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REVIEW

Individualized management objectives for hypoxic-ischemic brain injury after cardiac arrest

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Abstract

Hypoxic-ischemic brain injury after cardiac arrest is the main cause of death and neurologic dysfunction in patients after the return of spontaneous circulation. The mechanisms of ischemic and hypoxic brain injury include hypoxia of brain tissue caused by the cessation of cerebral blood flow during the initial cardiac arrest and cerebrovascular dysfunction and reperfusion injury after the recovery of circulation. Cerebral circulatory perfusion, cerebral autoregulation, and cerebral edema can be monitored and controlled as therapeutic targets. In this study, from the aspects of body temperature, mean arterial pressure, oxygen concentration, partial pressure of carbon dioxide in the artery, and cerebral edema, monitoring methods such as measurement of cerebral oxygen saturation, assessment of cerebral blood flow, imaging of the brain, and measurement of intracranial pressure were introduced to explore individual management objectives for hypoxic-ischemic brain injury.

Keywords

Cardiac arrest; Hypoxic-ischemic brain injury; Individual management; Cerebral monitoring

1. Introduction

Cardiac arrest (CA) is a common cause of death worldwide. In the United States alone, >400,000 people die of CA yearly. Annually, >350,000 people experience out-of-hospital CA (OHCA) in America, of whom 10.8% survive to discharge after being treated by emergency medical services (EMS) and only 9% obtain good functional outcomes. Additionally, >200,000 adult patients experience in-hospital CA annually, with a survival rate of 25.8%; among the survivors, 84.6% show a good functional status at hospital discharge [1]. In China, approximately 545,000 people die of sudden cardiac death every year [2]. The brain tissue is extremely sensitive to ischemia and hypoxia, and neuronal ischemia and cell death occur within minutes after CA. Although cardiopulmonary resuscitation education has become popular and advances in EMS have improved the success rate of CA resuscitation, abnormal cerebral perfusion and reperfusion injury after the return of spontaneous circulation (ROSC) cause persistent secondary brain injury. Brain injury is the leading cause of death in patients with CA [3]. In addition, most survivors develop neurologic dysfunctions, such as depression, anxiety, post-traumatic stress disorder, and cognitive deficits [4, 5], which seriously affect their quality of life. Therefore, preservation of neurologic function and reduction of brain damage are the key directions of CA therapy.

Bystander cardiopulmonary resuscitation and shortening the time to the initiation of EMS treatment can reduce cerebral ischemia and hypoxic damage during CA [6, 7]. In addition, the secondary cerebral injury that occurs after ROSC can be improved by maintaining cerebral perfusion and reducing oxidative stress. At present, many studies have shown that therapeutic hypothermia (TH), mean arterial pressure (MAP) elevation, atmospheric hyperoxia, normocarbia, and cerebral edema reduction have beneficial effects on the management of hypoxic-ischemic brain injury (HIBI) [8–12]. However, systematic reviews about the individual management of brain injury after CA are lacking. This review highlights the pathogenesis of secondary brain damage (Fig. 1) and the corresponding individual management objectives (Table 1).

2. Brain damage after CA

2.1 HIBI

With the interruption of cerebral blood flow (CBF), brain tissue hypoxia occurs, anaerobic glycolysis and lactic acid production increase, adenosine triphosphate (ATP) production ceases, and stored ATP is rapidly consumed [13, 14], resulting in the impairment of the ATP-dependent ion pump in the cell membrane [15]. Subsequent intracellular Na^+ accumulation results in cytotoxic edema, intracellular Ca^{2+} overload leading to activation of lyase activity [16], disruption of mitochondrial membrane integrity, irreversible oxidative damage, and loss of ATP production, finally resulting in cell death [17, 18]. Ischemic injury also promotes the release of glutamate from synaptic terminals, activating N-methyl-D aspartic acid and

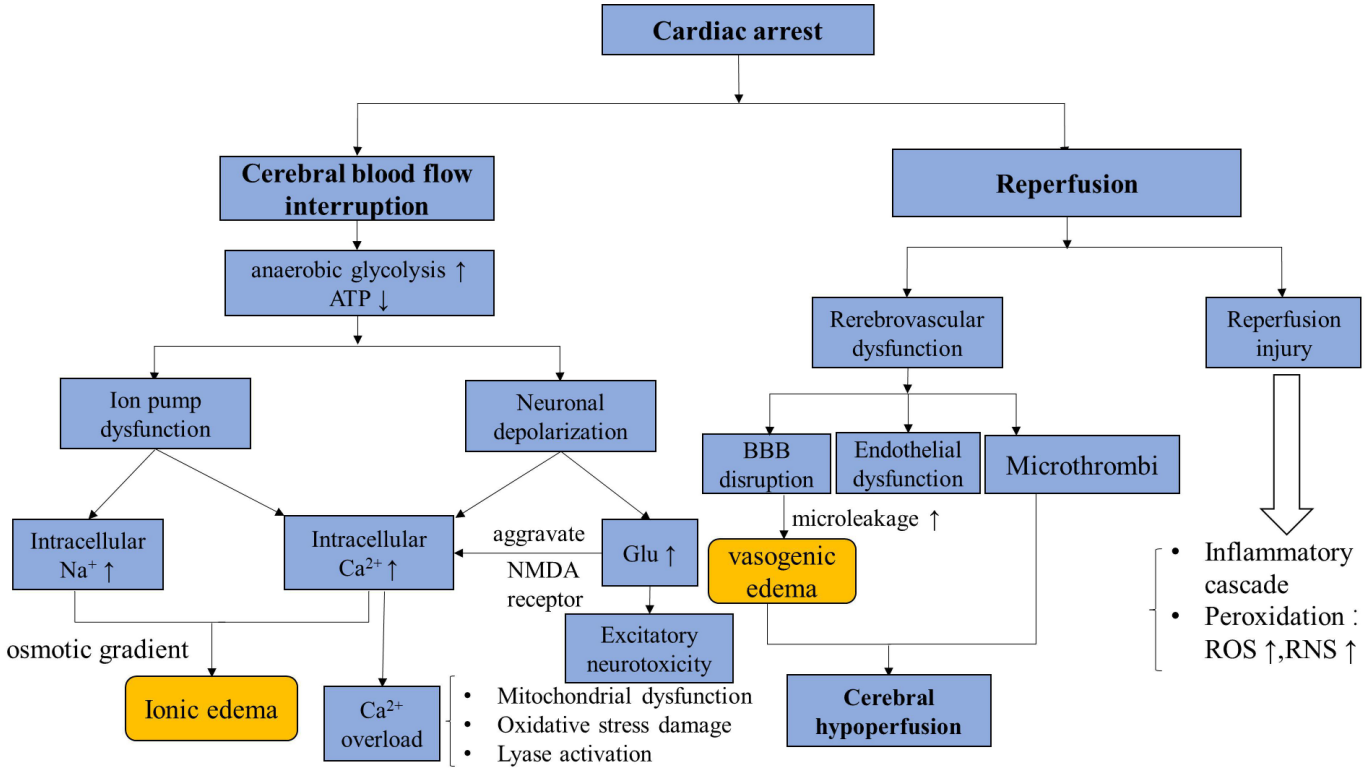

FIGURE 1. Pathophysiological mechanism of hypoxic ischemic brain injury after cardiac arrest. Abbreviations: ATP: adenosine triphosphate, Glu: glutamate, NMDA: N-methyl-D aspartic acid, BBB: blood brain barrier, ROS: reactive oxygen species, RNS: reactive oxide species.

causing further influx of Ca^{2+} into cells, thus exacerbating calcium overload [19]. The excitatory neurotransmitter glutamate also activates destructive enzymes (lipase, protease, and nuclease) that damage nerve tissue [20, 21], resulting in neuronal death.

Secondary injury results from cerebral vascular dysfunction and reperfusion injury after ROSC. After the ischemic injury, vascular endothelial injury [22] and brain autoregulation disorder [23] prevent the recovery of cerebral perfusion after ROSC. One study introduced the concept of "no reflow" [24]. With the inflow of blood flow, the presence of large numbers of white blood cells causes increased peroxide and inflammatory reaction, increased production of free radicals (superoxide, nitric oxide, and peroxynitrate), further release of glutamate and increased Ca^{2+} overload, and apoptosis induction due to peroxide and inflammatory damage [25, 26].

2.2 CBF, cerebral autoregulation, and cerebral edema

Cerebral perfusion pressure (CPP) is the driving force of CBF. CPP is defined as the difference between the MAP and the intracranial pressure (ICP) [27]. When the MAP fluctuates within a certain range (60–150 mmHg), the brain has an innate ability to maintain stable CBF through vasoconstriction or vasodilation (*i.e.*, brain autoregulation) [28]. Owing to the rigid encasement of the brain, abnormal increases in the volume of any component in the brain cavity may lead to ICP elevation.

Cerebral perfusion after resuscitation is characterized by early hyperemia, followed by hypoperfusion and restoration of normal blood flow [29]. Early congestion results from vascular paralysis caused by the accumulation of acidic metabolites after transient ischemia. Thereafter, diffuse cerebrovascular inflammation, intravascular microthrombus formation [30], perivascular cerebral edema, and dysfunctional nitric oxide signaling lead to increased vascular resistance and decreased CBF [24]. During this critical period, hypotension, especially blood pressure below the lower limit of autoregulation, may further aggravate the ongoing cerebral ischemia and secondary injury [31]. In patients hospitalized after CA in one study, the mean flow velocity in the middle cerebral artery gradually returned from low to normal at 48 h after admission [32].

Initially, Nishizawa *et al.* [33] demonstrated a linear relationship between MAP and CBF, suggesting complete dysfunction of cerebral autoregulation after CA. Transcranial Doppler sonography (TCD) monitoring of the middle cerebral artery flow rate and near-infrared spectroscopy (NIRS) monitoring of cerebral regional oxygen saturation (rSO_2) can reflect changes in CBF. Recently, several studies on the relationship between CBF and MAP after CA suggested that the cerebral autoregulation may remain intact, but with a narrowed and upward-shifted intact zone (MAP range, 80–120 mmHg) [23, 34, 35]. These studies demonstrated that MAP should be maintained at a level higher than the commonly accepted values to ensure cerebral perfusion [23].

Cerebral edema, which can predict poor neurologic outcomes, can be detected in patients after CA using computed tomography (CT) or magnetic resonance imaging (MRI) [36]. Cerebral edema after CA has two types: ionic edema and vasogenic edema [37]. These two pathologic processes can

TABLE 1. Objectives of individualized management of ischemic hypoxic brain injury.

Indicators	Target	Meaning
Therapeutic hypothermia	Maintain 32–36 °C for 24 h after the arrest, actively avoid fever.	Hypothermia can reduce oxygen consumption, reduce the production of inflammatory mediators, excitatory neurotransmitters and free radicals. Pay attention to complications such as tremor, immunosuppression and coagulation disease.
MAP	MAP $\geq$65 mmHg is recommended, preferably 80–100 mmHg to optimize perfusion. Brain oxygen monitoring is used to determine MAP_{OPT}.	The brain autoregulatory heterogeneity and MAP autoregulatory regions shift to the right after CA. MAP_{OPT} can be measured by rSO_2, and MAP_{OPT} can increase brain tissue oxygenation, but the neuroprotective effect of MAP_{OPT} needs further confirmed.
FiO_2	Titration of FiO_2 to maintain SpO_2 >94% of the lowest value after ROSC, avoiding exposure to PaO_2 >300 mmHg.	Hypoxia should be avoided after CA, but hyperoxia will promote the generation of free radicals and DNA damage, cause cerebral vasoconstriction, reduce cardiac output, aggravate nerve cell damage, reduce cerebral oxygen transport. It is feasible to titrate oxygen concentration according to SpO_2.
$PaCO_2$	In mechanically ventilated patients, $PaCO_2$ is controlled at 35–45 mmHg, allowing mild hypercapnia ($PaCO_2$ 50–55 mmHg).	Cerebrovascular response to $PaCO_2$ persist after CA. Normocarbia is associated with good prognosis, mild hypercapnia can improve cerebral oxygen delivery, and the prognostic effect of targeting mild hypercapnia remains to be further studied.
Cerebral edema	Monitor cerebral edema (CT, MRI) and ICP (invasive and non-invasive), Targeted treatment to improve edema.	GWR <1.1, ADC <650 $\times$ 10^{-6} mm^2/s, ICP >20 mmHg is associated with poor prognosis. Aquaporin-4, MMP-9 and SUR1-TRPM4 are feasible targets for improving edema.

Abbreviations: MAP: mean arterial pressure; MAP_{OPT}: optimal MAP; CA: cardiac arrest; rSO_2: cerebral regional oxygen saturation; FiO_2: fraction of inspired oxygen; SpO_2: oxygen saturation; ROSC: restoration of spontaneous circulation; PaO_2: arterial partial pressure of oxygen; $PaCO_2$: arterial partial pressure of carbon dioxide; CT: computed tomography; MRI: magnetic resonance imaging; ICP: intracranial pressure; GWR: gray matter/white matter ratio; ADC: apparent diffusion coefficient; MMP: matrix metalloproteinases; SUR1-TRPM4: sulfonylurea receptor 1/transient receptor potential melastatin 4.

overlap, and their clinical distinction from each other is challenging. Ionic edema results from cerebral ischemia and hypoxia. The osmotic gradient formed by intracellular Na^+ and Ca^{2+} accumulation causes interstitial water to flow into the cells, resulting in cellular edema [38, 39]. Meanwhile, increased interstitial osmotic pressure drives the outflow of intravascular fluid and causes interstitial edema [38, 39]. Vasogenic cerebral edema is a consequence of damage to the blood-brain barrier (BBB). Ischemia and reperfusion injury leads to dysfunction of the BBB cell components and disruption of the tight connections between endothelial cells. The increase in permeability across the capillary allows for an increased flow of protein-rich plasma driven by the hydrostatic gradient between the intravascular and extracellular spaces [37]. Aquaporins are membranes that assist in the passive transport of water [40]. Evidence exists for the role of aquaporin-4 in both edema formation and clearance in models of CA [41, 42]. Matrix metalloproteinases (MMPs), activated by inflammatory mediators after ischemia/reperfusion injury, are responsible for the degradation of the extracellular matrix and play a role in the loss of BBB function and the formation of vasogenic edema [43, 44]. The sulfonylurea receptor 1/transient receptor potential melastatin 4 (SUR1/TRPM4) channel regulated by SUR1 is a critical mediator of cerebral edema formation. ATP depletion after hypoxia leads to increased expression of SUR1/TRPM4 in the central nervous system, which promotes the influx of Na^+ into cells and the destruction of the BBB, leading to the formation of ionic and vasogenic edema [45, 46].

Therefore, maintaining cerebral perfusion, maintaining brain autoregulation, and reducing cerebral edema are feasible goals to improve the prognosis of HIBI.

3. Objectives of individualized management of HIBI

3.1 TH

TH or target temperature management (TTM) has been shown to prevent or relieve HIBI and has become the standard of care for comatose patients who survived CA [10]. Hypothermia plays a neuroprotective role through various mechanisms. Cerebral metabolism is reduced by 5–10% for every 1 °C decrease in the core body temperature, thus reducing oxygen consumption and CBF and preventing cerebral edema [47]. In addition, hypothermia can inhibit cell apoptosis and mitochondrial dysfunction, as well as reduce the production of inflammatory mediators, excitatory neurotransmitters, and free radicals [47, 48]. However, a persistently low temperature can cause adverse reactions such as immunosuppression, coagulation disease, arrhythmia, electrolyte disturbance, and hemodynamic disturbance. Therefore, the advantages and disadvantages of TH should be considered, and the process of low temperature induction and rewarming should be closely monitored [48]. Nevertheless, the optimal timing of TH initiation, target temperature, maintenance time, and reheating method remain controversial.

3.1.1 Timing of TH initiation

Although the optimal timing of initiating TTM and achieving the target temperature remains unclear, the consensus is to start cooling as soon as possible after the arrest. Animal studies have shown that shortening the time to TH initiation can lead to a better neurologic prognosis [49–52]; however, the results of studies on the optimal timing in humans have been inconsistent. Two studies by Mooney *et al.* [53, 54] have shown that delayed TH initiation after CA increases the risk of neurologic deterioration and death. In contrast, Haugk *et al.* [55] found that a shorter time to achieve the target temperature was associated with unfavorable neurologic outcomes. This raises the question of whether intra-arrest TH (IATH) improves prognosis. A systematic review of 23 animal studies and 5 clinical studies concluded that IATH improved survival and neurologic outcomes compared with maintenance of normal body temperature or the application of routine hypothermia [56]. However, some randomized controlled trials (RCTs) showed that prehospital TH only decreased body temperature at hospital arrival and did not improve the survival rate and neurologic outcome of patients with OHCA [57–59], whereas the prehospital administration of cold intravenous solution increased the incidence of re-arrest and pulmonary edema [58]. A recent large multicenter RCT confirmed that prehospital transnasal evaporative intra-arrest cooling did not improve the 90-day survival rate and neurologic outcomes of patients with OHCA compared with routine cooling after admission [60, 61]. Although evidence supporting the benefit of starting prehospital TH before ROSC is lacking, this method is safe and facilitates the application of TTM in hospitals [62].

3.1.2 Target temperature

The American Heart Association (AHA) recommends the application of TTM to all comatose adult patients after CA, with a target temperature between 32 ℃ and 36 ℃, maintained for 24 h after the arrest [63]. Two RCTs published in 2002 reported that the TH (32–34 ℃) group showed better neurologic outcomes than the normal body temperature group [64, 65] and fever was not prevented in the normal body temperature group, thus potentially exposing the patients to the harmful effects of hyperthermia. A large RCT study in 2013 challenged this result and demonstrated that maintaining TTM at 36 °C yielded a similar prognosis to that observed with TTM at 33 °C, without any difference in adverse effects [66]. Two meta-analysis studies suggested that TH (32–35 °C) does not affect the mortality rate or neurologic outcome in post-arrest survivors [67, 68]. A recent meta-analysis of 10 RCTs suggested that mild (35–36 °C), moderate (33–34 °C), or deep hypothermia (31–32 °C) may not improve the survival and functional outcomes of patients after OHCA [69]. Studies on the effects of therapeutic hypothermia TH on neurological neurologic outcomes in survivors after CA have reported mixed inconsistent results, which may stem from differences in TTM implementation. The implementation of TTM should be standardized to determine the optimal target temperature for improving the neurologic prognosis of patients.

3.1.3 Maintenance time

Current recommendations state that the TTM duration should be at least 24 h and fever should be avoided within 48 h of CA. These recommendations were primarily based on two classic TTM tests, in which patients were cooled for an average of 24 h [64, 66]. Observational trials have also shown that the optimal duration for improvement is 18–24 h [70–72]. In 2017, a large multicenter RCT demonstrated that TTM (33 °C) maintained for 48 h, compared with 24 h, did not improve the prognosis of the nervous system at 6 months, and prolonged hypothermia increased the risk of adverse reactions [73].

3.1.4 Cooling methods

Traditional cooling methods include the application of cold intravenous fluids, ice packs, water circulation blankets, and air circulation blankets. More modern methods include the use of water-circulating gel-coated pads and intravascular catheters that allow rapid cooling and precise temperature control [74, 75]; however, these methods are associated with increased complications of hypothermia. Transnasal evaporative cooling is a new cooling method used to induce the hypothermia stage of TTM therapy [76, 77]. At present, evidence is insufficient to recommend any particular cooling method. Therefore, the suitable cooling method should be selected according to the patient's condition and the hospital's facilities.

3.1.5 Rewarming rate

The European Resuscitation Council recommends a warming rate of 0.25–0.5 ℃/h during the rewarming process of patients receiving TH treatment after CA [78]. Rapid warming may lead to electrolyte abnormalities (*e.g.*, hyperkalemia), cerebral edema, seizures, and other problems. A retrospective cohort study of 128 patients with CA reported that neither the rewarming mode (active or passive) nor the rewarming speed ($\geq$ 0.5 °C/h or $<$0.5 °C/h) after TH had any effect on prognosis [79]. However, a prospective cohort study in Japan increased the rewarming temperature very slowly, by 1 ℃ every day, and the results showed that a longer rewarming duration was significantly correlated with the prognosis of neurologic func-

tion in patients with OHCA and was an independent predictor of a good prognosis [80]. Therefore, the effect of a slower rewarming rate on the prognosis of neurologic function and the adverse effects of prolonged hypothermia warrant further investigations.

3.1.6 Sedation and suppression of shivering

Shivering is a physiologic response of the whole body to an increase in body temperature and is caused by the contraction of muscles when the core temperature is lowered. Shivering can delay reaching the target temperature and influence the effects of TH. Therefore, shivering should be controlled when performing TTM. Full sedation should be maintained during TTM. In general, routine use of sedatives (fentanyl, propofol, or benzodiazepines) can control shivering [81]. To inhibit shivering, titration of sedatives is clinically recommended rather than using the standard doses [63]. If high doses of sedatives do not control shivering, neuromuscular blockade may be used; however, attention should be paid to electroencephalogram monitoring to prevent masked epileptic seizures [82]. Non-pharmacologic methods of skin counterwarming include the application of warm blankets and increasing the room temperature [83–85]. As skin temperature accounts for approximately 20% of the tremor threshold, increasing the skin temperature can reduce tremors without affecting the core temperature [83].

3.2 MAP

Hypotension after CA can aggravate secondary brain injury, and studies have shown that increasing the MAP can improve the neurologic prognosis [86]. The AHA guidelines recommend a MAP threshold of $\geq$ 65 mmHg [63], preferably 80–100 mmHg, to optimize cerebral perfusion. The heterogeneity of brain autoregulation and the application of automatic brain monitoring technology drive the development of brain resuscitation techniques toward individualized directions. TCD has been used to evaluate the middle cerebral artery blood flow index, and cerebral autoregulation curves of CBF and MAP have been established, which confirmed the right shift of the MAP autoregulation region (80–120 mmHg) and the heterogeneity of autoregulation [23]. However, the wide application of TCD was limited by the failure of long-term continuous monitoring. Recently, NIRS monitoring has attracted wide attention, and the relationship between MAP and rSO_2 can be used as a noninvasive parameter for assessing brain autoregulation. The correlation coefficient between MAP and rSO_2 is called cerebral oximetry index (COx). A positive COx value represents normal self-regulation [87], whereas a negative or close to zero COx value represents complete autoregulation [87]. After mapping the COx (Y-axis) relative to the MAP range in each patient, a U-shaped curve can be generated, and the lowest point of the curve corresponds to the optimal MAP (MAP_{OPT}) for each patient. In a prospective study using NIRS to evaluate MAP_{OPT}, a COx and MAP U-shaped curve was drawn and the MAP_{OPT} was identified (average, 75 mmHg) in 19 of 20 patients with CA, demonstrating the feasibility of using cerebral oxygen saturation (SPO_2) to determine the MAP_{OPT} after CA [88]. In 2019, Sekhon *et al.* [11] prospectively evaluated the MAP_{OPT} in patients after CA by using the pressure reactivity index (PRx), defined as the Pearson correlation coefficient between ICP and MAP, and reported that perfusion near the MAP_{OPT} was associated with increased oxygenation of brain tissue. Subsequently, Hoiland *et al.* [89] compared the MAP_{OPT} based on COx and that based on PRx, which showed a lack of consistency. A meta-analysis study found no consistent association between targeted MAP and neurologic function, which may be due to the difference in automatic adjustment monitoring methods. Further studies are needed to evaluate the clinical efficacy of brain resuscitation under MAP_{OPT} guidance in alleviating secondary ROSC injuries and improving the neurologic prognosis of patients [90].

3.3 Fraction of inspired oxygen (FiO_2)

Hypoxia should be avoided in patients after CA. The AHA recommends the use of the highest concentration of oxygen during cardiopulmonary resuscitation and titration of FiO_2 to the minimum value required to maintain an SPO_2 of >94% after ROSC [63]. Theoretically, high oxygen levels increase the dissolved oxygen content in blood, which is beneficial to achieving the combination of sufficient hemoglobin oxygenation and accelerated oxygen diffusion. However, the harms of high oxygen levels, including the promotion of free radical production [91], lipid peroxidation, DNA damage, and ultimately nerve cell dysfunction, are ignored [92]. Hyperoxia also causes cerebral vasoconstriction, decreased cardiac output [93], and pulmonary dysfunction [94], thus reducing the amount of oxygen delivered to the brain. A meta-analysis of animal experiments investigating the impact of high oxygen levels on the prognosis after ROSC showed that compared with low oxygen levels, inhaled 100% oxygen was associated with neurologic deterioration. However, the studies differed in terms of factors such as the timing and dose of hyperoxia and whether hyperoxia was combined with TH [95]. Furthermore, the results of animal models are not necessarily applicable to humans. Clinical studies on hyperoxic therapy in patients after CA have yielded inconsistent results. A arterial partial pressure of oxygen (PaO_2) of > 300 mmHg should also be avoided after ROSC, although no study has proved the adverse effects of hyperoxia in patients after CA. A retrospective multicenter cohort study in 6326 patients with nontraumatic CA demonstrated that hyperoxia ($PaO_2 \geq$ 300 mmHg) after resuscitation was associated with increased mortality [96]. Two meta-analysis studies identified that hyperoxia (PaO_2 >300 mmHg) was associated with increased in-hospital mortality [97, 98]. In a recent prospective study, Roberts *et al.* [99] reported that high oxygen levels in the first 6 h after ROSC (PaO_2 >300 mmHg) was associated with poor neurologic function. In contrast, another retrospective multicenter study demonstrated that hyperoxia ($PaO_2 \geq$ 300 mmHg) was not associated with mortality within the first 24 h of intensive care unit admission, after controlling for confounders such as disease severity [100]. Oh *et al.* [101] reported that high oxygen levels ($PaO_2 \geq$ 300 mmHg) within 2 h after ROSC was not associated with the discharge survival rate. In a prospective study, Vaahersalo *et al.* [102] calculated the proportion of time spent by each patient in various oxygen level zones based on the average PaO_2 within 24 h after admission. Their results

showed that the proportion of time spent in the high PaO_2 zone (>225 mmHg) was not associated with better neurologic outcomes [102]. At present, the optimal oxygen level after CA remains uncertain. Two prospective studies have confirmed the feasibility of titrimetric oxygen supply according to SPO_2 [9, 103], and further RCTs are needed to determine the optimal oxygen supply strategy for patients with CA.

3.4 Partial pressure of carbon dioxide in the artery ($PaCO_2$)

According to current clinical studies, the $PaCO_2$ during mechanical ventilation in patients after CA should be controlled at 35–45 mmHg (or at an end-tidal CO_2 of 30–40 mmHg) and mild hypercapnia ($PaCO_2$ = 50–55 mmHg) may be allowed. Cerebrovascular responses to $PaCO_2$ persist after CA [32]. The $PaCO_2$ level can directly affect cerebrovascular resistance and CBF, and hypocapnia ($PaCO_2$ <35 mmHg) induced by hyperventilation induces cerebrovascular vasoconstriction and decreases CBF by approximately 2–3% for every 1 mmHg decrease in $PaCO_2$ [104], thus exacerbating ischemic injury. Hypercapnia ($PaCO_2$ >45 mmHg) can cause cerebral hyperemia, exacerbate ICP, and reduce CBF [105]. However, mild hypercapnia ($PaCO_2$= 50–55 mmHg) may lead to mild cerebrovascular dilatation, thereby improving CBF and oxygen delivery and reducing neuronal injury [106, 107].

A large multicenter retrospective study found that hypocapnia ($PaCO_2$ <35 mmHg) was significantly associated with in-hospital mortality compared with normocapnia [108]. A retrospective study involving 9186 patients with OHCA demonstrated that the first 24 h of hypercapnia after ROSC ($PaCO_2$ >50 mmHg) was associated with increased in-hospital mortality, whereas hypocapnia ($PaCO_2$ <30 mmHg) was not associated with this outcome [109]. A systematic review of nine studies demonstrated that normocarbia ($PaCO_2$ = 35–45 mmHg) was associated with a higher survival rate and better neurofunctional status at discharge compared with hypocapnia or hypercarbia [110]. A prospective study confirmed the feasibility of targeting $PaCO_2$ and PaO_2 therapy in patients on post-ROSC mechanical ventilation and found higher cerebral oxygen saturation in patients with high-normal $PaCO_2$ (5.8–6.0 kPa, approximately 43.5–45 mmHg) but observed no improvement in neuron-specific enolase levels [111]. Another prospective study calculated the mean $PaCO_2$ in the first 6 h after ROSC and reported that the relationship between $PaCO_2$ and nervous system prognosis showed an inverted “U” shape, with mild to moderate hypercapnia (mean $PaCO_2$ of 51 mmHg in patients with metabolic acidosis and 68 mmHg in normal patients) being associated with a high likelihood of a good nervous system prognosis [12]. In most cases, $PaCO_2$ is elevated after ROSC; however, this situation corrects itself during the first hour, without a need to speed up the process [112]. Furthermore, the actual $PaCO_2$ of patients may be slightly lower than the $PaCO_2$ measured in the laboratory at 37 °C owing to the temperature correction during the treatment with induced hypothermia. Therefore, we believe that mild hypercapnia after ROSC is permissible. Future RCTs are necessary to further determine whether targeting mild hypercapnia ($PaCO_2$ = 50–55 mmHg) improves the prognosis after ROSC [12].

3.5 Cerebral edema

Cerebral edema is an important cause of secondary brain injury after CA and must be carefully monitored to reduce the risk of comatose and death in patients after ROSC [8]. Diffuse cerebral edema is common after CA. On CT, diffuse cerebral edema manifests with effacement of the cerebral sulci and gyri, as well as loss of the normal differentiation between the gray and white matters. However, these findings are dependent on the observer and are especially difficult to detect in the early stages [113]. By measuring the relative attenuation of gray and white matters in various regions of the brain, the gray matter/white matter ratio (GWR) can be calculated to quantify edema. In this way, cerebral edema can be detected as early as 1 h after CA. Clinical studies have confirmed the correlation between GWR measurements and prognosis. The studies reported that GWR <1.2 was a predictor of poor prognosis in patients after CA and GWR <1.1 predicted a mortality rate of nearly 100% [114–116]. These values remained consistent even in patients treated with TH. MRI can detect microscopic factors associated with edema formation. Cellular edema manifests as increased signal intensity on diffusion-weighted imaging and decreased signal intensity on apparent diffusion coefficient (ADC) imaging [117]. Conversely, edema of primarily vasogenic origin manifests as an increase in ADC signal intensity. The presence of both vasogenic and cellular edema can result in significantly normal ADC values, a phenomenon known as “pseudonormalization”. Several studies have shown that reduced ADC values ($<650 \times 10^{-6}$ mm^2/s) of quantitative edema are associated with a poor prognosis [118–120]. The optimal time window to perform ADC imaging to predict poor outcomes was reported to be between days 2 and 5 after CA [121, 122]. The early instability of patients after ROSC limits the early application of MRI. Moreover, pseudorthodontics may reduce the sensitivity of MRI in patients with CA at a later time point [37]. However, no unified standard currently exists for the quantitative measurement of CT and MRI parameters. Therefore, prospective multicenter studies with sufficiently large sample sizes are needed to determine specific imaging parameters or abnormal spatial and temporal patterns.

ICP is another clinical indicator for monitoring cerebral edema. The indications for ICP monitoring can be determined using predictive models, especially in patients presenting with initially unremarkable cranial CT findings after CA [123, 124]. Increased ICP can reduce the CPP and induce cerebral hernia [125]. Studies have demonstrated a strong association between high ICP (>20 mmHg) and increased mortality in patients with severe craniocerebral trauma [126]. At present, the most commonly used and gold standard method for ICP monitoring in clinical practice is intraventricular intubation; however, it is associated with a high risk of bleeding and infection [127]. In recent years, noninvasive ICP monitoring methods such as TCD, optic nerve cord diameter (ONSD) measurement, and pupillary measurements have been introduced [128–130]. A retrospective study concluded that TCD and ONSD measurement provide results consistent with those of invasive ICP

monitoring [131]. The prospective study by Chiara *et al*. [132] also confirmed that ONSD is a good predictor of ICP and can be used to identify patients with severely high cranial pressure. We believe that the usefulness and operability of noninvasive ICP monitoring merit further promotion in clinical practice.

Finally, preclinical models examining therapies that target key pathways (aquaporin-4, MMP-9, and SUR1/TRPM4) in post-arrest edema formation showed improved functional outcomes after CA [44, 128, 133]. The management of cerebral edema may be a feasible target to ameliorate ischemic damage; however, this needs to be confirmed by further clinical studies.

4. Conclusion

HIBI after CA can seriously affect the prognosis of patients. The duration of CA and individual differences in tolerance to hypoxia determine the complexity of the disease after ROSC. This review discusses the mechanism of ischemic–hypoxic brain damage after CA and introduces relevant monitoring methods to explore the individual management objectives of reducing brain damage, such as TH, maintaining cerebral perfusion (MAP_{OPT}), titrating the oxygen level, allowing mild hypercapnia, and monitoring of cerebral edema. The development of an appropriate post-CA brain protection scheme for patients, with comprehensive consideration of various factors, is still necessary.

ABBREVIATIONS

CA, cardiac arrest; ROSC, return of spontaneous circulation; CBF, cerebral blood flow; MAP, mean arterial pressure; ICP, intracranial pressure; OHCA, out-of-hospital cardiac arrest; EMS, emergency medical services; CPR, cardiopulmonary resuscitation; HIBI, hypoxic ischemic brain injury; ATP, adenosine triphosphate; NMDA, N-methyl-D aspartic acid; CPP, cerebral perfusion pressure; TCD, transcranial doppler sonography; NIRS, near-infrared spectroscopy; rSO_2, regional oxygen saturation; CT, computed tomography; MRI, magnetic resonance imaging; BBB, blood brain barrier; MMP, matrix metalloproteinases; SUR1/TRPM4, sulfonylurea receptor 1/transient receptor potential melastatin 4; TH, therapeutic hypothermia; TTM, target temperature management; IATH, intra-arrest therapeutic hypothermia; RCT, randomized controlled trial; AHA, american heart association; MAP_{OPT}, optimal MAP; PRx, pressure reactivity index; FiO_2, fraction of inspiration oxygen; SPO_2, oxygen saturation; GWR, gray matter/white matter ratio; ADC, apparent diffusion coefficient; ONSD, optic nerve cord diameter.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

ML, YF, XZ—designed the research study. YF, ML—performed the research. YF, XZ and BS—analyzed the data. YF and BS—wrote the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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