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Review

The utility of therapeutic hypothermia on cerebral autoregulation

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ABSTRACT

Cerebral autoregulation (CA) dysfunction is a strong predictor of clinical outcome in patients with acute brain injury (ABI). CA dysfunction is a potential pathologic defect that may lead to secondary injury and worse functional outcomes. Early therapeutic hypothermia (TH) in patients with ABI is controversial. Many factors, including patient selection, timing, treatment depth, duration, and rewarming strategy, impact its clinical efficacy. Therefore, optimizing the benefit of TH is an important issue. This paper reviews the state of current research on the impact of TH on CA function, which may provide the basis and direction for CA-oriented target temperature management.

Cerebral autoregulation (CA) dysfunction occurs after an acute brain injury (ABI), and impaired CA is a strong predictor of clinical outcome.[1–4] The clinical benefits of therapeutic hypothermia (TH) after cardiac arrest have been confirmed, and TH has been widely accepted as the gold standard treatment for surviving coma patients after a cardiac arrest.[5,6] Traumatic brain injury (TBI), ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) are more heterogeneous than hypoxic brain injury in terms of pathology, severity, and clinical course. What diseases benefit from TH remains unclear. This paper reviews our current understanding of CA changes during TH and may provide the basis and direction for CA-oriented target temperature management (TTM).

Changes in CA after an ABI

CA is a protective mechanism that maintains cerebral blood flow (CBF) at a relatively constant level despite fluctuations in cerebral perfusion pressure (CPP) or arterial blood pressure (ABP). This physiologic self-regulation protects the brain from ischemic and congestive injuries by optimizing CBF. One of the first reports to document CA was in 1928, when Forbes and Wolff[7] described pial arterial contraction in response to increased blood pressure. It was not until 1959, when Lassen[8] published the first blood pressure-CBF plot, that the concept of static CA (sCA) was formally introduced. Aaslid et al.[9] identified dynamic CA (dCA) using transcranial Doppler ultrasonography (TCD) in 1989. The regulatory mechanisms behind CA are not fully understood. CBF is thought to be regulated by myogenic, neurogenic, endothelial, and metabolic processes.[10,11] The plateau and upper and lower limits of autoregulation are affected by many factors such as age,[12,13] sex,[14,15] metabolic rate,[16,17] diseases, vasoactive drugs,[18,19] sympathetic tone,[20,21] hemoglobin and oxygen content,[22,23] anesthesia, and carbon dioxide.[24]

Brain parenchymal injury immediately after an ABI is only the initial insult. Subsequent secondary, non-mechanical injuries may play a more important role in long-term prognosis. After the initial injury, the regulation of CBF, brain volume/pressure, and metabolism changes significantly.[25] Cerebrovascular oxidative stress impairs the key mechanisms that regulate CA, such as endothelial function and neurovascular coupling.[26] Spread depolarization, i.e., depolarization waves propagating through gray matter, is also involved in microvascular dysfunction and secondary neuronal injury after an ABI. Subsequently, cerebral microcirculatory vasoconstriction, diastolic dysfunction, impaired CA, and posttraumatic hyperperfusion and congestion occur, leading to elevated intracranial pressure (ICP) and vasoparalysis.[27] These changes in blood flow may lead to increased anaerobic glycolysis, membrane permeability, and ultimately aggravated parenchymal edema, resulting in pathologic changes similar to those that occur during ischemia.[27] Post-traumatic ischemia can occur at multiple

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time points from the hyperacute to the late injury stage, potentially resulting from direct vascular rupture, hypotension, and metabolic decoupling.[27,28] The brain has a poor tolerance to energy depletion, leading to the depletion of stored adenosine triphosphate (ATP), excessive excitotoxic glutamate release, and calcium overload in mitochondria, resulting in further neuronal damage.[27–29]

It has also been increasingly recognized that, in addition to perfusion and impaired metabolism, CA dysfunction represents a potential pathological defect that can lead to a secondary injury and worse functional outcomes in the setting of several acute neurologic diseases.[30–32] CA impairment has been reported following acute nerve injuries, where CBF fluctuations in response to arterial pressure result in cerebral ischemia, infarction, or hemorrhage.[11] Impaired CA has been identified as a strong predictor of the clinical outcome of such nerve injuries.[1–4]

In 2000, Lang and Chesnut[33] made the first attempt to consider CA-oriented CPP as part of neurointensive care (NIC) management. Their prior works[34] reported that the pressure reactivity index (PRx) varies with CPP in a U-shaped pattern, and that the optimal CPP (CPP_{opt}) with the lowest PRx would best optimize CA. Maintaining a CPP close to CPP_{opt} has been associated with optimal brain tissue oxygenation ,[1] improved brain energy metabolism,[35] and favorable clinical outcomes.[36–38] Previous studies on patients with an acute ischemic stroke (AIS) following a mechanical thrombectomy have found that mean arterial pressure (MAP) deviation from an optimal level (MAP_{opt}) correlated with an increased risk of reperfusion hemorrhage and a poor prognosis better than a fixed MAP threshold.[39]

CA-guided therapy, which aims to minimize injury from hypoperfusion and hyperperfusion by targeting the optimal CA or the “optimal” blood pressure, is therefore a feasible therapeutic strategy for patients with an ABI. CA is not an “all-or-nothing” phenomenon but dynamic changes among and within patients, providing a strong theoretical basis for individualized treatment.[40]

Effects of Disordered Thermoregulation on CA after an ABI

Dysthermoregulation after a brain injury is thought to be multifaceted and interrelated, with an unclear etiology and pathophysiologic mechanism.[41] There are evidences that temperature instability after head injury is caused by a direct hypothalamic injury, abnormal CBF, vascular changes that limit heat dissipation, metabolic disorders, and a neurogenic inflammatory response.[28,42]

A body core temperature >38°C has a striking effect on brain metabolism and CBF. It can increase cerebral oxygen metabolism rate and the global and regional CBF.[28,43] The central nervous system is very sensitive to both absolute temperature and the duration of hyperthermia. Hyperthermia-induced secondary brain damage includes direct cytotoxic injury and indirect inhibition of neuronal function.[43–47]

Up to 70% of ABI patients treated in NIC develop hyperthermia within the first 2 weeks of admission. Hyperthermia has been associated with a longer stay in NIC and poor neurological functional outcome.[43,44,48,49] Fever occurs in up to 72% of SAH patients and is associated with an increased risk of death.[50,51] For every 1°C increase in body temperature, the mortality rate increases by eight times.[51] There is a temporal relationship between fever and vasospasm after SAH, suggesting that fever may play an important role in the development of diffuse cerebral ischemia.[51] Elevated body temperatures within the first 24 h are quite common in IS patients and may be due to metabolic dissociation and the release of inflammatory cytokines following the ischemic brain injury, and are associated with a worse prognosis. A meta-analysis including 19 preclinical studies on IS[52] reported that hyperthermia increased infarct size by 43.4% (95% confidence interval [CI]: 29.80–56.90) and worsened neurobehavioral outcomes by 48.5% (95% CI: 17.20–79.80). Moreover, cerebral infarction size increased with higher temperatures.[52]

Cremer et al.[53] noted that sCA is impaired when the body temperature exceeds 40°C. Unfortunately, the effects of body temperature on CA in the first few days of a coma remain unclear. The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study[54] conducted at 21 medical centers in the European Union continuously measured the ABP-ICP of 165 TBI patients for 72 h after admission. The PRx was calculated using ICM+ software (Cambridge Enterprises, Cambridge, UK), and the relationship between extracranial factors and CA was assessed. It was found that body temperature at admission (P=0.042) and white blood cell percentage (P=0.013) were statistically correlated with CA impairment. Lactate, hemoglobin, oxygen partial pressure, pH, coagulation indicators, C-reactive protein, and other indicators related to extracranial injury did not have a close relationship with CA.

The neurological intensive care unit (NICU) of Johns Hopkins Hospital, United States, began the multimodal monitoring of 85 patients with acute coma (Glasgow Coma Scale [GCS] ≤8 points)[55] within 12–48 h after coma onset for 3 days. The results of monitoring suggested that the cerebral oxygenation reactivity index increased (deteriorated) with increasing temperatures and decreased (improved) with decreasing temperatures, and that oxygenation reactivity index had a positive linear relationship with body temperature ($\beta = 0.04 \pm 0.10$; P=0.290). This relationship was significant in the multivariate analysis of the no change group (P=0.006) and the increasing group (P <0.001). CA impairment occurred at temperatures >38.6°C and improved <36.6°C. This study found that elevated body temperature was independently associated with CA deterioration in the setting of an acute coma and that even relatively small changes in body temperature may affect CA.[55]

Mechanisms of Hypothermia on CA

TH is defined as an intentionally induced, controlled hypothermia from a normal temperature of 37–38°C. TH is classified by the degree of cooling, including mild (32–35°C), moderate (28–32°C), deep (20–28°C), and profound (≤20°C). Early works used deep hypothermia as the target body temperature. However, mild to moderate hypothermia has become a more attractive option due to the numerous complications and difficulties related to deep hypothermia.[56]

Although the neuroprotective mechanisms of hypothermia in the setting of different diseases vary and are not yet fully understood, its neuroprotective effects are generally attributed to

decreased metabolic rate, reduced free radical generation and inflammation, and inhibition of excitotoxicity and apoptosis.[57]

Metabolism

Hypothermia can reduce metabolic rate, decreasing the oxygen consumption of brain tissues by 6–7% for every 1°C decrease in body temperature (from 37°C to 27°C).[58] Metabolic changes associated with hypothermia include preserving glucose,[59] inhibiting lactic acid accumulation due to anaerobic metabolism,[60] and increasing plasma levels of glycerol,[61] free fatty acids, and ketoacids.[62] These metabolic changes help to preserve the pH and ATP of the tissues and cells and promote homeostasis,[63] thereby limiting or preventing the development of ischemia when CBF is impaired or completely absent.[64]

Oxidative stress

Oxidative stress may play a central role in the inflammatory response during a brain injury. Reactive oxygen species (ROS), reactive nitrogen species (RNS), and other free radicals and nitric oxide (NO) production have been associated with neuronal damage.[65] Increased ROS can trigger an increased immune response, leading to the activation of pro-inflammatory transcription factors and endogenous immune molecules and the destruction of adjacent viable tissue surrounding the injured area.[66] ROS thus participates in a vicious cycle of immune response activation and direct cytotoxicity. Hypothermia significantly inhibits superoxide and lipid peroxidation to reduce the generation of free radicals[67] and inhibits NO production in the internal jugular after cerebral ischemia-reperfusion.[68]

Inflammation

Following an ABI, complement activation stimulates neutrophil pathways. This increases the levels of pro-inflammatory cytokines such as Interleukin (IL)-1β, IL-6, IL-18, and tumor necrosis factor (TNF), aggravating neuronal injury.[69,70] Hypothermia has been shown to decrease the production of pro-inflammatory cytokines and increase the production of anti-inflammatory cytokines, thereby inhibiting the inflammatory response.[71] However, hypothermia also inhibits the anti-inflammatory cytokines IL-10 and TGF-β,[72] suggesting that hypothermia does not always lead to pure anti-inflammatory results.

Excitotoxicity

Brain damage due to excessive neuronal depolarization leads to intracellular Ca^{2+} overload and sustained glutamate production.[73,74] The ultimate effect of these events is the rapid activation of extra-synaptic *N*-methyl-D-aspartate receptors (NMDARs), promoting intracellular apoptotic/necrotic signaling cascades and subsequent neuronal death.[75] Hypothermia can reduce the extent of neuronal damage by reducing the excessive extracellular release of glutamate and the production of hydroxyl radicals.[76] Hypothermia also prevents the surge in extracellular glutamate during post-traumatic ischemia.[77]

Apoptosis

Hypothermia plays a role by inhibiting neuronal apoptosis. Mild hypothermia can interfere with internal apoptosis and exogenous apoptosis via the mediation caspase family members and Fas/FasL, respectively. Mild hypothermia can increase Bcl-2, reduce the release of cytochrome C, inhibit the expression of BAX, and down-regulate the expression of caspase family members.[78–80] Mild hypothermia can also affect Fas by inhibiting the expression of matrix metalloproteinases (MMPs),[81] resulting in reduced Fas and caspase-8 production[82] and decreased neuronal apoptosis.

In addition to the above mechanisms, hypothermia also plays a vital role in blood-brain barrier (BBB) protection. Disruption of the BBB after ABI promotes results in edema formation and hemorrhage secondary injuries due to structural and functional impairment of the basement membrane tight junction proteins, transport proteins, endothelial cells, astrocytes, and neurons. Small changes in body temperature can affect the function of the BBB.[83–85] High temperatures increase albumin efflux, activate astrocytes, and increase the levels of markers of cerebral edema, suggesting that elevated body temperatures predispose to BBB leakage.[86] Mild and moderate hypothermia protect against BBB disruption[87] and reduce edema formation by attenuating the loss of vascular basement proteins.[88,89] Starting TH immediately after the onset of ischemia can alleviate BBB dysfunction in adult rodents.[90] Hypothermia in the setting of BBB dysfunction inhibits neuroinflammation by reducing chemokine expression, microglia conversion to an anti-inflammatory phenotype, and multiple markers of brain injury.[90] The effects of oxygen-glucose deprivation *in vitro* on brain endothelial cells, astrocytes, and neurons also depend on temperature.[91] Hypothermia can prevent the separation of pericytes from the basement membrane after an IS, which would result in dysfunction of the monolayer of brain endothelial cells.[92] Hypothermia can also inhibit the loss of basement membrane components such as type IV collagen and proteoglycans.[81,89,93]

As mentioned above, oxidative stress after a brain injury impairs vascular endothelial function, neurovascular coupling,[26] and other key mechanisms that regulate CA, resulting in CA damage. Cerebral microcirculatory vasoconstriction, diastolic dysfunction, impaired CA, and posttraumatic hyperperfusion and congestion occur as a result of CA dysregulation, leading to further neuronal damage.[27–29] Other CBF derangements are also improved and/or impacted by hypothermia, but their role in mediating hypothermic protection is much more complex. For instance, delayed hyperemia after a TBI exacerbates vasogenic tissue edema and promotes intracranial hypertension (ICP >20 mmHg) in brain regions where CA is dysregulated.[94] The protective impact of hypothermia may involve a decreased cerebral metabolic rate and a resultant decrease in CBF due to metabolic/flow coupling.[95] Hypothermia can also reduce cytotoxic edema formation by down-regulating brain aquaprin-4 (AQP4) water channels in a model of cerebral ischemia/reperfusion injury, which also contributes to reduced ICP and improved CBF.[96]

Goswami et al.[97] reported that hypothermic (20°C) piglets retained a static rate of autoregulation that was similar to that of normothermic piglets (0.65 *vs.* 0.72, P=0.40). The lower limits of autoregulation in hypothermic piglets was slightly lower

than that of normothermic piglets (35 mmHg *vs.* 39 mmHg, *P*=0.60). Another preclinical study[98] reported that the lower limits of autoregulation of hypothermia piglets was significantly decreased after cardiac arrest compared with a normothermic group, and CA was retained and stable in the setting of deep hypothermia. TH provides some form of protection to CA in animal experimental ABI models.[99] Bisschops et al.[100] performed 24 h of TH (32–34°C) immediately after admission on patients in a continuous coma after successful out-of-hospital resuscitation of a cardiac arrest. It was found that the average flow rate of the middle cerebral artery (MCA) changed by 3.60 ± 2.90% for every 1 mmHg change in $PaCO_2$ during TH while cerebrovascular reactivity to CO_2 was preserved, suggesting that CA was retained during TH.

Changes of CA During Hypothermia

Hypoxic-ischemic encephalopathy (HIE)

A systematic review and meta-analysis of 11 randomized controlled trials (RCTs) of TH initiated within 6 h after birth involving a total of 1505 neonates with moderate to severe HIE reported consistently beneficial effects of hypothermia.[101] Mild hypothermia was associated with a reduced risk of death or major neurodevelopmental impairment by 18 months of age (relative risk[RR]=0.75, 95% CI: 0.68–0.83). Importantly, cooling reduced mortality (RR=0.75, 95% CI: 0.64–0.88; 11 studies, 1468 infants) and reduced the incidence of neurodevelopmental disorders in survivors (RR=0.77, 95% CI: 0.63–0.94; 8 studies, 917 infants). Available evidence suggests that mild hypothermia can improve the middle childhood prognosis of patients with birth HIE.[84,102] The Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trail found that children in the hypothermia group had a higher survival rate without neurological abnormalities than those in the control group (45% *vs.* 28%; RR=1.60, 95% CI: 1.15–2.22) and were more likely to have an Intelligence Quotient score of ≥85 (52% *vs.* 39%; RR=1.31, *P*=0.04). The risk of cerebral palsy (21% *vs.* 36%, *P*=0.03) and moderate to severe disability (22% *vs.* 37%, *P*=0.03) was also reduced at 18 months of age.[102] To date, hypothermia to 33.5°C for 72 h is the only established treatment for reducing reperfusion injury after birth asphyxia.[103]

Hochwald et al.[104] reported on the effects of TH on cerebral circulation in 16 neonates with HIE. They found that superior vena cava flow was maintained despite a significant decrease in left ventricular cardiac output (LVCO) during TH, indicating that LVCO was preferentially redistributed to the brain. Furthermore, the CBF of neonates with brain injuries was significantly higher than those without brain injuries, a finding indicative of CA deficiency and excessive reperfusion after ischemia in neonates with severe brain injuries. Yoon et al.[105] examined the hemodynamics of 32 neonates with HIE and found that significant hemodynamic changes occurred during TH. The upper body blood flow (UBBF)/LVCO ratio was significantly higher in neonates with HIE than in healthy neonates. Neonates with a UBBF/LVCO ratio >55% had a significantly increased risk of hypoxic-ischemic lesions on brain magnetic resonance imaging (MRI) (odd ratio[OR]=13.0; 95% CI: 2.40–70.20). These observations indicate that LVCO has a clear preferential redistribution to the brain during a TH, with relatively reduced perfusion to other systemic organs such as the kidneys. The brain MRIs of neonates with HIE showed more pronounced cerebral preferential redistribution of LVCO, indicating that the degree of CA damage in neonates with brain injuries is more severe.

Smith et al.[106] lowered the body temperature to 18°C, 24°C, and 30°C in a total of 72 infants who received a cardiopulmonary bypass (CPB). The hemoglobin volume reactivity of infants at 30°C and 18°C was 0.0 (−0.020 to 0.004) and 0.59 (0.40–0.70), respectively. Lower level body temperature was positively correlated with hemoglobin volume reactivity, suggesting that TH may improve CA. However, the independent effect of body temperature on CA could not be determined in this study due to the inclusion of only two variables for analysis, i.e., body temperature and blood pressure. Burton et al.[107] measured MAP_{opt} during hypothermia, rewarming, and 6 h after rewarming in 19 neonates with HIE. At 2-year follow-up, neonates with ischemic brain injuries had a higher MAP_{opt} value, a longer period of blood pressure below MAP_{opt}, and greater deviation in blood pressure below MAP_{opt} during rewarming than those without impairments. Greater blood pressure deviation above MAP_{opt} during rewarming was associated with less disability and higher cognitive scores. Gilmore et al.[108] performed TH within 6 h of birth on HIE neonates, using diffusion tensor imaging MRI to suggest that faster cooling and strict adherence to 33–34°C might reduce cytotoxic edema, improve blood pressure regulation to within or close to MAP_{opt}, and decrease nerve damage.

Wang et al.[109] verified that TH can promote the recovery and maintenance of CBF after the return of spontaneous circulation (ROSC) after cardiac arrest. Twelve Wistar rats resuscitated after 7 min of asphyxial cardiac arrest were randomly divided into hypothermia (7H, *n*=6, 33–34°C) and normothermia groups (7N, *n*=6, 37.0 ± 0.5°C). Compared with the 7N group, TH continuously promoted CBF recovery to near baseline in the 7H group. CBF in the first 5–30 min after ROSC was 90.50 ± 3.40% in 7H and 76.70 ± 3.50% in 7N (*P* <0.01). The information quantity and neurologic deficit scores of the 7H ROSC group were significantly improved. This study therefore concluded that early TH facilitates the restoration of CBF back to baseline levels after cardiac arrest, thereby restoring brain electrical activity and improving neurological outcome.[109] Another result from the same research group demonstrated that, compared with normothermia, immediate hypothermia following ROSC can prolong the duration of hyperemia and delay the onset of hypoperfusion phase with a lower relative CBF, better neurologic deficit scores, and higher quantitative electroencephalogram-information quantity.[110]

Crippa et al.[111] performed TH on 50 patients with out-of-hospital cardiac arrest, with a core body temperature of 33.7°C (33.2–34°C) for 24 (23–28) h followed by rewarming and normothermia (NT) (36.9 [36.6–37.4]°C). The mean velocity index (Mx) during TH was lower than normothermia (0.33 [0.11–0.58] *vs.* 0.58 [0.30–0.83]; *P* = 0.03). During normothermia, Mx was higher in patients with a poor neurologic prognosis than others (0.63 [0.43–0.83] *vs.* 0.31 [−0.01 to 0.67]; *P*=0.03). In a multivariate analysis, high Mx (CA deterioration), initial non-shockable rhythm, and a highly malignant electroencephalography pattern (HMp) were associated with in-hospital mortality during NT. High Mx during normothermia and HMp was associated with a poor neurologic outcome. It was suggested that CA

deterioration was independently associated with poor prognosis, and that TTM survivors had improved CA.[111]

TBI

Clifton et al.[112] in their preclinical study were the first to report that mild TH improved the motor function recovery of TBI rats. Subsequent preclinical studies using similar or different TBI models demonstrated that an early posttraumatic hypothermic strategy (within 5 min) can reduce contusion volume and protect vulnerable neurons.[113,114] TH also mitigated the severity of diffuse axonal and BBB injuries.[115,116] Recent studies have shown that TH can also improve chronic behavioral outcomes, including sensorimotor and cognitive function.[117]

Although preclinical studies have concluded that hypothermia is an effective treatment for TBI, there appears to be a disconnect between clinical and experimental data. Clinical trial data are not very convincing. Marion et al.[118] published a randomized study in 1997 in which 84 patients with severe TBI were treated with hypothermia (33°C for 24 h). Patients with a GCS score of 5–7 at admission had significantly better neurological recovery at 3 months and 6 months. Jiang et al.[119] in their randomized study of 215 TBI patients reported that prolonged TH (5 days) was effective at improving neurological prognosis. However, higher quality clinical trials suggest a neutral or even negative effect of TH on long-term neurologic outcome, as exemplified by data from the Eurotherm3235 trail and Polar RCT.[120–124]

Although clinical evidence does not support the routine use of prophylactic TH in ABI, the hazards of hyperthermia support the role of TTM in the treatment of aggressive fevers. TTM remains an option for treatment-resistant refractory ICP and cerebral edema.

Animal studies have shown that blood vessels remain responsive to various stimuli during hypothermia and that hypothermia provides some form of protection to CA in TBI rats.[99] Oshorov et al.[125] measured CA function during TH in 14 severe TBI patients (Glasgow outcome scale [GOS] <9). The patients had an average body temperature of 38.2 ˚C (37–39.8 ˚C), an ICP of 27 mmHg (16–45 mmHg), and a PRx of 0.25 (−0.15 to 0.70) before TH. During the induction of TH, the patients' ICP, body temperature, and PRx decreased simultaneously. PRx did not change significantly during the hypothermia maintenance phase. This result suggests that TH improves CA. The CENTER-TBI substudy[126] enrolled 249 TBI patients who underwent continuous multimodal monitoring during the initial 7 days following trauma. Mild TH (core body temperature: >35°C), mild hyperventilation ($PaCO_2$: 35–40 mmHg), ICP-guided deep sedation, and CPP-guided vasoactive drug application decreased (improved) the daily average PRx and % time with PRx >0, suggesting that mild TH has a certain potential therapeutic effect on CA dysfunction.

IS

Strokes are the leading cause of death and disability worldwide, with IS accounting for 70% of all strokes.[127] The tenet "Time is Brain" underlies the current therapeutic approach to AIS, emphasizing that neural tissue is rapidly and irreversibly lost as stroke progresses. Interventional reperfusion therapy should therefore be initiated urgently. This time-ischemia relationship is mediated by the presence of collaterals that slow the progression of the infarct and prolongate the therapeutic window.[128] The main objective of AIS is to salvage the viable penumbra by restoring perfusion to the ischemic brain. However, morbidity and mortality from AIS remain high due to the narrow therapeutic window for recanalization.[129,130] Furthermore, not every patient who has a successful recanalization has a good clinical outcome, which is termed a futile recanalization.[131] It is therefore important to explore alternative and adjuvant therapies.[132,133]

Supportive hemodynamic therapies aimed at optimizing ischemia-area perfusion can protect the brain and may even prolong the therapeutic window for reperfusion therapies. However, our knowledge of how to implement these therapies in the setting of the complex pathophysiology of cerebral ischemia is incomplete. MAP_{opt} management is highly dependent on CA integrity to protect the brain from ischemia or hyperperfusion. Studying the CA characteristics of IS is therefore important to guiding therapies tailored toward improving cerebral hemodynamics.

dCA has different characteristics during the acute (<48 h), subacute (48 h to 7 days), and chronic (>7 days) phases of IS.

Acute phase (<48 h)

Petersen et al.[40] applied transfer function analysis (TFA) to patients within 48 h of a large vessel stroke and found that the affected hemisphere (AH) had significantly lower phase shift than the unaffected hemisphere (UH). The autoregulation index was reduced in AH patients with a mild IS at 36 h[134] and mild-to-moderate IS at 48 h regardless of sub-type.[135] In a study by Saeed et al.,[136] the autoregulation index decreased within 48 h of a mixed-etiological stroke compared with healthy controls, but there were no differences between hemispheres. dCA may also affect the incidence of brain injuries after recalcitrant events such as a hemorrhagic transformation and/or reperfusion injury.[39,137]

Subacute phase (48 h to 7 days)

In contrast with the acute phase, the majority of studies that evaluated dCA during the subacute phase reported impaired CA even during the early (48–96 h) subacute phase of mild to moderate AIS.[134,138–141] During the late subacute phase (5–7 days), dCA has been shown to be not only impaired[32,134,142–145] in the AH but the UH as well.[32,142,143]

Chronic phase (>7 days)

Novak et al.[146] reported that the dCA of the AH was still low in patients 2 months after mild MCA infarctions. Salinet et al.[147] observed that dCA was complete during the early subacute phase (72 h) and decreased during the late subacute phase (14 days), but recovered 30 days and 3 months post-stroke. Similarly, Kwan et al.[148] followed 10 patients with MCA infarcts >3 months, noting increased phase shift >3 time points (<7 days, 6 weeks, and 3 months), which represents improved dCA between the subacute and chronic phases. dCA changes sustained during the chronic phase (>6 months) may be associated with functional deficits and brain atrophy.[149]

In summation, CA may be an attractive therapeutic target that can benefit patients with IS by improving collateral vascular responses, maintaining blood flow to peri-ischemic regions,

and avoiding reperfusion lesions.[131,150] CA may be important to plan short- and long-term treatment strategies for IS. An ongoing multicenter project entitled "Identifying New Targets For Management and Therapy in Acute Stroke" (INFOMATAS)[151] was launched in 2016 to prove this inference and to improve our better understanding of dCA in IS.

TH is a novel treatment method for AIS that has been heavily studied and shown to be one of the most effective adjunctive therapies in preclinical models.[152–156] Mild or moderate TH initiated within a few hours of an ischemic attack has been shown to have a neuroprotective effect.[157,158] Mild TH initiated during or after a short delay following an acute IS reduces the infarct size and reduces functional impairment.[152,159] Furthermore, recanalization of occluded vessels within a specific time window after ischemia (recanalization therapy) increases the possibility of a favorable outcome.[157] TH was very effective after recanalization.[160,161] In a transient middle cerebral occlusion model, hypothermia demonstrated sustained neuroprotection. However, its performance in the setting of permanent middle cerebral occlusion was contradictory. The role of TH combined with recanalization in the clinical environment is therefore very important.[55]

SAH

Using diffusion-weighted imaging (DWI) and magnetic resonance spectroscopy (MRS), Schubert et al.[162] evaluated the neuroprotective effects of hypothermia on acute changes after experimental SAH. It was found that hypothermia improved early cytotoxic edema, lactate accumulation, and metabolic stress response in SAH rats.

Badjatia et al.[163] reported on the effects of TTM on the functional outcomes (GOS at discharge, MRS at 3 months and 12 months) on 40 SAH patients. TTM was activated with a target temperature of 37°C when core body temperature was ≥38.3°C for 2 h. Patients who received TTM had a better functional outcome than those who received "standard care."[163] Another study found that mild TH for 2 h after a SAH could improve neurologic deficits. Prolongation of TH therapy by 3 h led to decreased ICP and reduced water during the initial 7 days after intervention.[164]

Ianosi et al.[165] studied the effects of body temperature on CA in poor-grade aneurysmal SAH patients by using intravenous non-steroidal anti-inflammatory drugs and non-opioid analgesics to achieve a normal body temperature or relieve pain. Patients were divided into two groups: febrile episodes (T_{max} ≥38.3°C within 1 h before infusion) and non-febrile episodes (T_{max} <38.3°C). After drug administration, PRx decreased significantly from baseline 0.17 (IQR: 0–0.34) to 0.07 (IQR: −0.01 to 0.22; P <0.001). It was suggested that CA impairment improved significantly after antipyretic therapy (45% *vs.* 30%, P <0.001), although the cold temperatures may worsen complications related to elevated ABP. In a large multicenter randomized study, mild intraoperative hypothermia during intracranial aneurysm surgery failed to improve the neurologic outcomes of favorable grade (WFNS grade 1–3) SAH patients.[166] A clinical study conducted by Seule et al.[167] evaluated the feasibility and safety of mild TH for high-grade aneurysmal SAH patients with intracranial hypertension and/or cerebral vasospasm. Continuous systemic TH may be the last option for young SAH patients with refractory intracranial hypertension or cerebral vasospasm.

ICH

Spontaneous ICH accounts for 10–30% of all stroke cases, with a mortality rate as high as 30–50%.[168] Primary ICH is caused by the rupture of intracerebral vessels caused by chronic lesions created by arterial hypertension or cerebral amyloid angiopathy, whereas secondary ICH is associated with underlying causes such as arteriovenous malformations, aneurysms, sinus thrombosis, and brain tumors. Primary ICH is discussed in this section.

Because patients with a primary ICH often have chronic arterial hypertension, they may have an abnormal CA before the stroke with a right-shifted plateau.[169] Previous studies on CA after a primary ICH have been limited. The results of TCD-based CA studies are somewhat ambiguous, as some works suggest that CA is disordered after ICH[170,171] while others find it intact.[172] In two other studies based on PRx and hence patients with large ICHs, the CA status was commonly impaired and associated with a worse clinical outcome.[173,174] Diedler et al.[175] found in a small ICH case series that higher (worse) PRx was slightly associated with brain hypoxia and impaired energy metabolism. Three studies using TFA as an indicator of CA in ICH patients suggested that compared with controls, ICH patients had a slightly higher gain (standardized mean difference [SMD]=0.68, 95% CI: −0.05 to 1.40, P=0.07) in the AH and a significantly higher gain in the UH (SMD=0.98, 95% CI: 0.21–1.74, P = 0.01). Phase was significantly reduced in ICH patients, suggesting that CA of both cerebral hemispheres may be impaired. These inconsistent research findings may be the result of various factors, such as the selection of research subjects, sample size, timepoint selection, and CA monitoring methods.

The evolution of CA after ICH may be a dynamic process.[176] Compared with healthy controls, the phase shift of TFA was significantly lower during the early stage (1–6 days) of ICH, with further deterioration 7–13 days after hemorrhage.[171,177,178] CA rebounded 30 days after ICH, but did not recover completely.[171] Perihematomal edema, the size of the hematoma, and GCS score may contribute to dCA impairment 10–20 days after an ICH.[179,180]

A recent meta-analysis of preclinical studies evaluating TH in the setting of cerebral hemorrhage[181] concluded that hypothermia can reduce edema, protect the BBB, and improve behavioral outcomes. However, the optimism regarding the role of TTM in the early treatment of brain injuries has been weakened due to the failure of continuous clinical trials to improve clinical prognosis. Hypothermia can affect the procoagulant and fibrinolytic systems, predisposing to acute bleeding. Early cooling can increase bleeding, and the protective effects of hypothermia may only be observed if cooling is delayed for 12 h.[182,183] Kollmar et al.[184] reported that 12 patients with large ICHs were treated with TH (35°C) within 3–12 h of symptoms onset for 10 days. The edema volume in the TH group remained stable for >14 days, while it increased significantly in the control group (subjects from the local ICH database). A recent systematic review and meta-analysis[185] revealed that hypothermia can reduce the incidence of delayed cerebral ischemia, but had no effect on mortality or outcomes. The clinical effects of TH on

hemorrhagic strokes remain unclear. This may be due to the factors such as fever, vasospasm, surgical techniques, and the need for decompressive craniotomy, which can influence the patient's prognosis. Clinical trials of target temperature management after ICH (TTM-ICH)[186] and cooling in intracerebral hemorrhage (CINCH),[187] which seek to explore the safety and efficacy of hypothermia in patients with ICH, are ongoing.

Effects of Rewarming Strategies on CA

Reoxygenation increases oxidative stress after asphyxic injuries.[188] Although hypothermia can attenuate this reaction, oxidative stress may be restored during rewarming. Changes in proinflammatory cytokine levels during the rewarming may affect vascular reactivity[189] disrupting CA. Animal studies have shown that rapid rewarming may reverse the inhibitory effects of hypothermia on potentially injurious processes such as oxidative stress and excitotoxin release,[190,191] while slow rewarming may improve neurologic outcomes. In neonatal piglets exposed to severe hypoxic-ischemic, rewarming at 0.5°C/h following 18 h of hypothermia resulted in reduced caspase-3 activation in the cerebral cortex and white matter tracts compared with rewarming at 4°C/h.[192,193] Moreover, in adult gerbils subjected to transient forebrain ischemia, rapid rewarming after 2 h of hypothermia was associated with transient uncoupling of CBF and metabolism and lost neuroprotection in the hippocampal CA1 region, whereas slow or gradual rewarming prevented these processes.[194] Consistent with preclinical studies, clinical trials have shown that rapid rewarming can affect brain recovery and cerebrovascular reactivity by decoupling of brain circulation and metabolism.[195] This was prevented by slow or stepwise rewarming.[195]

Larson et al.[196] established a model of hypoxic asphyxial cardiac arrest in newborn piglets that was followed by 2 h of normal temperature and 20 h of TH. The lower limits of autoregulation was not affected by the arrest (P=0.60), temperature (P=0.08), or the interaction between the arrest and temperature (P = 0.73). In the hypothermia group, the slope of cortical laser Doppler flow (LDF) relative to CPP during induced hypertension was not significantly different from that of the initial blood pressure, regardless of rewarming (P=0.10). This suggests that rewarming does not change lower limits of autoregulation, nor does it affect the autoregulation of hypertension after an asphyxia cardiac arrest.

However, the results of clinical studies have been inconsistent. Joshi et al.[197] monitored the Mx values of 127 patients undergoing cardiac surgery before hypothermic CPB (baseline), during the cooling and rewarming phases of CPB, and after CPB. Mx was greater (deteriorated) during the cooling process (left: 0.29 ± 0.18; right: 0.28 ± 0.18) than at baseline (left: 0.17 ± 0.21; right: 0.17 ± 0.20; $P \leq 0.0001$), suggesting that CA is impaired during CPB. The Mx in rewarming phase was significantly higher (worsen) than before CPB or during the cooling phase (left: 0.40 ± 0.19; right: 0.39 ± 0.19) indicating that rewarming further aggravates CA. Oshorov et al.[125] observed that the PRx of severe TBI (GOS <9) patients began to rise to 0.2 (−0.2 to 0.32) during the rewarming phase after TH and lasted until the post-rewarming stage, although the ICP decreased slightly (15 mmHg *vs.* 18 mmHg) compared with the hypothermia maintenance stage. It is therefore thought that the rewarming phase after TH is the most dangerous period for CA dysfunction.

Lavinio et al.[198] performed moderate TH (34.2°C) in 24 TBI patients with refractory intracranial hypertension, during which the PRx did not change significantly from baseline (−0.01 ± 0.21 *vs.* 0.001 ± 0.20) or during slow rewarming to 37°C. However, the PRx was significantly increased (0.32 ± 0.24, $P < 0.0001$) in 17 patients (70.1%) whose rewarming temperature exceeded the 37°C threshold while although ICPs did not significantly change, indicating severe CA damage. These results suggest that CA is independently correlated with brain temperature after rewarming (R=0.53; P <0.05).

Similarly, Howlett et al.[199] found that compared with neonates with no or mild brain injuries, neonates with moderate/severe brain injuries had a longer duration and a greater magnitude of with MAP below MAP_{opt} during the hypothermia to rewarming process. The effects of rewarming strategies, such as rewarming timing, speed, and endpoint, on CA should not be ignored. Unfortunately, no relevant RCTs have been performed.

Conclusions

In summary, CA dysfunction is a potential pathologic defect that may lead to secondary injury and worse functional outcomes in the setting of various acute neurological diseases.[30,31] Compared with hypoxic brain injuries after cardiac arrest, TBI, IS, ICH, and SAH have more heterogeneous pathologies, severities and clinical courses. What diseases benefit from TH remains to be determined, and clinical trial findings are controversial. Patient selection, timing, cooling depth, duration, and rewarming strategy may affect results. Determining how brain injury patients benefit from TH needs to be addressed. The safety and feasibility of a CPP_{opt}-oriented treatment target has recently been explored in a multicenter prospective RCT (CPP_{opt} Guided Therapy, COGiTATE),[200,201] the results of which may provide a therapeutic basis and direction for CA-oriented TTM.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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