Review Article

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# Research progress of selective brain cooling methods in the prehospital care for stroke patients: A narrative review

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**Abstract:**

Over the past four decades, therapeutic hypothermia (TH) has long been suggested as a promising neuroprotective treatment of acute ischemic stroke (AIS). Much attention has focus on keeping the hypothermic benefits and removing side effects of systemic hypothermia. In the past few years, the advent of intravenous thrombolysis and endovascular thrombectomy has taken us into a reperfusion era of AIS treatment. With recent research emphasizing ways to plus neuroprotective treatments to reperfusion therapy, the spotlight is now shifting toward the study of how selective brain hypothermia can offset the drawbacks of systemic hypothermia and be applied in prehospital condition. This mini-review summarizes current brain cooling methods that can be used for inducing selective hypothermia in prehospital care. It will guide the future development of selective cooling methods, extend the application of TH in prehospital care, and provide insights into the prospects of selective hypothermia in AIS.

**Keywords:**

Acute ischemic stroke, neuroprotection, prehospital care, selective hypothermia, therapeutic hypothermia

## Introduction

Acute ischemic stroke (AIS) is a major cause of human death and long-term disability worldwide, leading to significant social and economic burden.[1] Therapeutic hypothermia (TH) is one of the most promising neuroprotective treatments for AIS.[2] TH has been demonstrated to be effective in exerting neuroprotective functions by regulating cerebral metabolism, inhibiting inflammation and apoptosis, eliminating reactive oxygen species, and maintaining the integrity of blood–brain barrier.[3] Disappointingly, the neuroprotective effects of TH on AIS have not yet been successfully translated to clinical treatment. Therefore, exploring effective and feasible cooling methods for AIS treatment are urgent.[4,5]

Since brain is one of the most energy-consuming organs, it is crucial to perform the neuroprotective treatment as early as possible to salvage more endangered cerebral tissues and achieve a superior outcome. Preclinical studies have suggested that initiating hypothermia in the early ischemic phase combining with successful reperfusion could induce the most beneficial effect.[3,6-8] In recent years, the treatment of AIS has been revolutionized by the development of reperfusion therapies including thrombolysis and endovascular thrombectomy. In this context, TH treatments, which may extend the time window of reperfusion therapies to benefit more patients, should be reconsidered an adjuvant treatment to reperfusion therapy.[9] Therefore, cooling methods, which can be used in prehospital setting by emergency medical service personnel and cover the time delay from the

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ambulance to admission, seem to be the ideal methods of TH for AIS patients.[10]

Hypothermia can be roughly divided into systemic cooling and selective cooling. Systemic cooling is the most common and classical method of hypothermia, which is relatively easy to practice. However, side effects along with the impractical depth and duration of systemic hypothermia, such as shivering, infection, and coagulation disorder, significantly narrow its clinical scope.[3] In contrast, selective brain cooling can avoid such side effects and retain the benefits of hypothermia.[11] Intra-arterial selective cooling infusion, as an invasive brain cooling method, can cool the brain rapidly to mild hypothermic status (34°C–36°C) in minutes. However, it is not fit for prehospital conditions because of endovascular procedures to flush the ischemic territory with cold solutions.[12] Noninvasive brain cooling methods, mainly including surface brain cooling and intranasal brain cooling, have progressed significantly over the past few years. More importantly, as AIS treatment has advanced to recanalization era, these noninvasive brain cooling methods will serve as an important adjuvant treatment which can be well combined with prehospital care and following endovascular therapy.[13]

In this review, we aim to summarize the research progress of noninvasive selective brain cooling methods, providing a brief assessment of laboratory and clinical data toward guiding the future development of selective cooling methods, extending the application of TH, and providing insights into the prospects of selective hypothermia in AIS treatment.

## Optimal Duration and Depth of Selective Brain Cooling in Prehospital Care

The duration and depth of hypothermia are two critical parameters in hypothermia therapy. When TH is considered a cytoprotective treatment, there has not been a consensus on the duration of TH. Although longer cooling duration has been suggested to offset the moderate delays in the cooling initiation, prolonged hypothermic therapy will also increase the risk of side effects, such as infections.[3,8] To balance the benefit and risk, a 12–24 h TH has been widely accepted as the optimum course.[3,14,15] However, as a conjunctive treatment in prehospital care, TH may only need to cover the time delay from the ambulance to admission. As a result, TH that maintained for at least 2–3 h may be appropriate during the patient transfer.

Likewise, the ideal temperature for therapeutic hypothermic is unknown. Wu *et al*. have analyzed and summarized the findings of preclinical and human studies on optimal depth of TH for AIS treatment and suggested that 33°C–34°C may be suitable.[3] Nonetheless, the neuroprotective effects of both mild (34°C–36°C) and moderate (30°C–33°C) hypothermia have been reported.[8] As an adjunct to reperfusion and a prehospital neuroprotective treatment, a mild hypothermia may be easier to achieve and can play a relatively effective role on stroke patients.

## Surface Brain Cooling

Surface brain cooling is the most practical and feasible method of noninvasive brain cooling, which has been used in improving the neurodevelopment of newborns with neonatal ischemic hypoxic encephalopathy.[16-18] Ice helmet is one of the most widely used methods, and the simple and noninvasive characteristics make it possible being used for prehospital emergency care. The decrease of surface temperature in head and neck by ice helmet can effectively conduct to brain tissues and lower the temperature there. Traditional helmets could lower the brain temperature by almost 1°C in 2 h.[19] The process of heat transfer makes the cooling rate not as fast as desired. Moreover, as other cytoprotective treatments, ice helmets have not been successfully applied in clinical trials to generate neuroprotection without reperfusion in previous studies.[20] After highly effective reperfusion therapy is widely available and the cooling rate is successfully improved, as adjuvant treatments to thrombolysis or endovascular thrombectomy, cooling helmets are promising to be neuroprotective for AIS.

Recent studies used novel technology in space to develop new helmets. Technology innovation has reduced the weight of helmets and improved the cooling efficacy, facilitating the clinical use of cooling helmets. Wang *et al*. designed and developed a cooling helmet by using the National Aeronautics and Space Administration spinoff technology, which could reduce the brain temperature (0.8 cm below the cortical surface) by 1.84°C on average (range: 0.9°C–2.4°C) within 1 h of application and lower than 34°C in a mean of 3.4 h (range: 2–6 h) without any severe complications. Moreover, it took about 6.67 h (range: 1–12 h) before systemic hypothermia (<36°C) occurred.[21] The delayed systemic hypothermia guarantees a distinct temperature gradient between the core and brain temperatures that can be maintained throughout the hypothermic period, which provides a significant local hypothermia to minimize the systemic complications. Diprose *et al*. recently developed a cooling cap that called WElkins Temperature Regulation System, 2nd Gen.[22] After wearing this cooling cap for 80 min, the mean brain temperature was reduced by 0.9°C ± 0.7°C, while the core body temperature only decreased by 0.3°C ± 0.1°C. These two methods have significantly improved the efficacy

of surface brain cooling. More importantly, as portable helmets, the convenience of the two methods makes it easy to be applied for prehospital care.

## Intranasal Brain Cooling

Cooling the nasal cavities can also lower brain temperature due to the anatomic proximity of the internal carotid artery to the cavernous sinus.[23] Although most intranasal cooling methods still fail to meet the clinically required standards of selective hypothermia due to sympathetic predominant vasoconstriction obstructs heat transfer, its advantageous anatomic position provides a good route to achieve a faster cooling rate than surface brain cooling.[8]

Covaciu *et al*., using intranasal balloons catheters with the circulation of 20°C saline for 60 min, successfully reduced the brain temperature by 1.7°C ± 0.8°C in 10 awake volunteers.[24] The cooling rate was relatively fast, and the only side effect was increased nasal secretion. More importantly, the good tolerance of this cooling method made it acceptable to the awakening patients. These advantages facilitated it as a potent TH method in prehospital care. However, more evidence was still needed to prove its neuroprotective effects on AIS patients as an adjuvant treatment to reperfusion therapy in future clinical trials.

Since the intranasal balloons improved the cooling efficiency but still failed to achieve the target temperature in limited time, researchers tended to develop more sophisticated equipment to achieve rapid and safe cooling. The RhinoChill device, a type of transnasal cooling device, can initiate a rapid brain cooling by delivering coolant and oxygen mixture to the nasal cavity through a catheter system.[25] The RhinoChill device decreased the tympanic temperature of cardiac arrest patients by an average of 1.3°C within about 26 min. RhinoChill device could also reduce brain temperature in patients with traumatic brain injury or stroke by 1.4°C ± 0.4°C after 1 h treatment.[26,27] The RhinoChill device was safe in both trials. Only three patients showed an increase in blood pressure when initiating RhinoChill treatment.[28] The RhinoChill device exhibited effective hypothermic potential and safety outcomes, thus it could be considered a choice for TH in the prehospital care. However, the efficiency of the RhinoChill device to reduce brain temperature was still needed in the future.

Seyedsaadat *et al*. developed a NeuroSave system which circulated chilled saline (1–3 L/min) within the pharynx and upper esophagus. The NeuroSave system could induce a rapid brain-targeted hypothermia, in which 6°C saline decreased brain temperature by 3°C within 15 min. What's more, the NeuroSave system simultaneously maintained a favorable body–brain temperature gradient throughout the cooling process.[29] The NeuroSave system was well tolerated as none of the device-related adverse effects occurred in this study. Therefore, this system was considered the most effective device in selective brain cooling at present.

When intranasal cooling is used in clinical care, the tissue damage in the nose and cheeks due to local overcooling should be improved in future studies.[13] Moreover, both the RhinoChill device and the NeuroSave system achieved the goal of rapid brain cooling, but the two devices needed to be used under anesthesia. The devices should be modified to be fit for awakening patients. Then, intranasal brain cooling device could be well used in selected AIS patients in prehospital care.

When the cooling velocity is not satisfactory, the noninvasive selective brain cooling methods can be used in conjunction with other hypothermia methods, such as pharmacological hypothermia. Chlorpromazine and other hibernate mixtures have been demonstrated to be effective in reducing brain temperature swiftly and smoothly in preclinical experiments.[30] An *et al*. have proved that phenothiazine neuroleptics (chlorpromazine and promethazine) combined with physical cooling achieved a more faster reduction of temperature in ischemic rats than physical hypothermia alone, accompanied by more obvious decrease of brain infarct volumes and improvement of neurological deficits.[31] Besides, of other classes of pharmacological agents/agonists with hypothermic effects, transient receptor potential vanilloid 1, neurotensin, and thyroxine families have been shown to have anti-shivering effects, whereas cannabinoid and opioid families have been linked to a thermoregulatory function.[32] Thus, after an optimum dose is determined and a reliable therapeutic window is established, these agents may be efficacious in combination therapy with physical hypothermia in reducing discomfort, quickening the cooling process, and prolonging tolerable cooling duration. The combination of these two hypothermia treatments has potential to become the mainstream method for clinical hypothermia therapy in the future.

## Prehospital Selective Hypothermia in the Reperfusion Era

The application of mobile stroke units, which are equipped with a trained staff and a computed tomography scanner, enable faster prehospital treatment with tissue plasminogen activator (tPA) and improve the outcome of AIS patients compared to standard thrombolysis in the emergency department.[12] Although thrombolysis of tPA is temperature-dependent and the activity of tPA

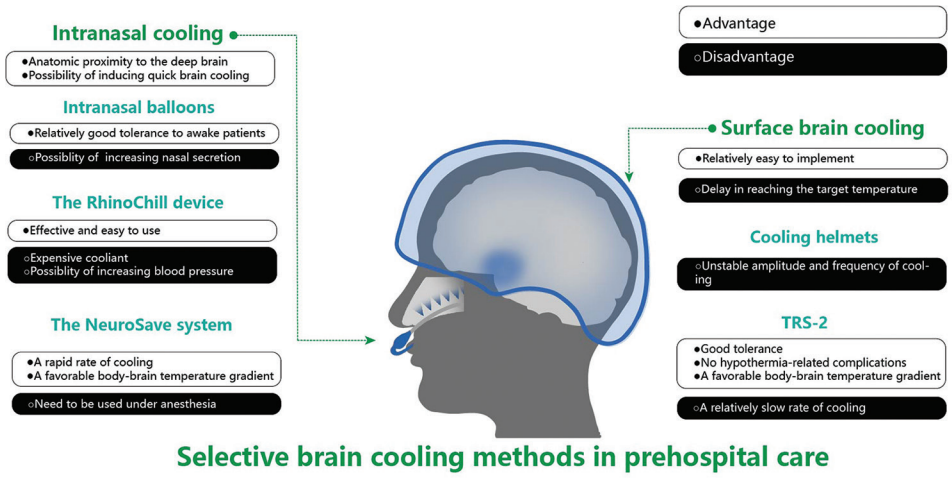


**Figure 1:** Advantages and disadvantages of different methods of selective brain cooling in prehospital care. TRS: Temperature regulation system

will be downregulated as the decrease of temperature,[33] TH reduces the risk of hemorrhage transformation caused by tPA.[34] Furthermore, the clotting and fibrinolytic systems including platelet production are also suppressed at lower temperature.[35] A recent meta-analysis demonstrated that tPA combining with mild hypothermia generated a more beneficial role in reducing nerve function impairment and inflammatory reactions compared to tPA alone.[36] These advantages highlight the possibility of selective hypothermia used in the prehospital setting.

## Conclusion

Prehospital selective hypothermia therapy for AIS might be more practicable when it has the following characteristics: (1) it can effectively and timely reduce brain temperature; (2) it does not significantly affect core temperature; (3) it can last 2–3 h to cover the time from the ambulance to admission; (4) it has no severe side effects; (5) it is easy to perform and transfer; and (6) it has economic applicability.

Selective brain cooling has been demonstrated to be effective in maximizing hypothermic benefits and minimizing relative side effects.[37] Selective brain cooling methods should have the dual characteristics of efficient and stable cooling as well as high selectivity, so as to extend the time window of reperfusion therapies. Current selective brain cooling methods are still limited in the prehospital emergency treatment of AIS patients and cannot provide comprehensive neuroprotective effects if applied sepatately [Figure 1]. Therefore, physical cooling methods including surface brain cooling and intranasal brain cooling can be combined with pharmacological hypothermia, as adjuvant treatments to reperfusion therapy, to achieve a better cooling efficacy and a superior clinical outcome.

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## Conflicts of interest

Dr. Xunming Ji is the Editor-in-Chief of *Brain Circulation*. The article was subject to the journal's standard procedures, with peer review handled independently of this Editor and their research groups.

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