Current Development and Clinical Usage of Therapeutic Hypothermia

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Therapeutic hypothermia was first applied to clinical use in the 1940s, but was complicated by severe adverse effects at deep hypothermic temperatures. However, many animal studies have revealed that it has strong neuroprotective effects to reduce brain damage. In 2002, two multi-center randomized clinical trials which applied mild to moderate hypothermia to out-of-hospital cardiac arrest patients with cardiogenic etiologies, proved the significant benefits of the neuroprotective effect and even improvement of mortality. Currently, therapeutic hypothermia is viewed as a new strategy for organ protection in the intensive care field. Many clinical trials have examined the safety, feasibility, and efficacy of therapeutic hypothermia in different etiologies with complications with brain damage such as perinatal asphyxia, acute stroke, traumatic brain injury or acute hepatic failure with cerebral edema and spinal cord injury. Other possible applications of therapeutic hypothermia include myocardioprotection and multiple organ protection in systemic inflammatory processes such as hemorrhagic shock and sepsis. Successful application of therapeutic hypothermia depends on a sensitive, stable and etiology dependent temperature control protocol with intensive care of multiple alternative physiological and adverse effects. This is probably why therapeutic hypothermia is still not popular in Taiwan or worldwide. The aim of this study was to provide a brief review of the current use of therapeutic hypothermia in different etiologies and mechanisms, clinical management of adverse effects and the other significant physiological changes during temperature change, and some details of temperature control techniques to promote a greater understanding and usage of therapeutic hypothermia.

key words: hypothermia, cardiopulmonary resuscitation, post-resuscitation care

Introduction of Therapeutic Hypothermia

Therapeutic hypothermia was introduced in the 1940s and was widely studied for neuroprotective and cardioprotective strategies. However, severe complications were found during applied hypothermia below 30°C and at deep or extreme hypothermia which once limited its usage. Recent clinical studies have revealed that mild to moderate systemic hypothermia is efficacious for organ protection and that it is possible to avoid the severe complications from severe or deep hypothermia. It is feasible not only in emergency departments and critical care units, but also in pre-hospital resuscitation. Two important randomized, multi-center clinical trials conducted by the HACA and Australia groups, used systemic hypothermia for cardiogenic out-of-hospital cardiac arrest patients and both proved that severe neurological
complications and even mortality were significantly mitigated compared to traditional normothermia patients\(^1,2\). These two landmark studies promoted other clinical application investigations on the use of therapeutic hypothermia such as in neonatal asphyxia and acute stroke.

**History of Therapeutic Hypothermia**

Cooling the body as a protective strategy has been applied since ancient times. Reports of children surviving after being immersed in icy water for long periods of time have long since captured the public’s imagination, suggesting that cooling can actually protect life. It is also well known that cooling decreases localized injury induced pain and swelling. However, it wasn’t until the 19\(^{th}\) century that medical science became interested in therapeutic hypothermia, connecting the imagination of the public to the medical professional field. Temple Fay in Philadelphia first reported the clinical uses of therapeutic hypothermia in 1942 on a series of severe head injury patients who made remarkable recoveries. In the 1950s, the introduction of cardiopulmonary bypass allowed for easier temperature control. In many centers, deep hypothermia and cardiac arrest in cardiac surgery were routinely used. Neurosurgery also applied hypothermia during operations to protect the brain. However, there were many severe complications associated with deep hypothermia and the interest of therapeutic hypothermia rapidly waned. In the 1980s several laboratories discovered that mild hypothermia could also achieve good brain protection in global or focal cerebral ischemia and traumatic brain injury. Therapeutic hypothermia was again applied in neurosurgery such as for intracranial aneurysms; however physicians still considered the adverse effects of cooling to be a problem\(^3\). In 2002, two randomized clinical trials conducted in Australia and Europe reported consistent beneficial neuroprotective effects of therapeutic hypothermia in comatose cardiogenic cardiac arrest survivors\(^1,2\). These landmark studies showed the potential of therapeutic hypothermia in organ protection. Many new techniques and strategies, such as intravascular cooling devices, circulated water garments and cooled crystalloid solutions, were developed to help with rapid cooling and sensitive temperature control. The International Liaison Committee on Resuscitation and Advanced Cardiac Life Support (ILCOR and ACLS) list therapeutic hypothermia as part of their post-resuscitation care guidelines. Many experts consider hypothermia to be the fifth part of the chain of survival\(^4\). Other investigators have tried to extend the usage of therapeutic hypothermia in different etiologies beyond cardiac origin out- of - hospital - cardiac arrests (OHCA), such as hepatic failure, perinatal asphyxia, traumatic brain injury and other fields\(^5\). However, several international investigations have disclosed that the application of therapeutic hypothermia is not frequent and that many clinical physicians are concerned about the adverse effects of hypothermia\(^6,8\). The aim of this study was to briefly review the literature and provide our experience in the clinical usage of therapeutic hypothermia.

**The Mechanism of Therapeutic Hypothermia in Neuroprotection**

Therapeutic hypothermia has been proven to reduce cerebral complications after multiple causes of brain injury, whether the injury originates from traumatic or vascular causes including vascular insult like blood vessel obstruction, hyperemia or cerebral edema or other etiologies such as cardiac arrest. Similar destructive cascades are found in different causes and persist from hours to days after the initial injury. Therapeutic hypothermia provides a therapeutic window for
brain protection, however it should not be delayed as injuries often occur early and develop rapidly. During therapeutic hypothermia, the metabolic rate decreases 6-10% for each 1°C temperature decrease. However, decreases of the metabolic rate and oxygenation demand are just a part of the therapeutic hypothermia physiological effect. Many neurologic injury processes involve temperature sensitive proteins and enzymes. Hypothermia can significantly and widely slow these injury processes by reducing proinflammatory cytokine production and further preventing lipid peroxidation and NO production. It is well known to decrease oxidative stress in ischemia-reperfusion and other neurological injuries. In addition, the cell apoptosis process is suppressed and neural cell damage diminished. Mitochondria dysfunction and increased calcium influx into cells also can be prevented or interrupted by therapeutic hypothermia. The correction of calcium overloading during injury also provides a chance to mitigate abnormally induced excitatory neurotransmitter cascades such as large amounts of glutamate release and excessive glutamate receptor activation. Intracellular acidosis in mitochondrial and other abnormal enzymatic activation during cell injury is also attenuated. The glucose utilization of the brain cells recovers sooner and good high energy preservation is found in therapeutic hypothermia. Blood-brain barrier disruption diminishes and further reduces cerebral vascular permeability to maintain membrane integrity. Therapeutic hypothermia has been shown to conclusively decrease cytotoxicity through multiple processes during neural injury and significantly ameliorate cerebral edema.

Possible Adverse Effects during Therapeutic Hypothermia

Shivering
Hypothermia has been viewed negatively as the bulk of adverse effects are observed in deep or profound and incidental hypothermia. During hypothermia, subjects physiologically develop severe shivering and cutaneous vasoconstriction to increase heat production and maintain homeostasis. Without controlled shivering, the induction of hypothermia often fails and the metabolic rate and oxygen demand increase. Strategies including skin-contact warmer improve the shivering threshold, and medications such as meperidine or other paralytics with sedative agents should be used.

Electrolyte imbalance
During hypothermia, cold diuretics, renal tube dysfunction and shift to intracellular compartments result in hypokalemia, hypomagnesium or hypophosphate. If this is not aggressively corrected it may worsen cardiopulmonary stability. In addition, the re-warming process brings rebound elevations of electrolytes and should be close monitored. Rapid warming processes should be avoided.

Hemodynamic instability and arrhythmia
During hypothermia the heart rate usually decreases and there is a prolonged PR interval with increased elongate QT interval. If the temperature is reduced to lower than 30°C or a severe electrolyte imbalance is neglected, more severe type ventricular arrhythmia may be induced. However, how hypothermia influences myocardial contractility is still controversial. Some investigations have revealed that hypothermia may improve cardiac performance in the disease model, but mild diastolic dysfunction has been noted in healthy hearts with decreased cardiac output.

Bleeding tendency
In in vitro studies, a temperature lower than 35°C has resulted in platelet dysfunction, and once
the temperature is lower than 33°C the coagulation cascade may be affected. However, in clinical studies on myocardial infarction, no significant increases of major bleeding events have been noted when compared with normothermia\(^{(12)}\), although this may result from the confounding of frequently used exclusion criteria for severe bleeding patients. When therapeutic hypothermia is indicated but there is a preexisting bleeding tendency or concurrent hemorrhage status becomes a cause of concern for the patients’ safety, Polderman et al. suggested maintaining hypothermia between 33-35°C to safely obtain hypothermia efficacy\(^{(13)}\).

**Risks of infection**

During the hypothermic period, pro-inflammatory and inflammatory responses are suppressed due to decreased leukocyte count and impaired leukocyte migration with phagocytosis. At the same time, the normal fever curve is abolished making it difficult to objectively observe signs of infection. In the post-resuscitation patients, infection is frequent. Hypothermia was reported to increase likelihood of pneumonia and sepsis. Fortunately, the benefits of hypothermia are not adversely affected by an increased risk of infection\(^{(1,2)}\). Prophylaxis antibiotics are therefore suggested.

**Abnormal metabolism and glucose usage**

During hypothermia, the energy subtracts become more prominent from fat metabolism. More lactate and ketonic acid production are noted and may result in extracellular acidosis. However, intracellular acidosis caused by multiple neuron injures is corrected by hypothermia, and it often does not require further management if the PH value isn’t lower than 7.25. In addition, hyperglycemia is frequently noted during hypothermia which results from a decrease in insulin sensitivity. The warming process may reversely increase insulin sensitivity and close monitoring to avoid hypoglycemia is often suggested.

**Abnormal amylase lipase and liver function enzymes**

Elevated amylase is a frequently encountered adverse effect of hypothermia, but clinically it is usually not correlated to acute pancreatitis. In addition, a mild raise in liver functions, adrenal cortisone and catecholamine levels were also reported in the literature review.

**Who Would Benefit from Therapeutic Hypothermia?**

**Post-resuscitation syndrome**

In 2002, important studies about the successful application of therapeutic hypothermia in adult cardiogenic origin our of hospital cardiac arrest (OHCA) were reported in the New England Journal of Medicine\(^{(1,2)}\). The most common results revealed that therapeutic hypothermia induced in comatose subjectives with a return of circulation for 12-24 hours significantly improved neurological outcomes and even mortality. The ACLS guidelines strongly recommend the use of therapeutic hypothermia for cardiac arrest patients and suggest extending usage to non-VT/Vf patients due to the theoretical effectiveness\(^{(14)}\). Regardless of the solid evidence and recommendations, therapeutic hypothermia is still underused according to many surveys\(^{(6-8,15)}\). Therapeutic hypothermia is highly resource intensive and becomes labor intensive if there are no adequate medical devices to help with temperature control. Many physicians fear the adverse effects due to a lack of experience limited by equipment resources and a lack of comprehensive temperature control protocols in critical care\(^{(15)}\). Many medical devices and
temperature control protocols have been developed which help to resolve the clinical difficulty of temperature control\(^\text{(16)}\). Reports from different protocol trials have also helped to optimize more efficient and safe protocols. Recent reports have revealed that it took 4-5 years to achieve widespread acceptance in the United Kingdom\(^\text{(17)}\). It is recommended now that post-resuscitation comatose patient who cannot follow verbal command should receive therapeutic hypothermia and transfer to the medical centers with facility of primary coronary intervention and care unit of therapeutic hypothermia\(^\text{(18)}\). In addition, cardiac arrest patients with pulseless or asystole electrical activity usually have the poorest prognosis. Several historical controlled trials have reported benefit effects of neurological outcomes even a retrospective observational study by Vanston revealed that non-VT/Vf rhythm patients had a significantly poorer neurological recovery than VT/Vf patients among all patients receiving therapeutic hypothermia\(^\text{(18)}\). Oddo et al. reported a small prospective study which revealed that only the collapse time before return of spontaneous circulation but not the non-Vf rhythm was an independent prognostic factor of survival to discharge in patients receiving therapeutic hypothermia due to cardiac arrest\(^\text{(19)}\). In 2010 Oct, the latest revised ACLS guideline for post-resuscitation care still recommends the therapeutic hypothermia use is ClassI indication for VT/Vf OHCA patients and Class II indication for non VT/Vf OHCA patients\(^\text{(18)}\). The extent of benefits that therapeutic hypothermia can provide needs further clinical trials to elucidate.

**Intra-Hospital-Cardiac Arrest (IHCA) and current status**

In the ACLS guidelines for post-resuscitation care, therapeutic hypothermia is class IIb for in-hospital cardiac arrest patients for theoretically effectiveness\(^\text{(14)}\). Some authors consider therapeutic hypothermia to be part of the chain of survival\(^\text{(4)}\). The randomized actively controlled clinical trial, “Hypothermia After in-Hospital Cardiac Arrest” is currently recruiting adult patients in Germany, and the Therapeutic Hypothermia to Improve Survival After Cardiac Arrest in Pediatric Patients (THAPCA-IH) study is evaluating the safety and efficacy of therapeutic hypothermia in pediatric patients.

**Neonatal asphyxia, pediatric cardiac arrest and preterm Necrotizing Enterocolitis (NEC)**

Perinatal asphyxia results in cerebral palsy and may cause severe disabilities and mortality. Many clinical trials have investigated the neuroprotective effects of therapeutic hypothermia, and almost all have concluded that those receiving therapeutic hypothermia have significantly lower neurologic disabilities and better functional recovery. However, whether therapeutic hypothermia can actually prevent mortality and severe disabilities is controversial due to different study designs. In 2008, ILCOR recommend routine use of therapeutic hypothermia for neonatal resuscitation as there are no other better strategies to improve neurological prognosis\(^\text{(20)}\). Azzopardi et al. reported the largest randomized clinical trial (the TOBY study) of perinatal asphyxia with 72 hour hypothermia at a target temperature of 33.5\( ^\circ \)C induced within 60 minutes, but the results failed to prove whether hypothermia improved survival and severe disabilities at 18 months as the primary outcome\(^\text{(21)}\). A meta-analysis by Edward et al. in 2010 reported on 10 randomized clinical trials revealed that therapeutic hypothermia could significantly reduce both mortality (relative risk 0.78, \( p=0.005 \)) and severe disabilities (risk ratio 0.81, \( p=0.002 \)) at 18 months. In addition, hypothermia increased survival with normal neurological function
(risk ratio 1.53, p<0.001), reduced the rates of severe disability and cerebral palsy (p=0.006 and p=0.004, respectively) and lowered the mental and psychomotor development indices (p=0.01 and 0.02, respectively).

In resuscitation of pediatric arrest, two retrospective observational studies revealed that therapeutic hypothermia had no strong benefits on the patients’ prognosis. In 2005, the AHA guidelines recommended 32-34°C for 12-24 hours in comatose pediatric survivors, but the evidence base is lacking and some authors have recommend that further investigations for the indication, timing and detailed protocol are necessary. Doherty et al. reported that therapeutic hypothermia was associated with significantly higher mortality in pediatric IHCA. However, this observational study found that the hypothermia was applied in patients with more complications or difficulty to achieve return of spontaneous circulation (ROSC) such as more resuscitation interventions, longer resuscitation and cardiac arrest periods and higher post-resuscitation lactate levels which very possibly confounded the results. Currently, the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) multicenter randomized clinical trial, is designed to separately evaluate the effects of therapeutic hypothermia in pediatric IHCA and OHCA. Strict treatment protocols and temperature control, even prolonged after re-warming, are given. Therapeutic hypothermia has also been proven to be safe and feasible for preterm NEC. In a safety and feasibility study, there were no significant adverse effects and hypothermia was easily applied in preterm babies, however coagulation parameters impaired the hypothermia group. It was noted that applying surface cooling mattresses to maintain a stable temperature in preterm infants was labor intensive, and whether neurodevelopment was affected still requires evaluation. The beneficial effects of hypothermia in preterm NEC should be concluded only after large scale studies for further investigations.

**Traumatic brain injury**

There are many clinical investigations on how hypothermia benefits traumatic brain injury patients with regards to mortality and neurological function. However, these studies have had a high variability of treatment protocols and consciousness levels of included subjects. Two meta-analyses in 2003 reported that hypothermia has a marginal effect on the mortality and neurological recovery of traumatic brain injury patients, but the results are questionable due to the wide variety of study methods. Kochanek et al. suggested lowering the target temperature and prolonging the duration of hypothermia with slow re-warming from subgroup analysis. In 2008, Peterson et al. published a meta-analysis report and summarized that therapeutic hypothermia is indeed beneficial for traumatic brain injury patients, at least in neurological recovery. The patients’ mortality and neurological recovery had best improvement if hypothermia was maintained for more than 48 hours.

**Acute hepatic failure**

The etiologies of acute hepatic failure include viral, toxic, metabolic and vascular insults. Although the pathogenesis of acute hepatic failure is different, complications such as cerebral edema are similar. During acute hepatic failure, ammonia and other anisosmotic conditions increase intracranial astrocyte osmolarity resulting in brain swelling due to water passive diffusion. Besides ammonia, glutamate via glutamine synthase triggers mitochondrial dysfunction leading to oxidative metabolism and lactate accumulation. Oxidative stress further triggers cerebrovascular dilatation and cerebral hyperemia. More anisosmotic agents are delivered to astrocytes creating...
a vicious cycle. IICP then induces brain herniation which accounts for about 20-25% of deaths from acute hepatic failure. Therapeutic hypothermia can significantly reduce ammonia transfer from blood to the brain, reversing cerebral blood flow abnormalities and preventing the development of brain edema. Cooling also prevents cerebral glutamate NMDA (N-methyl D-aspartate) receptor activation\(^{(31,32)}\). Therapeutic hypothermia can also reduce hepatic cell apoptosis and limit injuries to the liver. The current standard treatment for cerebral edema in acute hepatic failure limits the use of osmotic diuretics which may be prevented by high concentrations of saline administration. Jalan et al. first reported the clinical usage of therapeutic hypothermia in patients with acute hepatic failure in 1999\(^{(33)}\), and then conducted several clinical trials\(^{(5,34-36)}\). The target temperature was set at 32-33°C and was maintained for different periods of time from 4 hours to almost 120 hours according to the study design. There was a good response to reduced IICP or cerebral blood flow, and even the cardiac index was improved. However, the prognosis only improved in those who were successfully bridged to liver transplant after therapeutic hypothermia. The trend from all reports revealed that the prognosis was still disappointing if liver transplantation was not available after therapeutic hypothermia\(^{(5,33-38)}\). Nevertheless these studies were not designed to evaluate the efficacy of therapeutic hypothermia in survival analysis, and the number of enrolled patients was small. During acute hepatic failure, immunosuppressed status and bleeding tendency may further worsen the possible side effects of therapeutic hypothermia resulting in morbidity and mortality. Jalan et al. did not observe increased bleeding episodes during serial clinical trials, but a high prevalence of pneumonia was noted. It is necessary to provide more sensitive and stable temperature control using adequate medical devices with intensive care protocols, and consider using prophylactic antibiotics. Whether therapeutic hypothermia also works for patients with chronic hepatic function impairment is as yet not well understood due to a lack of evaluations. It would be worth evaluating the efficacy of therapeutic hypothermia in patients with acute or chronic hepatic impairment with randomized clinical trials\(^{(32)}\).

### Acute ischemic stroke

Although thrombolytic therapy with rt-PA has been approved for the treatment of acute ischemic stroke, the narrow therapeutic window and risk of systemic or intracranial bleeding limits the use less than 10% in survey\(^{(39)}\). During ischemic stroke, cellular, biochemical and metabolic processes are involved in neuron damage, but other neuroprotective strategies apart from therapeutic hypothermia have failed to prove effective benefits in clinical trials, probably due to a lack of numerous pathway protection. Therapeutic hypothermia can decrease brain metabolic demand and improve extracellular potassium rise, allowing for the correction of ischemic depolarization and mitigation of pathological depolarization. Pathological depolarization induced neurotoxic glutamine is also suppressed during hypothermia therapy. Hypothermia also inhibits free radical production and other inflammatory responses by activating NF-kB and lower stream protein activities. The apoptosis process is reduced and blood-brain barrier disruption attenuated. Several clinical studies on traumatic brain injury showed that hypothermia was effective in controlling intracranial cerebral pressure\(^{(40)}\). Some clinical trials have also shown that hypothermia is feasible for acute stroke patients and that milder target temperature control (below 35°C) may be effective, but slow re-warming is necessary to avoid rebound IICP\(^{(41-44)}\). The Intravascular Cooling in the Treatment of Stroke study (ICTuS), a large scale
randomized clinical phase I trial, was conducted to assess the effect of hypothermia in acute stroke patients within an onset time of 12 hours with NIHSS $\geq 4$. The target temperature (33°C) was maintained for 12-24 hours with re-warming for 2 hours$^{(44)}$. The ICTuS study combines therapeutic hypothermia with thrombolytic t-PA therapy and is now preparing to enter phase II and III trials (ICTuS-2/3).

**Spinal cord injury**

There is very significant morbidity in spinal cord injuries. Except for surgical intervention and fixation, corticosteroids and other anti-inflammatory agents are used to blunt the secondary damage responses of inflammatory, neurotoxic and secondary ischemic processes. However in cases of initially near complete neurological and motor function loss, there is a very low chance (1.05-30%) of improving to independent ambulation. Therapeutic hypothermia has also been shown to lower metabolic demand and decrease inflammatory cell injuries, as with the benefits in acute stroke. Local hypothermia therapy has been investigated both in animals and humans for over 40 years$^{(45)}$, but the response has not been satisfactory. This is probably due to the impact of local blood flow and local spinal cord physiology, and it is not recommended as formal therapy strategy. In applied systemic therapeutic hypothermia, blood flow can be maintained and benefits in spinal cord injuries could be expected. Although there are very few clinical reports available for the application of systemic hypothermia in spinal cord injury patients, both the theoretical rationale and the few case reports available show that it is highly probable to significantly improve the neurological outcomes of spinal cord injury$^{(46,47)}$. Currently a randomized clinical trial from the Miami Project is being conducted to further evaluate the clinical efficacy of therapeutic hypothermia in spinal cord injury$^{(46)}$. If the efficacy of systemic therapeutic hypothermia is proven for spinal cord treatment, it will most likely lead to dramatic changes in treatment guidelines.

**Acute myocardial infarction**

Myocardium is also a high energy required, high metabolism tissue like brain. Ischemia-reperfusion injury also results in myocardial apoptosis in acute myocardial infarction. Several animal studies have shown that local or systemic hypothermia may significantly reduce the infarction size and preserve systolic and diastolic function. Human clinical trials have successfully evaluated the safety and feasibility of therapeutic hypothermia in acute myocardial infarction patients, and even in patients with cardiac arrest or cardiogenic shock$^{(12,48-52)}$. However, larger scaled randomized clinical trials failed to prove a significant benefit in reducing cardiac enzymes and other biomarkers, which may be confounded by the delay in renal secretion in hypothermia$^{(53,54)}$. Dixon et al. evaluated infarction size with radioisotope nuclear scanning in 2002, and they also failed to prove the efficacy of reducing infarction size by therapeutic hypothermia$^{(5)}$. To evaluate the efficacy of therapeutic hypothermia in acute myocardial infarction, reliable conclusions will only be established by well designed studies combining large scale randomized trials with objective evaluation methods such as radioisotope nuclear scanning or contrast enhanced MRI, and the use of efficient medical devices or cooling methods to achieve successful cooling before reperfusion$^{(55)}$. However, the acute myocardial infarction may complicated with cardiac arrest, too. The current guideline strongly recommend the emergency and critical care physicians should not defer primary coronary intervention when concomitant use of therapeutic hypothermia in the post-resuscitation comatose patients$^{(18)}$. 
Other Potential Uses of Therapeutic Hypothermia from Animal Studies

Post-resuscitation heart failure

The cardioprotective effect of deep hypothermia is well known. In well controlled mild to moderate therapeutic hypothermia, several laboratory studies focused on the cardioprotective effect of therapeutic hypothermia in post-resuscitation myocardial dysfunction, which accounts for nearly 70% of mortalities after resuscitation. The animal studies showed that therapeutic hypothermia was beneficial in prognosis, hemodynamic parameters and myocardial apoptosis and further disclosed its protective mechanism from myocardial AKT activation\(^{9-11,56}\). In a study on the clinical application of hypothermia in pigs\(^{57}\), it was also notable that cardiac performance was improved. It would be worth conducting clinical trials to further investigate the clinical benefits of therapeutic hypothermia in post-resuscitation cardioprotection.

Pulmonary embolism

Pulmonary embolism is a common cause of dyspnea and can lead to cardiac arrest. Air embolism is also a life-threatening complication in diving accidents. Penk et al. reported an animal study on therapeutic hypothermia in air embolism induced in rats, and they found that acute lung injuries were significantly reduced compared to the normothermia group, and that air embolism-induced inflammatory responses were significantly attenuated\(^{58}\). Hovland et al. reported a case suffering from a massive pulmonary embolism-induced cardiac arrest, who received thrombolysis therapy with hypothermia without a significant increase of bleeding complications\(^{59}\). However, further randomized clinical trials are needed to evaluate whether patients with different severities of pulmonary embolism can benefit from therapeutic hypothermia.

Traumatic hemorrhagic shock

In the case of traumatic hemorrhagic shock, multiple organ failure is responsible for the third peak of mortality due to global ischemia-reperfusion injury\(^{(60)}\). However, therapeutic hypothermia is often considered to be contraindicated due to possible coagulopathy and platelet dysfunction, which would further affect clinical stability. However, an animal study by Iwamoto revealed that rats receiving hypothermia at 33°C had a significantly better prognosis than the normothermia group. In addition, Kim et al. reported that lower hypothermia (27-30°C) was efficient in decreasing acute lung injuries in a rat model of hemorrhagic shock\(^{(59,61)}\). Coagulation parameters are impaired if the temperature is lower than 33°C, but clinically there have been no significant increases in major bleeding events in different therapeutic hypothermia trials for variable etiologies. Strict and careful temperature control to avoid core temperatures below 33°C and aggressive bleeding control may be helpful. Clinical trials on the efficacy, safety and feasibility of therapeutic hypothermia in traumatic hemorrhagic shock, especially for those prepared for surgical homeostasis, would be worthwhile.

Practical Issues of Applying Therapeutic Hypothermia

Prognostic predictors of neurological outcomes

Therapeutic hypothermia is beneficial for neurological recovery, but not for all patients receiving this treatment. In cardiac arrest patients, many factors may significantly alter a patient’s prognosis such as time of collapse,
initial rhythm, causes of cardiac arrest, and bystander resuscitation. Young et al. reviewed the neurological prognostic predictors of poor prognosis from clinical signs to biomarkers and electrophysiological and neurological imaging, and found that myoclonus at day 1, an absence of N20 response on SSEP between days 1-3, elevated neuron-specific enolase between days 1-3, and an absence of pupil or corneal reflex or motor response other than decerebrate response at day 3 were all indicators of a poor prognosis with low false positive rates\(^{(62)}\). However during therapeutic hypothermia the patients are often sedated and use paralytic agents, making the evaluation difficult. A retrospective review by Vanston et al. on cardiac arrest patients with therapeutic hypothermia found that non-VT/Vf rhythm, acute renal injury and any arrhythmia after admission were independent and significant prognostic factors for a poor neurologic recovery\(^{(63)}\). However, Oddo et al. reported prospective observational studies which found that collapse time duration\(^{(19)}\), the presence of at least two independent predictors of incomplete brainstem reflexes, myoclonus, unreactive EEG, and absent cortical SSEP with 72 hours of cardiac arrest may accurately predict poor long-term neurological recovery\(^{(64)}\). Some studies have used the bispectral index (BIS) after resuscitation, and suggest that it may be of high value in predicting the prognosis at the moment of 30 minutes after successful resuscitation and at the initial dosage of neuroblockers when starting to induce therapeutic hypothermia\(^{(65-67)}\). However, it should not be applied during chest compression due to much artifact result in unreliable data\(^{(68)}\).

**Temperature detection**

The temperature of the brain is 0.1-2\(^\circ\)C higher than the core temperature in neurologically injured patients. The local injury area has a higher temperature than other healthy areas due to local neuron hyperactivity, inflammatory response and radical production. Local cerebral edema also limits the normal heat dissipation mechanism creating a “cerebral thermo-pooling” process\(^{(13)}\). In addition, the speed of hypothermia induction and re-warming rate play very important roles in determining therapeutic hypothermia benefits. An accurate temperature detection method would help clinicians to provide more accurate and sensitive temperature control for the cooling, maintaining and re-warming phases of therapeutic hypothermia. Although some observational studies have revealed very little bias between tympanic temperature and esophageal or bladder temperature\(^{(69)}\), the esophageal temperature is still much closer to the blood temperature than tympanic or rectal temperature in our experience, and it is easy to take via the mouths of therapeutic hypothermia patients. However, liquid diet feeding and neurolization therapy frequently cause esophageal temperature sensor disturbance and may lead to errors in temperature detection, resulting in the mismanagement of some automatic temperature controlling medical devices. If use bladder temperature, the temperature discrepancy is worth of notice especially in oliguria patients\(^{(8)}\). New endotracheal tubes with temperature detection sensors in the cuff surface have been developed and observational studies have proven the feasibility and temperature accuracy\(^{(70)}\).

**Timing of cooling and cooling rate**

The cooling rate is definitely a key factor in the successful application of therapeutic hypothermia. A post-injury free radical and inflammatory cascade storm occurs immediately reperfusion is achieved\(^{(71)}\). Several small and large animal studies have revealed that a delay in cooling decreases the therapeutic hypothermia protective effect\(^{(72)}\). Different resuscitation models in animal studies have proven that intra-arrest cooling provides much better neuroprotection than
immediately cooling at post-resuscitation\(^{(73,74)}\). Therefore the earlier and faster cooling is started and achieved, the better the effects on organ protection. Multicenter randomized clinical trials combined with pre-hospital emergency systems and emergency departments are being conducted to further explore the intra-arrest hypothermia effect in OHCA patients, and intra-arrest cooling by rapid infusion of cold fluid has been proven to be feasible in clinical application\(^{(72)}\). However, several human trials revealed if the cooling start within 2 hours or achieved target temperature in 4 to 9 hours, the prognosis is not time dependent\(^{(76,77)}\). Another concern is how soon hypothermia should be achieved. Neurological researches by Hayashi et al. revealed that 34°C is a critical point. Free radicals are significantly suppressed until 34°C, but stress induced hyperglycemia leads to a metabolic shift, binding hemoglobin 2,3-DPG to lactate production and worsening neuronal hypoxia. Therefore, some authors suggest two steps cooling. First, cool to 34°C as soon as possible to ameliorate free radical and neurotoxic transmitters such as glutamate and dopamine. Second, after achieving 34°C, strict glucose control to decrease the serum glucose level below 180 mg/dl is important for successful neural protection\(^{(78)}\). However, further clinical investigations are still needed to explore the effects of two step cooling compared to the current commonly used protocol.

**How long to maintain hypothermia?**

According to resuscitation guidelines, post-resuscitation hypothermia should be maintained for 12-24 hours after ROSC and most reported 24 hour use in post-resuscitation care\(^{(18)}\). However, different indications of the use of therapeutic hypothermia may require different maintenance periods to achieve a therapeutic effect. In traumatic brain injury, the maintenance phase is suggested to be prolonged to 48-72 hours for better control of IICP.

**Re-warming technique**

Several studies have revealed that the re-warming rate is an important variable for neuronal protection. Slower patient re-warming from cardiopulmonary bypass has been shown to have a better long term neurological outcome than a rapid warming process\(^{(79)}\). Rapid warming may cause adverse effects such as electrolyte imbalance, in particular hyperkalemia which shifts from the intracellular to extracellular space, insulin sensitivity increase and hypoglycemia, instability of cerebral-vascular reactivity and hypotension. Rebound increasing intracranial pressure, intracranial hyperthermia and inducing seizures have also been found. The possible mechanism is that rapid warming may result in mitochondria dysfunction from an exacerbated radical mediate process further depleting the amount of ATP, but slow warming can help to maintain the integrity of mitochondria function\(^{(80)}\). Baena et al. reported a 2.6-fold increase in neuronal injuries if mild fever (1-2°C higher than usual) was induced after hypothermia\(^{(81)}\). Although no clinical studies have been conducted to determine the optimal re-warming rate, it should be well controlled and slow, below a rate of 0.2-0.5°C/hour for cardiac arrest patients and 0.1-0.2°C/hour for other causes of brain injury patients\(^{(13)}\). Maintaining the post re-warming phase temperature at normothermia to avoid fever, which is a independent variable for a poor prognosis, is also recommended.

**Strategies and medical devices for therapeutic hypothermia**

Several cooling and temperature control methods have been developed to provide more rapid cooling, more stable maintenance of hypothermia and a well controlled re-warming process. Surface cooling is simpler in clinical use, but traditional water pads or ice blankets lack sensitive temperature control and require
manpower-consuming maintenance during the re-warming phase. An invasive endovascular catheter can provide smaller temperature fluctuations, better temperature control during re-warming, and less failure to reach the target temperature or overcooling than conventional surface cooling methods. However, it has been shown that mortality and neurological outcomes are not different between surface cooling or endovascular catheter groups. Newly developed water circulation pad systems (e.g. ArticSun, Medivance, Colorado, US) provide a temperature feedback system for automatic and more accurate control of temperature in surface cooling, however they are not cheap. Other invasive methods such as intravascular cooling catheters (ICY, Forties, Zoll, Massachusetts, US) are usually more technique-dependent but can provide excellent and easy temperature control. Many studies encourage starting cooling with rapid cold fluid infusion (4°C crystalloid, 30 ml/kg or 2 L in 30 minutes) which has been proven to be efficient, cheap and easily feasible in pre-hospital ambulances and critical care. However, further temperature maintenance and re-warming equipment should be seriously considered to provide better and efficient care quality and avoid adverse effects. Polderman et al. conducted a comprehensive review of cooling methods in 2009, and it is a good reference for physicians to aid in choosing feasible and affordable methods.

Pharmacological adjustment
During the application of therapeutic hypothermia, many preclinical investigations have revealed a high percentage of differences in pharmacokinetics and pharmacodynamic parameters when compared with normothermia. The enzyme activity and liver perfusion may decrease during therapeutic hypothermia resulting in decreased clearance and changes of drug distribution. It is very possible that patients will be at risk of drug intoxication or therapeutic failure if the clinicians use the usual dosage recommendations for normothermia. In contrast, the re-warming process has the exact reverse effect on pharmacological change. Therefore, drug dosage adjustment and drug monitoring during therapeutic hypothermia is considered important, especially for known specific organ toxicity such as aminoglycoside.

Ventilator readjustment
During therapeutic hypothermia, the metabolic rate reduces to 50-65% when 32°C is achieved. The ventilator setting should be readjusted to avoid hyperventilation and hyper-oxygenation, which separately induce cerebral vascular contractions and large scale oxidative stress production. The blood gas should be analyzed at the patient’s temperature, which is different from the usual normothermic setting. If correction is not easily available, 0.012 PH units should be added and 5 mmHg PO$_2$ and 2 mmHg PCO$_2$ should be subtracted per °C decrease in body temperature. It is suggested that the ventilator setting be maintained at PCO$_2$ 32-36 mmHg in the corrected sample, which would be around 42-26 mmHg in the uncorrected sample to avoid hyperventilation.

Insulin sensitivity change
During hypothermia, insulin secretion is diminished and insulin resistance leads to hyperglycemia. In the re-warming phase, insulin sensitivity is restored which may lead to hypoglycemia, especially in cases of rapid re-warming.

Electrolyte disturbance
During induction of hypothermia, intracellular shift and renal tubular excretion result in multiple electrolyte imbalances. Hypokalemia, hypomagnesium, and hypophosphate are frequent
complications which may aggravate arrhythmia, attenuate neuroprotection and worsen respiratory function. During the re-warming phase, hyperkalemia rebound may develop due to previous intracellular compartments sequestering, which can be prevented by slowing the re-warming rate. In patients who develop anuric/oliguric renal failure, renal replacement therapy should start before warming to avoid severe hyperkalemia and induced arrhythmia complications.

Other adverse effects management

During therapeutic hypothermia, stable temperature control is important for the patient’s safety, especially in the case of arrhythmia. In mild hypothermia, defibrillation is more easily achieved than normothermia, however the myocardium becomes less responsive to antiarrhythmia agents, becomes more difficult to defibrillate and more sensitive to mechanical manipulation in deep hypothermia (≤ 28-30°C). Some authors have suggested that atrial fibrillation is an early warning sign for those progressing to more severe ventricular tachycardia in deep hypothermia patients. During mild to moderate therapeutic hypothermia, sinus bradycardia and prolonged QT are the most commonly occurring electrocardiography abnormalities. Electrolyte imbalance may further raise the probability of severe arrhythmia(89). During the clinical application of hypothermia, we recommend the usage of lidocaine, instead of the commonly used amiodarone, as prophylaxis treatment for frequent ventricular premature beat to avoid further elongated QT intervals and ameliorate electrolyte imbalance more aggressively. In addition, some authors have suggested that cardioversion for non-life threatening arrhythmia may further trigger ventricular arrhythmia if the core body temperature is 34°C or less, and the usage of cardioversion should undertaken carefully.

References

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治療性低體溫的發展與臨床應用

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治療性低體溫曾因嚴重副作用而惡名昭彰，但在許多實驗室研究顯示只要溫度控制得宜，治療性低體溫是可以減少器官組織傷害的利器。在西元2002於新英格蘭雜誌上發表的兩篇隨機多中心臨床試驗報告證實了由中度到輕度低體溫可以有效幫助心因性心跳中止病患腦部的恢復並顯著減緩病患殘障，甚至增加病患的預後。在近幾年的急救指引中各方專家皆十分強調與推廣對於急救後病患使用治療性低體溫的重要。除此以外，目前在急救醫學界治療性低體溫已經被許多其他相關領域專家視為器官保護的明日之星。例如與腦部保護相關的新生兒窒息、急性腦中風、創傷性腦外傷、急性肝衰竭、急性脊椎損傷；心臟保護相關的急性心肌梗塞、多重器官衰竭相關的出血性休克與敗血症等等都有相當程度的研究與機制的瞭解，甚至已經開始進行相關臨床試驗。然而要成功以治療性低體溫幫助病患，施行治療性低體溫時需要特別注意許多細節。包括施用對象不同可能會有不同的施用時機與溫度、施用期間不同的差異，同時需要控制的方法與升溫降溫速度的調整。低體溫溫控的穩定度亦與使用後是否有效以及低體溫導致的併發症息息相關。在本文中吾人對於治療性低體溫的發展與臨床應用以及臨床使用上需要注意的細節進行簡要的文獻回顧與經驗分享。

關鍵詞：低治療性低體溫，心肺復甦術，急救後治療