

## REVIEW ARTICLE

# Methods and clinical applications of targeted temperature management

Sombat Muengtawepongsa MD

Division of Neurology, Faculty of Medicine, Thammasat University, Bangkok, Thailand

### Abstract

Hypoxic/ischemic brain damage is well-known catastrophic injury. The specific treatment, so-called neuroprotective therapy, aims to prevent or diminish this havoc damage. However, approved neuroprotective therapy in clinical practice is limited. Targeted temperature management (TTM) shows the most promising neuroprotective therapy. Moreover, TTM is also useful for intracranial pressure (ICP) control. Many methods of TTM have been reported. TTM can apply to several clinical conditions associated with hypoxic/ischemic brain injury or elevated intracranial pressure.

### INTRODUCTION

Targeted temperature management (TTM) has substituted therapeutic hypothermia in the various recommendations from the major medical professional societies.<sup>1</sup> TTM is a kind of therapy that lowers a patient's core temperature with the intention to help reduce the risk of brain injury from impairment of cerebral blood flow.<sup>2</sup> Neuroprotection is a well-known indication of TTM.<sup>3</sup> Almost all of neuroprotective therapies for ischemic brain insult do not show any benefit in human.<sup>4</sup> TTM is the only one neuroprotective treatment that shows benefit in clinical trials.<sup>5-7</sup> Standard guidelines recommend TTM as a neuroprotective treatment in patients after cardiac arrest.<sup>8,9</sup> TTM is also an effective option for treatment of elevated intracranial pressure.<sup>10</sup>

### MECHANISM OF HYPOXIC/ISCHEMIC CASCADE

Hypoxic/ischemic brain injury is a damage that results from the cessation of cerebral blood flow. Interruption of cerebral blood flow results in multiple neurologic injuries, the so-called hypoxic/ischemic cascade.<sup>11</sup> Lack of oxygen and blood supply leads to adenosine triphosphate (ATP) producing failure.<sup>12</sup> Neurons and glial cells switch to anaerobic process, result in lactic acidosis.<sup>13</sup> Na<sup>+</sup>-K<sup>+</sup> ATPase pumps fail, causing cells to become depolarized, allowing ions, especially calcium (Ca<sup>++</sup>) to influx

the cells. Intracellular calcium levels rises, then stimulate the release of the excitatory amino acid neurotransmitter glutamate.<sup>14</sup> Glutamate allows more calcium influx by trigger opening of Ca<sup>++</sup>-permeable NMDA receptors and AMPA receptors. The generation of dangerous chemicals including free radicals, reactive oxygen species, endonucleases, ATPases, and phospholipases, the so-called excitotoxicity, begins after excess calcium influx.<sup>15</sup> Cell membrane and mitochondria break down causing necrotic cells and apoptosis. Glutamate and other toxic chemicals are released into the environment by these necrotic cells.<sup>16</sup> These toxins damage surrounding cells. Further damage, the so-called reperfusion injury, begins when the brain is reperfused.<sup>17</sup> Inflammatory cells accumulate to swallow up damaged tissue and release many cytokines.<sup>18</sup> Harmful chemicals destroy the blood-brain barrier (BBB). Damaged BBB leads to leakage of large molecules especially albumins causing cerebral edema.<sup>19</sup> Cerebral edema causes compression of and further damage to brain tissue.<sup>20</sup> A summary of the ischemic cascade is shown in Figure 1.

### MECHANISM OF ACTION

The protective effects of TTM on ischemic cascade are thought to be multiple sites of actions.<sup>21</sup> There are several postulated mechanisms, however, the main mechanisms are protection on reperfusion injury.<sup>8</sup> Many of the chemical reactions associated with reperfusion injury, including free radical

Address correspondence to: Dr.Sombat Muengtawepongsa, Division of Neurology, Faculty of Medicine, Thammasat University, Pathum Thani, Thailand 12120.

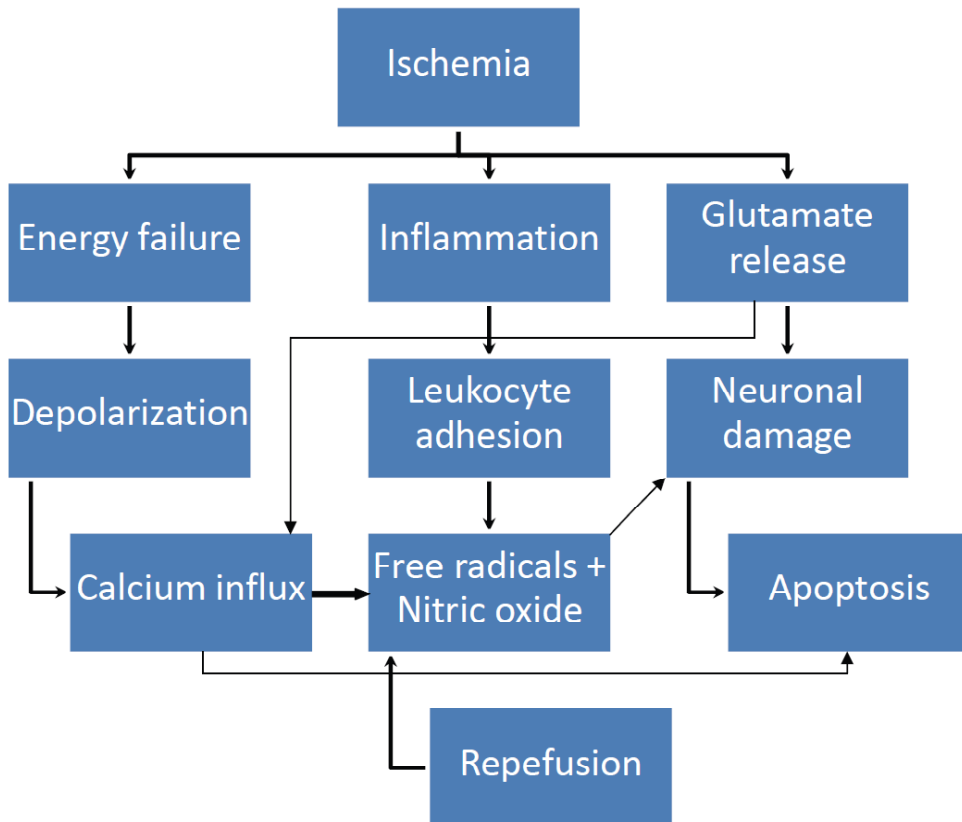


Figure 1. Ischemic cascade

production, excitatory amino acid release, and calcium influx, are suppressed by TTM.<sup>3,8,21</sup> Significant reduction in cerebral metabolic rate is another important mechanism of TTM.<sup>22,23</sup> There are also evidence of mitochondrial protection and prevention of cell membrane leakage by therapeutic hypothermia.<sup>21</sup> These effects help to prevent the cell to become apoptosis.<sup>23</sup> Protection of blood-brain-barrier damage is another proven effect of TTM.<sup>24</sup> Reduction of blood-brain-barrier leakage helps to control cerebral edema and intracranial pressure (ICP).<sup>23</sup> ICP reduction by hypothermia is demonstrated in many experimental studies.<sup>25,26</sup> Clinical evidence of ICP control by TTM in different conditions has been reported in the literature.<sup>27-29</sup> However, benefit of ICP control by TTM in various clinical entities needs to be proved in large scale trials.<sup>1,10</sup>

## METHODS OF TTM

Several methods of TTM have been described. Some methods are rarely utilized for TTM in clinical trials due to its ineffectiveness or its unfeasibility. Antipyretic drugs alone are

not enough to induce or maintain targeted temperature.<sup>30</sup> Intravenous 4 degree Celsius crystalloid solution is useful for induction of TTM in lack of energy source circumstance such as pre-hospital setting.<sup>31,32</sup> However, it is not feasible to maintain targeted temperature with intravenous cool fluid due to large volumes infusion. Cooling caps or helmets have been used to cool the head and neck to produce selective cerebral hypothermia in infants, however, its effectiveness in adults need to be determined by clinical trial.<sup>8,33</sup> The two most popular methods in clinical practice are non-invasive surface cooling and invasive endovascular cooling.<sup>34</sup>

### *Non-invasive surface methods*

Application of ice packs to the groin, axillae, and neck is simple and has been reported to be effective in the landmark clinical trial.<sup>5</sup> However, temperature control by using ice packs method is unreliable. The auto-feedback temperature regulated machine with circulating cold water blankets/pads and cold air-forced blankets are the most preferred technique for surface method

in clinical practice.<sup>30</sup> The machine offers reliable temperature control and convenient to use in clinical practice. Many brands of machine are available in the market, for examples, Blanketrol®, CritiCool® and ArcticSun®. All of them come with automatic cooling system to rapidly bring core temperature down to the target and gradually rewarm up to the normal temperature. Core temperature assessment directly connected to the machine is mandatory for this system. The temperature of blankets or pads is automatically adjusted by the machine upon feedback data from core temperature.

EMCOOL® is another cooling pad consisting of graphite elements which applied directly to the skin surface. The pads need to be frozen before use but do not need energy source during application.<sup>35</sup> Therefore, this device is very feasible in pre-hospital setting. The novel non-invasive method, esophageal cooling device, the results of its use has been preliminary reported in post-cardiac arrest patients.<sup>36</sup>

#### *Invasive endovascular methods*

Indwelling venous catheter with extracorporeal cooling machine is the most common technique for endovascular method. The catheter may be inserted via femoral, subclavian or jugular vein. The machine also comes with the auto-feedback temperature regulation system. Two brands are available in worldwide market including CoolGard 3000® and Celcius Control System®. Achievement of rapid temperature lowering to the target, tightly maintained target temperature and actively controlled rewarming with endovascular methods have been reported in the literature.<sup>37,38</sup> Shivering control with skin counter-warming can easily be applied to the patients undergoing endovascular



Figure 2. A patient is undergoing targeted temperature management (TTM) with cold water pads.

cooling.<sup>39</sup> Reduction of sedative agents use for shivering control by the use of skin counter-warming can avoid intubation in patients treated with TTM. For this reason, endovascular cooling technique is the prefer method in clinical trials of TTM in acute ischemic stroke patients.<sup>40-42</sup>

### **STEPS TO ACHIEVE EXCELLENT TTM**

TTM process is categorized into three steps.<sup>21</sup> The first step is induction, which aims to change the current core temperature to the target. Then, the target temperature is tightly controlled for certain duration, so-called maintenance or sustainment step. The final step is rewarming. The temperature is returned to the normal level with actively control rate. Most of the major complications occur during this last step when temperature is passively rewarmed with uncontrolled rate.<sup>2</sup> The temperature record of a patient with cardiac arrest treated with TTM is showed in Figure 3.

### **PHYSIOLOGIC EFFECTS AND POTENTIAL COMPLICATIONS**

Shivering and peripheral vasoconstriction are the most common physiologic responses when temperature goes down.<sup>43</sup> Shivering is the basic response to prevent decline of temperature.<sup>2</sup> Occurrence of shiver does not indicate poor neurologic outcomes.<sup>44</sup> Prompt treatment of shivering is an important component of TTM protocol.<sup>39,45</sup>

Peripheral vascular resistance is temporarily raised during induction step of TTM process. However, associated hypotension is reported in one study.<sup>46</sup> Sinus bradycardia (heart rate < 50 / min) develops in almost half of patients with post-cardiac arrest undergoing TTM.<sup>47</sup> However, this bradycardia should be seen as a physiologic response. It does not affect hemodynamic status and may predict favorable outcomes.<sup>47,48</sup> Prolonged coagulation and lowering platelets function are well-known physiologic effects of hypothermia in animal models.<sup>2,43</sup> However, bleeding complications are rarely reported in human.<sup>1</sup> Augmentation of urine flow during temperature decline leads to obligate water wasting.<sup>49</sup> Lowering of serum potassium due to renal loss and intracellular shift is commonly found during sustainment phase; but it will be raised when temperature is rising during rewarming phase.<sup>2</sup> Rising of serum amylase is common during temperature reduction. However, associated pancreatitis is rare.<sup>50</sup> Hyperglycemia due to decreased insulin level commonly occurs

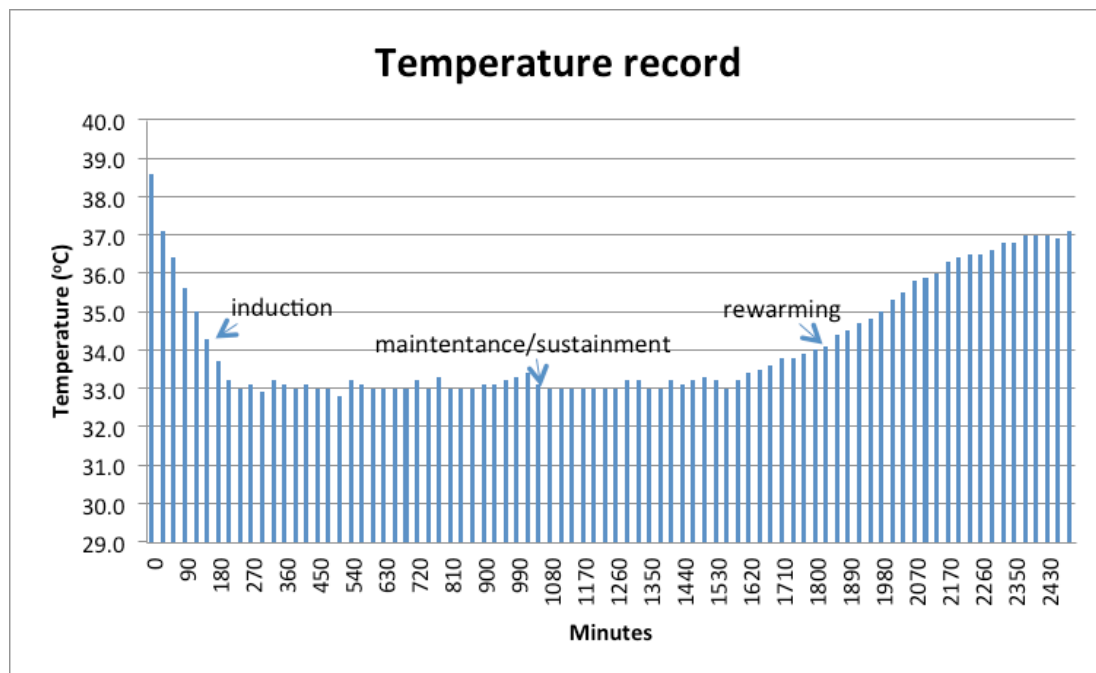


Figure 3. Temperature record of a patient with post-cardiac arrest with TTM

when temperature declines.<sup>51</sup> Insulin treatment for hypoglycemia also lowers serum potassium.<sup>51</sup>

## CLINICAL APPLICATION

### *Post-cardiac arrest*

There is evidence for clinical application of TTM in two major indications: neuroprotective therapy and ICP control.<sup>3</sup> The best clinical evidence of benefit for neuroprotective effects of TTM is in patients with post-cardiac arrest. There were two landmark studies from Europe and Australia that showed promising clinical outcomes.<sup>5,6</sup> Ventricular tachycardia (VT) / ventricular fibrillation (VF) or shockable rhythm related cardiac arrest patients are the population who get the best benefit from the treatment, with the number-needed-to-treat (NNT) of 5 for prevention of dead, and 6 for good neurological outcomes.<sup>5,6,52</sup> Recommendations announced by International Liaison Committee on Resuscitation in 2003 and by American Heart Association in 2010 stated that unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest with VT/VF should be cooled to 32°C to 34°C for 12 to 24 hours.<sup>8,9</sup> Clinical benefit of TTM in cardiac arrest patient from any causes other than VT/VF is not well established.<sup>53</sup> However, there is some evidence of marginal clinical benefit in out-of-hospital cardiac

arrest with asystole / pulseless electrical activity (PEA) or non-shockable rhythm as well as in in-of-hospital cardiac arrest.<sup>8,9,53</sup> The randomized control trial of TTM after non-shockable cardiac arrest is ongoing.<sup>54</sup>

Although the evidence of benefit is strong, the rate of TTM use in clinical practice is low.<sup>55</sup> TTM after cardiac arrest has been successfully implemented in many countries, including some countries in Asia.<sup>56-58</sup> Japan and Korea are two countries in Asia that have a lot of experience in use of TTM in post-cardiac arrest patients.<sup>57,59</sup> Unfortunately, TTM after cardiac arrest is not well established in South East Asia.<sup>60,61</sup> Thammasat University Hospital is the first center in Thailand that implements TTM in post-cardiac arrest treatment protocol. Suggested indications / contraindications for TTM in patients with cardiac arrest at Thammasat University Hospital were based on American Heart Association guidelines are showed in Table 1.

The exact target temperature for treatment is controversial. In November 2013, a TTM trial reported that the outcomes with target temperature of 33°C were not superior to those of 36°C.<sup>62</sup> Moreover, at two years after treatment, quality of life and cognitive function in both groups were similar.<sup>63</sup> The benefit of TTM with target temperature of 33°C was not statistically superior to aggressive fever control (36.8°C) in pediatric

**Table 1: Suggested indications / contra-indications for TTM in patients with cardiac arrest at Thammasat University Hospital**

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**Inclusion and exclusion criteria for targeted temperature management after cardiac arrest**

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**Inclusion Criteria**

1. Witnessed arrest
2. Initial rhythm VF or pulseless VT
3. Time to ACLS was less than 15 minutes and total of ACLS time less than 60 minutes
4. GCS of 8 or below
5. SBP of > 90 with or without vasopressors
6. Less than 8 hours have elapsed since return of spontaneous circulation (ROSC)

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**Exclusion Criteria**

1. Pregnancy
2. GCS 10 and improving
3. Down time of > 30 minutes
4. ACLS preformed for > 60 minutes
5. Known terminal illness
6. Comatose / Persistent vegetative state prior to cardiac arrest
7. Prolonged hypotension (ie MAP < 60 for >30 minutes)
8. Evidence of hypoxemia for > 15 min following ROSC
9. Known coagulopathy that cannot be reversed

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cardiac arrest patients.<sup>64</sup> Also, how early should the treatment be initiated is not well established.<sup>65</sup>

### ***Ischemic stroke***

TTM shows a very promising neuroprotective effect on focal brain infarct in animal models.<sup>66</sup> However, there are too few clinical trials to make conclusion on clinical benefit.<sup>67</sup> The previous clinical studies just show feasibility and safety to apply TTM with endovascular method in patients with acute ischemic stroke.<sup>68,69</sup> With endovascular method, shivering is mainly treated with skin counter-warming technique to avoid sedative effect of medicine for shivering control.<sup>38,69</sup> Endovascular technique is also safe to apply even in patients who received intravenous thrombolysis in one study.<sup>69</sup> The large scale clinical trial of endovascular TTM at 33°C after intravenous thrombolytic therapy in patients with ischemic stroke is still ongoing.<sup>40</sup> With its BBB protective effect, TTM may help to prevent hemorrhagic transformation after intravenous thrombolysis or after interventional therapy.<sup>70,71</sup> The large scale clinical trials of TTM at 34 to 35°C as neuroprotective therapy in patients with acute ischemic stroke are ongoing.<sup>72</sup> In the mean time, standard guidelines do not recommend routine use of TTM in patients with acute ischemic stroke.<sup>73</sup>

Fever control with TTM machine (target temperature < 37.5°C) is recommended by standard guidelines.<sup>74</sup> TTM may be applied for ICP control in patients with malignant middle cerebral artery (MCA) infarct.<sup>27</sup> ICP reduction by TTM in large cerebral infarct is well documented in both experimental animal models and clinical trials.<sup>25,27,75</sup> However, there is insufficient data to support routine use of TTM for ICP control in large cerebral or cerebellar infarct.<sup>1,74</sup>

### ***Traumatic brain injury (TBI)***

TTM shows clear benefits to use as neuroprotective treatment or ICP control in many animal models with traumatic brain injury (TBI).<sup>76-78</sup> Some small scale clinical trials show benefit of TTM in patients with TBI.<sup>79,80</sup> However, the landmark phase III clinical trials of TTM in TBI fail to demonstrate any benefits of the treatment in term of neuroprotective therapy in neither adults or children.<sup>46,81,82</sup> Meta-analysis, which is inclusive of all types of clinical trials, also does not show benefit to using TTM in patients with TBI.<sup>83,84</sup> Elevated ICP in patients with TBI is a well-known predictor of poor outcomes.<sup>85,86</sup> Most of TTM trials begin rewarming at around 48 hours after onset of TBI when the peak elevated ICP occurs. Rebound elevated ICP is postulated to be one of the major reasons for lack of benefit in the landmark

clinical trials.<sup>87</sup> Nevertheless, selected group of TBI patients with elevated ICP may benefit from ICP control with TTM.<sup>28</sup> TTM pertaining to elevated ICP is proposed for clinical trial.<sup>88</sup> Large scale clinical trials of therapeutic hypothermia in particular TBI patients with elevated ICP are ongoing.<sup>89</sup> In the meantime, routine use of TTM in patients with TBI outside clinical trial is not recommended by standard guidelines.<sup>90</sup>

### ***Fever controls in intensive care unit (ICU)***

Fever in patients with critical neurologic conditions is common, leading to increased length of stay, and usually associated with poor clinical outcomes.<sup>91,92</sup> For example, every one degree Celsius above 37 in patients with ischemic stroke is estimated to have 2.2 times risk of poor outcomes when compared with patients with normal temperature.<sup>93</sup> Fever control in Neuro ICU using similar method of TTM should have add-on benefits in many neuro-critical conditions.<sup>94,95</sup> Both surface and endovascular cooling methods are feasible and safe to apply in Neuro ICU.<sup>94,95</sup> Fever control in patients with severe stroke is associated with favorable outcomes.<sup>96</sup>

### ***Other clinical applications***

TTM may be used as ischemic protection during some surgery with circulatory arrest.<sup>97,98</sup> However, the landmark trial does not show any clinical benefit of TTM during surgery in patients with mild grade (World Federation of Neurological Surgeons score I – III) intracranial aneurysm.<sup>99</sup> Some experimental and small clinical studies show benefits of TTM in patients with intracerebral hemorrhage, spinal cord injury and fulminant hepatic encephalopathy.<sup>100-102</sup>

TTM at 34 – 35°C in donors has protective effect on kidney in recipients.<sup>103</sup> The process of TTM in kidney donors in the study is also very simple to use and the cost of treatment is low.<sup>104</sup> This is the first clinical trial which shows organ protective effect of TTM outside the brain. TTM in kidney donors should be the standard treatment as well in the near future.

### **CONCLUSION**

With multiple mechanisms of action on ischemic / hypoxic cascade, TTM has promising neuroprotective effect. Neuroprotection is the most well-known indication of TTM. Surface and endovascular cooling technique are the two most common methods of TTM used in clinical practice.

The best clinical evidence of neuroprotective effect by TTM is in patients with cardiac arrest. It is accepted as standard treatment for cardiac arrest with initial shockable rhythm group. It may also have some minor clinical benefit in non-shockable group. TTM may have a role in neuroprotective treatment in patients with acute ischemic stroke. It may also be useful for ICP control in patients with malignant MCA infarct. Although clinical trials fail to demonstrate neuroprotective effect of TTM in patients with TBI, TTM may help to control ICP in selective cases. Fever control in Neuro ICU using similar method of TTM should have add-on clinical benefits in many neuro-critical conditions. TTM in donors has protective effects to kidney in recipients with kidney transplantation.

### **ACKNOWLEDGEMENT**

This work was supported by the National Research University Project of Thailand Office of Higher Education Commission.

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