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# Targeted Temperature Management in Traumatic Brain Injury

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## Abstract

Traumatic brain injury (TBI) remains an important health problem worldwide. Pathophysiology of TBI has been intensively investigated. Many novel theories related with pathophysiology of TBI have been regularly proposed. Targeted temperature management (TTM), previously known as therapeutic hypothermia, has a well-established benefit for application as neuroprotective therapy and intracranial pressure (ICP) control. With the novel automatic feedback machine, application of TTM in clinical practice becomes much feasible and safe. Many pre-clinical trials of TTM in models with TBI demonstrated usefulness in multiple aspects. The successful story of TTM in patients with restore of spontaneous circulation (ROSC) after cardiac arrest is a good example for bench to bedside. In the past decade, many clinical trials of TTM in patients with TBI have been conducted with the hope to be another successful study.

**Keywords:** targeted temperature management, traumatic brain injury, intracranial pressure, surface cooling, endovascular cooling, shivering, skin counter warming

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## 1. Introduction

Therapeutic hypothermia provides neuroprotective effects against acute brain injury with hypoxic ischemic encephalopathy in patients with post-cardiac arrest [1, 2]. However, since the meeting of five major professional physician societies, the term “therapeutic hypothermia” has been substituted with “targeted temperature management (TTM)” [3]. TTM is characterized as a kind of therapy that patient’s core temperature is reduced until a therapeutic

target with the rationale in salvaging or relieving damaged brain [4]. TTM is accepted as an established treatment in patients with restored spontaneous circulation following cardiac arrest [5]. Pertaining to standard guidelines for resuscitation, TTM is a class I recommendation in the post-cardiac arrest care section [6–10].

Traumatic brain injury is a catastrophic health problem with high morbidity and mortality rate throughout the world [11]. One of the most important characteristics of TBI is its heterogeneity [12]. The heterogeneous nature of TBI leads to broad spectrum of clinical features, variable in outcomes, and unpredictable prognosis [13]. These heterogeneities are also related with failure to demonstrate effectiveness of the treatment in many clinical trials leading to the wide gaps of evidence-based treatment for TBI [14]. Among several options of treatments available for TBI, TTM is one of the potentially effective treatments in patients with TBI.

## 2. Pathophysiology of traumatic brain injury (TBI)

The primary pathological damage of brain in TBI derives from two important mechanisms. The first mechanism is mechanical insult or direct brain injury that leads to parenchymal contusion, bruise, laceration, and hemorrhage [15–17]. This direct brain injury leads to auto-regulation break down and then impairment of cerebral blood flow (CBF) [15]. This so-called “neurometabolic cascade” mechanism resembles the ischemic-mimic pathophysiology [18]. In this cascade, brain tissue switches the energy resource to anaerobic metabolism, leading to the collection of lactate and sodium-potassium pump failure [19]. Cells become depolarized after the pump failure before calcium gets influx [20]. Accumulation of intracellular calcium leads to uncontrolled release of excitotoxic proteins [21]. Mitochondrial dysfunction and cell membrane disruption produce necrotic cells and then programmed cell death by apoptosis. Excitotoxic proteins and other toxic chemicals, including free oxidative radicals, reactive oxygen species, endonucleases, phospholipases, and ATPases, are released into the surrounding by these death cells [22]. These insults further harm adjacent cells. Immunoinflammatory cells come in to eat up death cells and liberate many mediators and cytokines [23]. Blood-brain barrier (BBB) is destroyed by this immunoinflammatory process before leakage of large protein molecules from disrupted BBB especially albumins lead to cerebral edema causing pressure effect and further destruction to environmental brain tissue [24–26]. The inducible nitric oxide synthase (iNOS), which is related to severity of TBI, is significantly expressed during day 3–7 after onset of TBI [27]. Autophagy, previously known as autophagocytosis, is a housekeeping mechanism to remove cellular degradation [28]. Autophagy plays a major role in eliminating debris after TBI [29]. Dysfunction of autophagic activities leads to neuronal cell death in animal models with TBI. Autophagy has neuroprotective properties against TBI [30].

Another primary damage is indirect brain injury related with acceleration or deceleration of the brain. This indirect insult leads to widespread axonal injury and then generalized brain edema. Clinical manifestations of these primary insults begin right at the initiation of TBI. The secondary injury subsequently comes after the primary damage. Therefore, the clinical presentations of this secondary injury, including elevated intracranial pressure (ICP) and brain

ischemia, come a bit late [31]. Once the primary damage occurs, it is almost impossible to be salvageable. Any treatments seem to be not effective to relieve the primary pathological damage [32]. The secondary insults may show responsiveness to the treatments [15, 16].

### **3. Pathophysiology of intracranial pressure (ICP)**

Alexander Monro was the first scientist who presented the theory about intracranial pressure during eighteenth century before George Kellie presented his article confirmed Monro's theory 40 years later, known as Monro-Kellie doctrine [33, 34]. This doctrine describes that due to the brain which is surrounded by rigid meninges and skull with constant volume, increment in the quantity of the intracranial compartments will have an effect on intracranial pressure (ICP) [35]. The intracranial compartments, which are actually persistent, consist of brain tissue, cerebrospinal fluid (CSF), and blood. An expansion in either compartment or growth of a space-occupying lesion is going to raise intracranial pressure and may need a reduction in other compartments so as to maintain the constant intracranial volume [36]. A further volume expansion can firstly push CSF and venous blood away from the skull to avoid ICP elevation. However, the ability for ICP protection from volume expansion has significant restriction. If the expansion still goes on until beyond capacity of compensation, ICP finally becomes elevated [37]. ICP elevation produces cerebral herniation [38]. Cerebral perfusion pressure (CPP), which is calculated by mean arterial pressure (MAP) minus ICP, is lower when ICP is elevated. Then, depressed CPP leads to diminution of cerebral blood flow (CBF) [39].

The neurometabolic cascade from primary brain damage leads to cerebral edema and then elevated ICP as mentioned above. This secondary damage by ICP elevation is due to depressed CPP and declined CBF [40]. When CPP or CBF is declined, there is no enough blood to deliver nutrients for the cells [41]. Elevated ICP, particularly which of more than 20 cm of water, in patients with TBI is associated with unfavorable outcomes and increased mortality [42, 43]. The level of CPP in patients with severe TBI should be kept above 60 mm of mercury to achieve favorable outcomes [44].

### **4. Mechanisms of TTM actions on TBI**

The defensive properties of TTM on neurometabolic cascade of TBI are considered to be numerous mechanisms of actions [45]. The best known effect of TTM is the protective function against hypoxic/ischemic encephalopathy [46]. Similar protective actions of TTM against ischemic cascade, for example, reduction of oxygen free radical, inhibition of excitatory amino acid release, prevention of calcium influx, and reduction of cytokines and mediator release are all protective effect against neurometabolic cascade [6, 45, 47]. TTM also relieves TBI via its alternative actions including brain metabolism reduction, prevention of cortical spreading depolarizations, mitochondrial protection, and preventive effect on cell membrane disruption [40, 47]. These effects can delay the neurons and the glials to deteriorate into apoptosis [48].

TTM suppresses iNOS expression leading to outcomes improvement in animal models with TBI [49]. Protective effect on blood-brain barrier disruption is another well-known action of TTM, which helps to reduce brain swelling and lower ICP [48, 50]. Effectiveness of ICP reduction by TTM in various models with TBI has been demonstrated in many clinical and experimental studies [51–53]. However, the benefit of ICP control by TTM in various clinical entities needs to be proven in large-scale trials [54].

## 5. The course of TTM in clinical practice

The process of TTM is ideally separated into three stages including induction, sustainment, and rewarming [45, 51]. The induction is the initial stage of TTM. The core temperature is rapidly declined to the target during induction stage [55, 56]. The rate of temperature reduction usually depends on the performance of available methods in the center [45]. With effective methods of cooling, core temperature can be brought down with the rate of 2–4°C/h [51]. The target temperature then is smoothly maintained during sustainment stage. Good methods should not allow more than 0.5°C fluctuation of temperature [4]. After the target temperature is sustained until the setting duration, it is slowly elevated back to normal destination during rewarming stage [46]. The rate of temperature rising depends on the indication of TTM. The usual recommended rate of rewarming is 0.2–0.5°C/h. The rapid increasing temperature is associated with rebound rising of ICP and higher risk of infection [57].

## 6. Methods of TTM

Effective methods are the key of success to achieve excellent process of TTM. Although there are several methods available to use, some of them are not quite popular and no longer in use as a solitary method in clinical practice [46]. According to some pilot studies, the selective brain TTM with cooling helmet or cap may be safe and feasible; however, this method is not accepted to use as a principle method for TTM in patients with TBI [58–61]. The antipyretic drugs alone or combination with other conventional methods may be useful for fever control; however, they are not effective enough to be used as solitary method for TTM [62–64]. The intravenous 4°C normal saline may be advantageous to launch TTM in the absence of energy condition such as pre-hospital setting [65–67]. However, huge volume of saline infusion requirement to lower temperature is usually associated with complications and becomes a major disadvantage to its use as a principle method for TTM [62]. The endovascular cooling technique is somehow invasive but very effective and reliable to use as a principle method for TTM [68, 69]. The surface cooling technique is the most popular method for TTM due to its feasibility, noninvasiveness, and effectiveness [70].

### 6.1. Invasive endovascular methods

A central venous heat exchange catheter connected with extracorporeal cooling machine is an important characteristic of invasive endovascular techniques [4]. This intravenous catheter is able

to insert through femoral, subclavian, or jugular vein [68, 71]. The auto-response temperature modulated system is integrated with the extracorporeal cooling machine [71]. The advantage of invasive endovascular method is efficient accomplishment including fast temperature lowering to the destination, smoothly maintenance during sustainment stage and rewarming with reliably controlled rate [72, 73]. Shivering is a common physiological reaction in patients treated with TTM [74]. Shivering control is an important step during the course of TTM [46]. Anti-shivering therapy includes pharmacologic treatment with many kinds of sedative drugs and nonpharmacologic treatment with skin-counter warming [51, 75]. Sedative effects from pharmacologic anti-shivering therapy may lead to impairment of consciousness and associated complications in patients undergoing TTM [75]. These complications are associated with unfavorable outcome in patients treated with TTM [76]. Skin counter warming can help to avoid many complications by lessen use of pharmacologic anti-shivering therapy [77]. As compared with surface technique, application of skin counter warming as nonpharmacologic anti-shivering therapy is much more possible during treatment with endovascular technique [78]. Due to lacking of drowsiness effect from pharmacologic anti-shivering therapy, skin counter warming can be applied in patients treated with TTM without need of intubation [79]. For this reason, endovascular technique is the most recommended method for patients with conditions that basically do not need intubation and require neurological observation such as patients with acute ischemic stroke [78, 80, 81]. However, not only technical difficulties in venous access but also complications associated with catheter are disadvantage concerns for endovascular technique [82, 83].

## 6.2. Noninvasive surface methods

The easiest technique for surface method is application of ordinary ice packs to neck, axilla, and groin. Before the era of automatic feedback machine, this simple ice pack was the most popular technique recommended in clinical practice [1, 2, 84]. However, the care team usually becomes exhausted after ice pack application because the team needs to give a very strenuous care and monitoring during the procedure [85]. Other than that, limitations of ice packs include its clumsiness, difficulty in temperature management, and high rate of adverse reactions [86]. The novel machine with automatic feedback temperature modulated system offers favorable temperature control, effortlessness of application, and rapid initiation [87]. This system facilitates its use in clinical practice [57]. This TTM machine is connected with circulating cold water blankets/pads or cold air-blow blankets [88, 89]. Core temperature measurement is mandatory for automatic feedback system. Temperature probe straight connected to the machine provides input data for automatic feedback system [90, 91]. The temperature of fluid or air within the pads or blankets is automatically modulated by the system dependent on the setting of target temperature and input data from the temperature probe [92]. The effectiveness of this system helps to achieve the ideal process of TTM including rapid lowering the temperature to the target, smooth maintenance of the target temperature, and slow rewarming back to the normal setting [46].

There is a surface cooling technique which is designed to use under the circumstance of lacking electrical source. EMCOOLS® HypoCarbon pads consist of graphite elements. This graphite has prominent heat conductivity. The pads are able to apply directly to the superficial skin. Before application, these pads must become frozen up in regular freezer. Electrical supply is

not necessary during application. For this reason, HypoCarbon pads are feasible to apply for TTM induction in pre-hospital setting [93–96].

### 6.3. The novel cooling method

RhinoChill intra-nasal cooling system is a portable device for selective brain cooling. It has a nasal tube to disperse evaporating coolant liquid in nasal cavity [97]. The coolant does not need to be frozen up, and the device is battery-based operation. This system should be feasible for pre-hospital setting [98, 99]. An observational study enrolled 17 patients with out-of-hospital cardiac arrest showed that the intra-nasal cooling device was safe and feasible to apply in pre-hospital setting. Two events of nonfatal adverse reactions included epistaxis and white nose were reported [100]. Rising blood pressure during treatment by this device in patients with acute ischemic stroke was concerned in another observational study [101]. Moreover, there was a case report of a serious adverse event with fatal pneumocephalus. The authors postulated that the air from nasal tube penetrated cribriform plate of ethmoidal sinus leading to pneumocephalus [102]. This serious adverse effect raises concerns to apply the intra-nasal device in patients with traumatic brain injury.

The novel esophageal cooling device helps to achieve rapid induction in patients with post-cardiac arrest [103]. According to its noninvasive property, it is also feasible for fever control in intensive care unit [104]. The device has been approved by The United States Food and Drug Administration (USFDA) and clinical trial [105].

## 7. Shivering and common physiologic response

When temperature starts to decline, the early physiologic response, such as peripheral vasoconstriction, occurs [57]. Behavioral compensations are the next response. When temperature continues to go down below the threshold, shivering inevitably develops [4, 75]. Shivering is the last resort of the defensive mechanisms against hypothermia, which occurs when vasoconstriction and behavioral compensations are not enough to prevent hypothermia [75]. Heat production increases two-fold to five-fold with shivering [106]. Appearance of shivering may indicate unimpaired neurophysiologic response and should be related with favorable neurologic outcomes [107]. Shivering management is a milestone in the course of TTM and should be integrated in the protocol of TTM [77, 108]. Bedside shivering assessment score (BSAS) is helpful for measuring degree of shivering (**Table 1**) [76].

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0	No shivering
1	Mild: shivering confines to cervical and/or thorax only
2	Moderate: shivering extends to whole movement of upper limbs
3	Severe: shivering spreads to overall movement of trunk, upper limbs, and lower limbs

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**Table 1.** Bedside shivering assessment score (BSAS) [76].

Increased peripheral arterial resistance during induction stage of TTM is common but usually temporary and does no harm to systemic blood pressure [51]. Sinus bradycardia is also commonly presented during sustainment stage. Heart rate usually lowers less than 50 beats per minute without any effect to hemodynamic status, therefore, requires no treatment [109]. However, this bradycardia should represent intact autonomic function and indicate favorable outcomes [110]. In the experimental animal model with hypothermia, prolonged coagulation and diminution of platelets function are common [111]. However, in the real world practice, clinical bleeding associated with hypothermia is not quite common [112]. During sustainment stage, kidneys are influenced by hypothermia to excrete more water leading to volume contraction [113]. Serum potassium is significantly declined during sustainment stage [114]. The most likely mechanisms of hypokalemia are hypothermia induced both intracellular shifting and renal loss of potassium [115]. However, serum potassium is anticipated to become elevated when temperature gets raised during rewarming stage [116]. It is safe and practical to keep serum potassium above 3.0 milli-equivalents per liter during sustainment stage to avoid both related fatal arrhythmia during sustainment stage and overt hyperkalemia during rewarming stage [114, 116]. Raised serum amylase is also common during sustainment stage; nonetheless, this elevated serum amylase is not related with clinical pancreatitis any more [117]. Sustained hyperglycemia (serum glucose > 8 mmol/L for at least 4 hours duration) is common during the course of TTM and may be associated with unfavorable outcomes [118]. Multiple mechanisms associated with hypothermia-induced hyperglycemia are postulated including decreased sugar utilization, reduced endogenous insulin production, and elevated resistance to exogenous insulin [119]. However, supplementary insulin during sustainment stage may shift potassium into cells then worsen the pre-existing hypokalemia [120]. Infection, particularly pneumonia and sepsis, is the most unwanted adverse event in patients treated with TTM, however only uncontrolled infection that should lead to unfavorable outcomes [57, 121].

## **8. Application of TTM in traumatic brain injury (TBI)**

### **8.1. TTM in animal model with TBI**

Benefits of TTM in animal experimental models with TBI have been demonstrated in several studies. Protective effects of TTM against neurometabolic cascade of TBI were proved with many studies in animal models. These protective effects were also histopathologically demonstrated in rats with a liquid percussion TBI. Overall number of necrotic neurons in both CA3 and CA4 layer of hippocampus and thalamus was reduced with hypothermia [122]. Post-traumatic hypothermia is able to suppress both glutamate release and hydroxyl radical elevations in rat models with induced TBI [123]. As mentioned above, disruption of BBB is one of the important steps in neurometabolic cascade leading to cerebral edema. The leakage of endogenous vascular proteins from the disrupted BBB was reduced with hypothermia in rats with the acute hypertensive response after TBI [124]. In the developing brain, TBI may also cause neonatal seizures and epilepsy due to the hyperexcitability of neurons and neural circuits, resulting in long-term functional impairments. Hypothermia improved functional



recovery after TBI in developing brain of neonatal rats [125]. As mentioned above, autophagy plays a major role in eliminating function after TBI and has neuroprotective effects. Hypothermia enhances autophagy resulting in improved behavioral outcomes in rats with lateral fluid percussion TBI [126].

Most of studies, animal models demonstrated protective effects of TTM against catastrophic cascade of TBI in many aspects. However, confirmation of its benefit in clinical trials is necessary before application in routine practice.

## 8.2. Clinical trials of TTM in patients with TBI

Pertaining to very promising outcome of TTM for TBI in pre-clinical trials, many clinical trials have been conducted to prove its benefit in human. Earlier, small scale, single-center, clinical trials demonstrated benefit of TTM in patients with TBI. In 1997, Marion et al. reported a landmark clinical trial of TTM in patients with severe TBI. This study recruited 82 patients with Glasgow Coma Score 5–7 which was relatively small sample size. The favorable outcomes were demonstrated in 3–6 months after treatment with TTM, but no benefit was presented when following up at 12 months [127]. The similar benefit was again supported by later single-center trials. Two clinical trials in patients with severe TBI from China demonstrated good effect of TTM on ICP control with favorable outcomes after 6 months to 1 year [128, 129]. However, the National Acute Brain Injury Study Hypothermia (NABISH), the multi-center landmark trial, reported not only lack of benefit but also potentially harmful of TTM in patients with TBI [130]. Moreover, the following systematic review and meta-analysis, which includes clinical trials before 2003, reveal no benefit of TTM in patients with TBI [131–133]. The inter-center variance in NABISH, which could confound the outcomes of the study, was reported thereafter [134]. This leads to conduct the National Acute Brain Injury Study Hypothermia II (NABISH II) many years later. Unfortunately, as well as the initial one, the NABISH II proved no benefit of TTM in patients with TBI [135]. The negative results in the NABISH I and II were confirmed by the Brain-Hypothermia (B-HYPO) Study from Japan. The B-HYPO showed that TTM with target temperature between 32 and 34°C did not provide any benefit as compared with fever control in patients with TBI [136].

As mentioned above, elevated ICP is a common secondary insult in patients with TBI and associated with unfavorable outcomes [137, 138]. Most of the previous clinical trials of TTM in patients with TBI start rewarming when the peak of ICP is approaching at around 48 h after the onset of TBI, leading to augmentation of ICP [139]. This phenomenon is presumed to be one of the important reasons of negative results in previous clinical trials of TTM in patients with TBI [54]. As mentioned above, ICP reduction is one of the well-known properties of TTM. ICP reduction with TTM should provide some benefit to the specific group of patients with elevated ICP in TBI [52]. Clinical trial of TTM pertaining to level of ICP in patients with TBI was then conducted [140]. A small-scale, single-center, prospective clinical trial demonstrated improvements of survivals and neurological outcomes with TTM in patients with TBI plus refractory intracranial hypertension [141]. Unfortunately, the large scale, multi-center, clinical trial of TTM in patients with TBI pertaining to elevated ICP more than 20 mm Hg (Eurotherm3235 Trial) again reported no clinical benefits [142]. Large scale,

multi-center, clinical trial of TTM as second-line treatment for elevated ICP in patients with TBI has still been ongoing [143].

Recent systematic review and meta-analysis of TTM versus normothermia in adult patients with TBI reveals not only no clinical benefit of TTM as compared with normothermia but also increased risk of developing pneumonia and cardiovascular complications associated with TTM [144]. At this moment, application of TTM as routine practice in adult patients with TBI without enrolment into clinical trial is not recommended [145].

As well as in adult, similar results of clinical trials for TTM in children with severe TBI revealed no benefit. Clinical trial of TTM in children with severe TBI conducted by Hutchison et al. reported not only no evidence of a benefit with respect to any short-term or long-term outcomes but also potential complications related with TTM particularly critical hypotension [146]. Several confounding factors in Hutchison's trial such as late treatment initiation, too short treatment duration, and rapid rewarming were reported. However, without all these confounding factors, the Cool Kid Trial reported no benefit of TTM in children with severe TBI [147]. Moreover, preliminary report of early initiation of TTM in children with severe TBI revealed infeasibility with low rate of recruitment [148]. The recent systematic review and meta-analysis confirmed no benefit of TTM in both adults and children with TBI [149].

## 9. Conclusions

Neurometabolic cascade is a key of primary pathologic damage in traumatic brain injury (TBI). Elevated intracranial pressure (ICP) is a well-known secondary damage related to unfavorable outcomes in patients with TBI. Targeted temperature management (TTM), previously known as therapeutic hypothermia, has many well-established protective effects against catastrophic cascade in TBI. TTM is also a good option for ICP reductive treatment. However, how to transfer from bench to bedside is still controversial for TTM in patients with TBI. The available methods for TTM are feasible and effective to apply in patients with TBI. The course of TTM is easy to achieve under the novel automatic feedback machine. The physiologic response and related complications with TTM are able to be controlled and treated. Routine use of TTM in patients with TBI outside clinical trial is still not recommended.

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