rates of severe neurological dysfunction (cerebral performance category (CPC) > 3) when MAP thresholds were < 75 mmHg. Roberts *et al*. [73] observed that elevated blood pressure during the initial 6 hours after OHCA was independently associated with good neurologic function at hospital discharge, with a high MAP (over 90 mmHg) associated with good neurologic function (adjusted RR: 2.46; 95% CI, 2.09–2.88).

Recent RCTs have compared different MAP targets [75–77]. The COMACARE (Carbon dioxide, Oxygen and Mean arterial pressure After Cardiac Arrest and Resuscitation) trial compared low normal (65–75 mmHg) versus high normal (80–100 mmHg) MAP values, reporting that a MAP range during post-resuscitation intensive care was reasonable without affecting brain markers like neuronal specific enolase (NSE) concentration at 48 h [75]. The Neuroprotect trial randomized patients to a MAP of > 65 mmHg versus 85–100 mmHg, aiming to investigate whether early goal-directed haemodynamic optimization (MAP 85–100 mmHg, venous oxygen saturation [SvO_2] 65–75%) could improve cerebral oxygenation, reduce anoxic brain damage and improve outcomes. Although no significant differences were found in anoxic brain damage extension or neurological outcomes, the study demonstrated the safety of targeting higher MAPs [77].

The subsequent combined analysis [78] of the COMACARE and Neuroprotect trials [75,77] showed that targeting a MAP between 80 and 100 mmHg in patients with acute myocardial infarction (AMI) and shock was associated with a lower area under the 72 h high-sensitivity troponin-T curve (median: 1.14 μg 72 $h\,l^{-1}$ (interquartile range: 0.35–2.31 μg 72 $h\,l^{-1}$) versus median: 1.56 μg 72 $h\,l^{-1}$ (interquartile range: 0.61–4.72 μg 72 $h\,l^{-1}$); $p = 0.04$) compared with lower MAP, proving that higher MAP targets are not associated with more adverse cardiac outcomes. Another double-blind RCT compared comatose patients resuscitated after OHCA to a MAP of 77 versus 63 mmHg, finding no difference in multiple outcome measures [76].

A recent systematic review and meta-analysis on RCTs [75–77,79] proved that higher MAP target may also reduce ICU stay (MD: −0.78 with a 95% CI [−1.54 to −0.02], $p = 0.04$) and MV duration (MD: −0.91 with a 95% CI [−1.51 to −0.31], $p = 0.003$) but did not demonstrate improvements in mortality (RR, 1.07 with a 95% CI [0.91–1.27], $p = 0.4$) or neurological outcome (RR, 1.02 with a 95% CI [0.93–1.13], $p = 0.68$) [80]. A recent substudy of the BOX (Blood Pressure and Oxygenation Targets in Post-resuscitation Care) trial analysed cerebral metabolism during post-resuscitation care dividing patients into low (63 mmHg) or high (77 mmHg) MAP groups and found no significant difference in cerebral biochemical variables between the groups, suggesting that targeting a higher MAP did not affect cerebral energy metabolism within 96 h after ROSC [81].

The 2023 Scientific Statement from the American Heart Association and Neurocritical Care Society suggests individualized post-CA care, promoting invasive brain tissue oxygen monitoring. In the absence of advanced cerebral monitoring in general ICUs, a target MAP >80 mmHg is recommended [24]. The goal is to guarantee an 'optimal' CPP with a target MAP ≥80 mmHg and a CPP ≥60 mmHg in unconscious patients, while MAP targets should be individualized and titrated according to neurological clinical examination in awake subjects [65].

Current guidelines present conflicting recommendations based on available evidence. The 2021 ERC guidelines recommend a MAP target of >65 mmHg [21], while the more recent American Heart Association guidelines suggest aiming for a MAP >80 mmHg [24]. However, it is important to note that evidence from RCTs does not conclusively support either approach. Niemelä *et al*. [74] recently compared higher MAP targets (>65 mmHg) with lower targets (<65 mmHg), finding no significant differences in mortality (RR, 1.08; 95% CI, 0.92 – 1.26) or poor neurological outcomes (RR, 1.01; 95% CI, 0.86–1.19).

As such, new knowledge is expected from the ongoing STEPCARE trial (NCT05564754), which will analyse the effects of higher versus lower blood pressure targets on mortality and neurological function in post-CA patients.

2.4. Gas exchanges

After resuscitation from CA, patients often experience pathophysiological derangements, such as brain oedema, reperfusion injury and oxidative stress, which can lead to neuronal damage and brain injury [82]. The majority of patients who survive CA undergo endotracheal intubation and mechanical ventilation. In these cases, an appropriate mechanical ventilation strategy is crucial to ensure optimal gas exchange while avoiding ventilator-induced lung injury and CBF impairment. A lung-protective ventilation strategy with low tidal volumes (6–8 ml kg^{-1} predicted body weight (PBW)), low positive end-expiratory pressure (≤5 cmH_2O), low plateau pressure (< 30 cmH_2O) and driving pressure (< 14 cmH_2O) is recommended [83,84].

2.4.1. Oxygenation

Both hypoxemia (PaO2 <65 mmHg) and hyperoxemia (PaO2 >100 mmHg) should be prevented in post-CA patients. Hypoxemia can lead to oxidative stress, the formation of reactive oxygen species (ROS), altered cerebral metabolism and neuronal cell damage [85]. In the EXACT trial, Bernard *et al*. [86] analysed the effect of different oxygen targets on survival and hospital discharge in OHCA patients. They reported a lower survival rate to hospital discharge (38.3%) in the group treated with lower oxygen targets (SpO2: 90–94%) compared with 47.9% in the standard care group with higher oxygen levels (SpO2: 98–100%) (difference: −9.6% (95% CI, −18.9 to −0.2%); OR, 0.68 (95% CI, 0.46–1.00); $p = 0.05$).

Many studies have described the negative association between hyperoxemia and worse outcomes [87,88]. A meta-analysis of preclinical data from animals studying the effect of hyperoxia after CA have demonstrated that hyperoxia can intensify brain damage and dysfunction [89]. In humans, small trials have reported higher levels of NSE, but not S-100B in patients treated with high fraction of inspired oxygen (FiO2) (100%) compared with those treated with small FiO2 = 30% [75]. A recent RCT analysed the effects of oxygenation after OHCA on markers of cerebral injury (NSE, S-100B), finding that moderate hyperoxia could affect near-infrared spectroscopy (NIRS) values, but no effect on NSE as a surrogate marker of anoxic brain injury [75].

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Awad *et al*. [90] found that hyperoxemia was associated with lower survival at 30 days compared with the normoxemia group (RR, 0.87; 95% CI, 0.82–0.91). Roberts *et al*. [88] reported a correlation between early exposure to high PaO2 levels (> 300 mmHg during the first 6 hours after ROSC) and poor neurological outcomes. Robba *et al*. [91] in their sub-analysis of the TTM2 trial studied oxygenation during the first three days of mechanical ventilation in OHCA patients and found a U-shaped association between hypoxemia (cutoff < 69 mmHg; RR, 1.009; 95% CI, 0.93–1.09) or hyperoxemia (cutoff > 195 mmHg; RR, 1.006; 95% CI, 0.95–1.06) and mortality at six months, suggesting individualized titration of oxygen delivery in these patients. The BOX trial examined the effects of two oxygenation strategies in comatose patients after resuscitation from CA: a restrictive approach with low-normal PaO2 (9–10 kPa) and a liberal approach with high-normal PaO2 (13–14 kPa). Researchers found no significant difference in the primary outcome (death or worse neurological outcome) between the two groups (32% in the restrictive target group versus 33.9% in the liberal target group; HR, 0.95; 95% CI, 0.75–1.21; $p = 0.69$). This was confirmed in the 90 day analysis, where death occurred in 28.7% of the low-normal target group and 31.1% of the high-normal target group [92].

It remains uncertain whether oxygenation and ventilation targets should be adapted in patients undergoing TTM. The 2015 ERC-ESICM guidelines recommend oxygen saturation values of 94–98% after OHCA [93]. More recently, the 2021 update of ERC-ESICM guidelines declared a target PaO2 of 75–100 mmHg, as preferable [21].

2.4.2. Carbon dioxide

The optimal target for carbon dioxide levels in post-CA patients remains controversial [73,94]. There is a strict relationship between $PaCO_2$ and CBF [95]. High $PaCO_2$ levels cause brain vasodilation, while low $PaCO_2$ leads to vasoconstriction, increasing the risk of cerebral ischemia. Standard $PaCO_2$ values may be inadequate to achieve adequate CBF and oxygenation when cerebral hypoperfusion and reduced cerebrovascular autoregulation occur [24].

A wide observational cohort study evaluated the relationship between $PaCO_2$ and outcomes in post-CA patients. The results reported higher mortality rates in the hypocapnia group compared with the normocapnia group (OR, 1.12; 95% CI, 1.00–1.24; $p = 0.04$) and a lower rate of discharge home (OR, 0.81; 95% CI, 0.70–0.94; $p < 0.01$). Nevertheless, no difference in mortality was found between the hypercapnia group and the normocapnia group (OR, 1.06; 95% CI, 0.97–1.15; $p = 0.19$), but a higher rate of discharge home (OR, 1.16; 95% CI, 1.03–1.32; $p = 0.01$) characterized the hypercapnia group [96].

Similarly, Helmerhorst *et al*. [97] described that hypocapnia was significantly associated with in-hospital mortality ($p < 0.001$), but no association was seen for hypercapnia. Okada *et al*. [98] found that poor neurologic status at one month was more likely in patients with severe hypocapnia (< 25 mmHg) (OR, 6.68; 95% CI, 2.16–20.67), mild hypocapnia (25–35 mmHg) (OR, 2.56; 95% CI, 1.30–5.04) and severe hypercapnia (> 55 mmHg) (OR, 2.62; 95% CI, 1.06–6.47) compared with mild hypercapnia. Mild hypercapnia, which has anti-inflammatory and anti-oxidant effects [99], has been suggested to improve cerebral perfusion [100].

The recent TAME study, evaluating the effect of mild hypercapnia on patient outcomes in comatose patients resuscitated after OHCA, found no benefit in neurological outcome at six months in patients treated with mild hypercapnia compared with normocapnia (RR, 0.98; 95% CI, 0.87–1.11; $p = 0.76$) [100].

Specific carbon dioxide thresholds in OHCA patients are not yet defined. Current knowledge recommends normocapnia in patient with acute brain injury [65]. Therefore, normocapnia should be aimed for in critically ill patients after CA to protect the brain.

2.5. Glucose levels

Glucose levels in critically ill patients affect mortality and are the pivotal source of energy for the brain. Both severe hyperglycemia and hypoglycemia are considered potentially dangerous and needed to be avoided [101,102]. After ROSC, the global ischemia-reperfusion state can affect endocrine organs, leading to reduced hormonal production, such as insulin and glucagon-like peptide-1 (GLP-1) [102]. Pharmacological treatments such as epinephrine during resuscitation manoeuvres may also influence glycemia levels [102]. Hyperglycemia is common in patients after OHCA [103], can be influenced by phase of TTM [104] and is associated with poor outcomes [102]. However, it is unclear whether poor neurological outcomes are directly due to hyperglycemia, the severity of illness or ICU care [105–107]. Conversely, hypoglycemia can also worsen secondary brain injury [101]. Conventional glucose control (140–180 mg dl^{-1}) is recommended over intensive glucose control (81–108 mg dl^{-1}) in general critically ill patients according to current Society of Critical Care Medicine and American Society for Parenteral and Enteral Nutrition guidelines [108]. Accordingly a small RCT conducted in CA survivors compared strict (72–108 mg dl^{-1}) with moderate (108–144 mg dl^{-1}) glucose control, reporting no mortality benefit at 30 days with a strict glucose control strategy [109]. In patients with brain impairment, strict glycemic control may not significantly improve outcomes and could potentially increase the risk of hypoglycemia [110], which can alter brain metabolism [111]. A threshold of euglycemia (80–180 mg dl^{-1}) is reasonable in cases of acute brain injury [65] and this same threshold seems reasonable for CA survivors to protect the brain. Given the low certainty of evidence, endocrine management and fluid resuscitation are important themes for further investigations.

2.6. Sodium levels

Serum sodium, as a key determinant of free water shifts and intracellular hydration, has a significant impact on brain volume, potentially affecting patient outcomes following CA [112]. However, there are limited studies on natremia in comatose patients post-CA. In a large observational study, Shida *et al*. [113] reported that a higher survival rate (17.6% versus 8.2% and 5.7%) with

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a favourable outcome in patients with normonatremia compared with those with hypo- or hypernatremia. Similarly, Cho *et al*. [114] in a retrospective study demonstrated an association between early hypernatremia and a lower likelihood of favourable functional outcomes one year after CA (adjusted OR for each 1 mmol l^{-1} increase in sodium level: 1.13; 95% CI, 1.04–1.23; p = 0.004). Lascarrou *et al*. [115] in a recent *post hoc* analysis explored the relationship between dysnatremia and neurological outcomes and mortality after CA. They found that hyponatremia was linked to worse functional outcomes at six months (24% of patients in the hyponatremia group achieved CPC 1 or 2 versus 41% in the normonatremia group; p = 0.001; adjusted OR, 0.45; 95% CI, 0.26–0.79; p = 0.005).

Despite these findings, further research is needed to fully understand the relationship between brain injury following CA and dysnatremia. Based on current knowledge, maintaining normonatremia (135–145 mmol l^{-1}) seems reasonable to prevent secondary brain injury in post-CA patients.

2.7. Haemoglobin levels

Haemoglobin (Hb) is crucial for tissue oxygen delivery (DO_2) and cerebral brain oxygen saturation [116]. Avoiding secondary brain injury is a key goal in post-CA resuscitation care. Among CA survivors, anaemia is considered to play an important role in the development of secondary brain injury [117]. Low Hb levels are indeed correlated with brain hypoxia, cell energy impairment and worse outcomes [118]. Several retrospective studies have found an association between Hb levels and outcomes among CA survivors [119–122].

Kim *et al*. [121] in their analysis showed a better neurological outcome at hospital discharge in patients with higher levels of Hb in comparison to those with lower Hb levels (14.4 ± 2.0 versus 12.8 ± 2.5 g dl^{-1}; $p < 0.001$). Johnson *et al*. [122] confirmed these findings. Albaeni *et al*. [120] conducted a study on post-CA patients and reported that post-ROSC Hb levels above 10 g l^{-1} were related with better neurological outcome (OR, 8.31; 95% CI, 1.89–36.52; p = 0.005). In agreement with these results, Wormsbecker *et al*. [119] described a relationship between lower Hb values (107 versus 115 g l^{-1}; p = 0.05) and worse neurological outcome at 48 hours (OR, 0.69; 95% CI, 0.54–0.88; $p < 0.01$) and seven days (OR, 0.75; 95% CI, 0.57–0.97; p = 0.03) in hypoxic-ischemic brain injury (HIBI) after OHCA.

Current knowledge about the optimal Hb threshold for post-CA patients or those with brain impairment is limited and research is needed. A threshold of Hb above 7 g dl^{-1} seems reasonable [116] following guidelines for general critically ill patients [123], to optimize cerebral oxygen delivery [24]. However, this statement should be further discussed. A recent study measured Hb levels using regional cerebral oxygenation (rSO_2) during the first day of ICU stay during TTM and described a linear correlation between Hb levels and mean rSO_2. A Hb level below 12.3 g dl^{-1} was associated with worse neurological outcomes in patients with SvO_2< 70% or low rSO_2 (< 62.5%) [117], suggesting that a routine restrictive transfusion threshold of 7 g dl^{-1} may be inadequate for these patients [117].

3. Managing specific cerebral complications

After CA, brain injury is a frequent complication representing the major cause of death and disability [103]. The pathophysiology of HIBI after CA involves a heterogenous cascade that results in both primary and secondary injuries. The damage consists of two phases: the first, primary injury due to the global brain ischemia because of no flow to the brain and the reperfusion and the second, secondary injury, due to ongoing ischemia, brain oedema, elevated ICP and hypoperfusion and seizures, oxidative injury, hyperpyrexia which occur hours to days after ROSC [124].

3.1. Seizures

After OHCA, as a result of HIBI, the frequency of seizure is estimated from 9% to 36% independent of TTM [125–127]. Seizures can have harmful effects on patients, leading to additional neurological damage [127]. Seizures can occur any time after CA [126–128].

Seizure diagnosis is primarily clinical in cases of generalized or focal convulsions or myoclonic activity, but in patients after OHCA sedation and NMB can mask clinical presentation, making EEG the only reliable detection method [128].

Knowledge about the treatment of post-CA seizures is derived from a few retrospective studies. Kim *et al*. [106] reported a correlation between anticonvulsant treatment and poor neurological outcome (OR, 1.69; 95% CI, 1.03–2.77). Recently, Ruijter *et al*. [129] in the TELSTAR study analysed neurological outcome of patients after OHCA randomly assigned to a suppressing rhythmic and periodic EEG activity with antiseizure medication for at least 48 h or to standard care group. Although no difference in mortality (80% versus 82%) or outcome (90% versus 92%) at three months was shown between the antiseizure treatment group and the control group respectively, a predefined subgroup analysis (with a limited sample size) suggested a potential difference across the two groups not allowing definitive conclusions. In addition, it is worth considering that the small sample size and challenges in detecting clinically significant effects, as accepted by most clinicians, likely resulted in the analysis being underpowered.

Additional research on this topic is needed to better understand the impact of anticonvulsant drugs, whether, when and how to treat seizures in patient who have undergone CA to optimize outcomes.

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4. Brain monitoring

Monitoring methods are necessary to guide clinicians in detecting and quantifying cerebral injury processes after OHCA. Clinical examination and neuroimaging studies, invasive and non-invasive neuromonitoring methods and serum biomarkers can help predict outcomes in comatose resuscitated patients.

4.1. Clinical neurological examination

Clinical neurological examination, especially evaluating pupillary light reflex (PLR) [93,130], corneal reflex, motor response to pain and myoclonus, is a key component of the prognostic assessment of CA patients. To avoid false predictions, it is necessary to exclude or minimize confounding factors such as temperature and sedation before performing a clinical examination on comatose patients after CA, even if it means postponing the evaluation. In patients who underwent TTM, clinical evaluation is usually performed at 72 h after rewarming or later (up to 118 h after ROSC) [6,131].

The PLR should be assessed daily, but its absence during the first 24 h after ROSC should not be considered definitive, as it could lead to a false prediction of poor outcome in 30% of subjects [132]. However, a bilaterally absent PLR after 72 h is considered highly specific for poor neurological outcome [131,133]. Due to the risk of subjectivity, quantitative pupillometry is suggested if available [134]. Corneal reflex may also be evaluated as its absence is related to worse outcomes, although its specificity is considered lower than PLR [135]. In addition, PLR is not affected by NMB.

Motor response to pain (absent or in extension) at ≥72 h from ROSC is considered sensitive of poor outcome [136]. Myoclonus, especially prolonged (>30 min), should be evaluated in comatose patients after CA as predictor of poor outcome [137]. Care must be taken not to confuse myoclonus from a particular form of post-anoxic myoclonus: the Lance–Adams syndrome (LAS) [138]. LAS in fact is related with a generally favourable prognosis. An EEG recording is crucial in evaluating post-hypoxic myoclonus and predicting outcome as it may help distinguish LAS from more malignant forms of myoclonus [139].

Based on these considerations, current guidelines recommend that clinical neurological examination should be performed daily to early detect signs and symptoms of neurological recovery [134]. It is well known that clinical examination may be tainted by confounding factors such as sedation and NMB. So that, short-acting agents are preferable.

4.2. Imaging

Brain CT, broadly used after CA, represents an important instrument for evaluating neurological causes of arrest [140] and measuring the severity of PCABI and brain oedema: the vasogenic oedema with sulcal effacement, restricted cerebral ventricle size and decreased density ratio between grey and white matter (GWR) and the cytotoxic oedema due to the neuronal swelling [141].

An important sign on brain CT is represented by a reduced visibility of the grey/white matter interface because of a decreased density ratio between grey (neurons) and white (axons) matter.

Although brain oedema is invariably associated to poor outcome, the prognostic value of GWR on brain CT in predicting neurological outcomes in OHCA patients is uncertain and discussed because of different measurement techniques and its intrinsic nature of a continuous variable. Lee *et al.* [142] demonstrated a poor predictive performance of GWR due to extremely low sensitivity (3.5–5.6%). Hong *et al*. [143] found no significant correlation ($p = 0.727$) between GWR and neurological outcomes in subjects treated with TTM after CA. Kirsch *et al.* [144] defined GWR as a highly specific prognostic value. Current guidelines consider that a diffuse pattern of GW differentiation with sulcal effacement performed at least 48 h from ROSC may be considered a moderately reliable predictor of poor functional outcome at three months [134].

Magnetic resonance imaging (MRI) could be useful for analysing cytotoxic oedema and its hyperintensity on diffusion weighted imaging (DWI) with the corresponding hypoattenuation on apparent diffusion coefficient (ADC) values [138]. Although a defined threshold for predicting outcome is not yet established, some studies have considered it [145,146]. Hirsch *et al.* [146] evaluated the prognostic value of DW-MRI for comatose patients after CA finding that an ADC $< 650 \times 10^{-6}$ mm^2 s^{-1} in >10% of brain tissue is highly predictive for poor outcome in comatose patients after CA, with a sensitivity of 0.63 (95% CI, 0.42–0.80), a specificity of 0.96 (95% CI, 0.77–0.998) and a positive predictive value of 0.94 (95% CI, 0.71–0.997). A recent meta-analysis by Lopez Soto *et al*. [145] evaluating the accuracy of CT and MRI in neuro-prognostication after CA found GWR on CT (20 studies) useful for predicting poor neurological outcome (sensitivity 0.44, 95% CI, 0.29–0.60; specificity 0.97, 95% CI, 0.93–0.99) as well as DWI on MRI (16 studies; sensitivity 0.77, 95% CI, 0.65–0.85; specificity 0.92, 95% CI, 0.85–0.96).

The optimal timing of imaging studies as prognosticators is not yet defined. Although brain CT can show early (<1 h after ROSC) signs of severe brain injury [142], some studies described late signs (2–6 days after ROSC) [147] suggesting that serial CT scans may increase its sensitivity for predicting poor outcome [148]. For MRI, signs of altered diffusion are more evident during the first three days after ROSC [149]. In *et al*. [150] compared the ability of brain CT and MRI in predicting neurologic outcomes in OHCA survivors, reporting that MRI and a delayed CT scan (72–96 h after the ROSC) may help predict poor neurological outcomes in patients after OHCA treated with TTM. More research is needed to better understand the prognostic role of imaging in comatose patients after OHCA.

4.3. Neuromonitoring

The majority of mortality in survivors after OHCA admitted to an ICU is due to HIBI [138]. This condition can be associated with seizures, brain oedema, altered cerebral autoregulation and brain tissue hypoxia, which may aggravate brain injury. EEG

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is useful in HIBI for an early seizure detection; while monitoring ICP, TCD, brain tissue oxygen (PbtO2) and NIRS can provide information on brain oxygenation and perfusion. Neuromonitoring is vital for limiting brain damage during post-resuscitation care [21,138].

Various methods, both invasive (ICP monitoring, cerebral microdialysis and direct $PbtO_2$ monitoring) and non-invasive (quantitative infrared pupillometry, TCD, ONSD ultrasound, NIRS and NPi monitoring), can be used [151]. This review focuses on non-invasive and bedside monitoring methods.

4.3.1. Brain oedema and elevated intracranial pressure

Cerebral oedema, both cytotoxic and vasogenic, can develop early after CA or during the rewarming phase if hypothermia is applied, and is related to worse outcomes [146,152]. During secondary and primary injury in HIBI, endothelial dysfunction leads to a porous blood brain barrier, permitting extravasation and the formation of cerebral oedema [153]. Metter *et al*. [154] analysed the brain oedema on CT after CA, demonstrating that patients with severe cerebral oedema had higher mortality. Reducing oedema should theoretically improve cerebral physiology, enhancing CBF and ICP.

The same brain oedema could be the cause for intracranial hypertension after CA. ICP elevation > 20 mmHg occurs in a subset of patients during both hypothermia and rewarming, and like cerebral oedema, is associated with poor outcomes [63,155,156]. In the absence of a specific invasive ICP monitoring, ICP could be hypothesized through imaging (i.e. cerebral oedema on CT or optic nerve sheath diameter (ONSD) at transcranial Doppler (TCD)) or through typical signs (i.e. loss of pupillary reflex) [70,155,156]. Few studies have investigated ICP monitoring in the OHCA population, and current evidence does not demonstrate whether it improves outcomes [157,158]. However, ICP monitoring may be particularly beneficial in specific populations, such as those with acute brain injury [159]. Although the ICP limit considered reasonable after CA is not well established, a threshold of ICP < 20 mmHg adapted from traumatic brain injury is considered prudent [95].

There is limited data on brain oedema in patients with CA and more research is needed to better understand timing, therapy and then patient outcomes. The lack of sufficient knowledge prevents the development of a specific management strategy for brain oedema in patients following CA; however, an individualized post-resuscitation ICU care, focusing on the physiological parameters, such as pH, pCO_2, blood pressure, body temperature, body position and serum osmolality, which could influence brain oedema development, is crucial [153,160,161]. Moreover, strict monitoring with non-invasive measurements bedside, such as TCD and quantitative pupillometry, may significantly guide patient care [162].

4.3.2. Electroencephalogram

Immediately after ROSC, the amplitude of EEG is often depressed or discontinuous. While patterns like suppression (background amplitude below 10 µV in the entire EEG record) or burst-suppression can still be compatible with long-term recovery, they almost invariably predict poor neurological outcomes if recorded 24 h after ROSC [163,164]. Conversely, an early continuous and normal-amplitude EEG predicts a favourable outcome [165].

In comatose patients following CA, EEG plays a crucial role in detecting and managing seizures, which can occur in up to 30% of cases with HIBI and are frequently non-convulsive [166]. Seizures post-CA are strongly associated with poor neurological outcomes, particularly when they occur soon after ROSC. EEG is also valuable in identifying covert consciousness and electrographic patterns associated with recovery in patients with post-anoxic myoclonus [167].

Continuous EEG monitoring is more sensitive than intermittent EEG for detecting epileptiform activity after CA [168]. However, there is currently no evidence demonstrating clinical benefit or cost-effectiveness for routine use [169,170].

4.3.3. Ultrasound (transcranial Doppler and optic nerve sheath diameter)

TCD is a non-invasive bedside method used to assess cerebral haemodynamics and estimate ICP in patients after ROSC following CA [162,171]. In patients with HIBI, immediate post-ROSC hyperemia is often followed by a significant reduction in CBF, leading to changes in CBF velocities and cerebral metabolism [172]. TCD is valuable for measuring CBF velocities and assessing cerebral autoregulation in these patients [173]. Hoedemaekers *et al*. [174] and Lemiale *et al*. [175] described a transient decrease in mean CBF velocities (CBFV) in the middle cerebral artery (MCA) immediately after ROSC, with a return to normal values within 72 h. The same trend was observed in cerebral oxygen extraction fraction (CEO_2) among patients who survived after CA. Richter *et al*. [176] demonstrated high levels (> 75%) of jugular venous oxygen saturation ($SjvO_2$) in HIBI patients with poor neurological outcomes 90 days after CA and elevated NSE levels at 48 and 72 h post-CA, indicating transient reduction in cerebral metabolism after CA. TCD at bedside could be useful for assessing CBFV and rapidly detecting complications. Ultrasound can also be useful for investigating ONSD. A large ONSD is well associated with high ICP in various patient groups [177–179], including HIBI patients after CA [180]. Research has shown the association between large ONSD and poor neurological outcome after CA [181–184]. Current knowledge defines ONSD thresholds, associating values < 5.4 mm with good outcomes [183] and ONSD values > 5.11–7.0 mm with poor outcomes [184,185]. Verhulst *et al*. [186] found that combining ONSD monitoring, EEG and somatosensory evoked potential (SSEP) increased the sensitivity for reliable prediction of poor outcomes from 25% to 41%, suggesting the utility of multimodal monitoring in predicting neurological outcomes after CA.

Increased ICP is a common complication in HIBI patients after CA. Cardim *et al*. [180] demonstrated the good ability of TCD (area under the curve (AUC) = 0.91 (95% CI, 0.83–1.00)) and ONSD ultrasound (AUC = 0.96 (95% CI, 0.90–1.00)) in predicting intracranial hypertension in HIBI patients after CA. An ongoing trial (NCT04000334) is exploring the feasibility of early-goal-directed haemodynamic management guided by TCD during the first 12 hours after ROSC.

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4.3.4. Near-infrared spectroscopy

Monitoring brain oxygenation post-CA is crucial for achieving favourable neurological outcomes and survival. Near-infrared spectroscopy (NIRS) is a non-invasive method that monitors tissue oxygenation and haemodynamics by measuring the absorption of near-infrared light, like pulse oximetry. It calculates regional cerebral oxygen saturation (rSO2), which reflects the balance between oxyhaemoglobin and deoxyhaemoglobin [187,188]. In addition, NIRS may allow one to assess non-invasively cerebral autoregulation, thus contributing with a MAP challenge strategy to define the 'optimal MAP' [189].

Studies on NIRS in critically ill patients after OHCA have shown mixed results. Some studies suggest higher rSO2 levels in survivors compared with non-survivors early after OHCA, indicating a potential association with outcomes [190]. However, other research notes overlapping rSO2 ranges between outcome groups, questioning the accuracy of NIRS in predicting outcomes consistently [66,191]. Recent multicentric studies have found that early rSO2 levels post-return of spontaneous circulation correlate with good neurological outcomes [192], but these findings are not universally supported [193].

Despite these insights, uncertainties remain regarding the use of cerebral oximetry as a biomarker for guiding clinical decisions in neurological prognostication after CA. Current guidelines do not recommend its routine use in this context due to the variability in study results and the need for further validation [21,194].

4.3.5. Pupillary light reflex and neurological pupil index

Quantitative pupillometry, particularly using the neurological pupil index (NPi), offers significant advantages over traditional manual pupillary light reflex (PLR) assessments. NPi incorporates multiple pupillary variables to provide a numerical score from 0 to 5, where an NPi below 3 indicates abnormal pupillary function [195–197].

In a multicentre European study by Oddo *et al*. [198], NPi demonstrated superior predictive value for unfavourable neurological outcomes compared with standard and quantitative PLR methods (sPLR and qPLR). This superiority was observed across multiple time-points post-CA. Specifically, NPi had higher AUC values for outcome prediction: 0.77 on day 1, 0.76 on day 2 and 0.78 on day 3, compared with qPLR. Notably, an NPi ≤2 was 100% specific for predicting unfavourable outcomes as early as day 1, while bilaterally absent sPLR could lead to overly pessimistic predictions, especially in patients with small pupils. Combining NPi ≤ 2 with other neurological assessments, such as absent N20 waves in somatosensory evoked potentials (SSEPs), enhanced sensitivity for predicting poor outcomes. This underscores the clinical utility of NPi in providing precise and early prognostic information in post-cardiac arrest care.

4.3.6. Brain biomarkers

Serial biomarkers of HIBI are useful for predicting the outcome of patients who are comatose after CA. Grey and white matter involvement in brain damage after CA can be monitored through biomarkers released into cerebral spinal flow and systemic circulation. The most common biomarker used in clinical practice is NSE [199]. NSE, a dimeric enzyme mainly expressed in the grey matter (neuron cell bodies, dendrites, unmyelinated axons and glial cells) and in neuroendocrine cells, has a half-life of 24 h [200]. Current guidelines recommend NSE as a prognostic tool for HIBI, but other potentially more accurate biomarkers are under investigation [21,201]. Neurofilament light (NFL), glial fibrillary acidic protein (GFAP) and tau protein have shown potential for predicting poor neurological outcomes after CA with similar or superior accuracy to NSE [202–207].

NFL has been shown to have higher accuracy than other biochemical markers (Tau, NSE and S100) in predicting poor neurological outcomes, with significantly greater area under the ROC (AUROC) ($p < 0.001$). It is also noted for its high predictive performance as early as 24 h after CA [197]. A recent meta-analysis highlighted NFL as having the highest accuracy in predicting outcomes in HIBI patients at 48 h after ROSC, reflecting white matter damage and axonal injury [208]. However, challenges such as low availability, limited evidence compared with NSE and difficulties in measurement (due to blood levels in the range of trillionths of grams) complicate its widespread use and standardization of measurement methods among biomarkers of brain injury.

GFAP's accuracy in predicting neurological outcomes appears to improve at 48 and 72 h after CA compared with earlier time points, with AUROC ranging from 0.65 to 0.89 [207,209], although it remains less sensitive than NSE [209]. In a study by Mattsson *et al*. [204] tau was found to estimate neurological outcomes more accurately than NSE, with higher AUROC values (0.81, 0.90 and 0.91 at 24, 48 and 72 h, respectively) in later samples compared with earlier ones.

Despite these advancements, current guidelines for post-CA care only recommend NSE for predicting neurological outcomes [21].

5. Conclusion

The heart and brain have a profound interconnection, and brain injury following CA carries a significant risk of mortality. Current guidelines advocate for neuroprotective strategies aimed at mitigating secondary brain injury after OHCA, although the efficacy of some treatments remains under debate. Maintaining normal neurophysiological parameters is essential in pathological conditions such as post-CA. Neuro-monitoring plays a pivotal role in identifying complications, tailoring treatments to individual patients and predicting prognosis in CA-related brain injuries. Continued research is crucial to deepen our understanding of neurological damage in these contexts, ultimately aiming to optimize care and prognosis following CA.

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Ethics. This work did not require ethical approval from a human subject or animal welfare committee.

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