

## Untoward Effects in the Practice of Therapeutic Hypothermia: A Literature Update

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### Abstract

Out-of-hospital cardiac arrests (OHCA) is the plague of the modern day and therapeutic hypothermia (TH) is launched to be a remedy against this. TH is practised mainly in the treatment of adult cardiac arrest and neonatal hypoxic-ischemic encephalopathy. Despite the improved benefits of mild TH, there are commonly overlooked complications associated during management. TH may cause an increase in insulin resistance and a reduction in insulin levels which result in hyperglycemia. Studies showed a significantly increased incidence of meningitis, pneumonia and wound infections. Hypothermia was also reportedly associated with increased blood loss and transfusions. In addition, electrolyte abnormalities such as hypokalaemia, hypomagnesaemia, hypophosphatemia, hypo- and hyperglycaemia have been described during TH. The procedure has also been shown to incite mild metabolic acidosis.

This article reviews the current literature to provide systematic data regarding adverse and untoward effects attributed to the procedure of TH in the emergency setting.

**Keywords:** Cardiac arrest; Therapeutic hypothermia; Adverse effects; Side effects; Targeted temperature management

### Introduction

Annually, there are 356,500 out-of-hospital cardiac arrests (OHCA) in the US, with a median survival rate of 12% [1]. Neurologic injury is the most common cause of death in patients with OHCA and contributes to the mortality of in-hospital cardiac arrest [2]. In the post-resuscitative period, therapeutic hypothermia (TH) is thought to mitigate neurologic reperfusion injury by decreasing cerebral oxygen consumption and biochemical damage [3]. TH was postulated to offer an extended therapeutic window to restore the integrity of circulation, with the brain maintained in a protective, hypometabolic state.

The promising idea of 'human refrigeration' was advocated first for the management of traumatic brain injury (TBI) and brain tumours by Fay in the 1940s who reported its application in 124 cases and also invented one of the earliest 'cooling blankets' [4].

TH has been historically classified into: mild (34.5-36.5°C), moderate (34.5-32°C), marked (28-32°C) and profound hypothermia (<28°C) [5,6]. The administration of 'mild TH' has been shown to improve neurological outcomes and can prevent severe brain damage after OHCA [3,7]. In this context, induced hypothermia is evaluated in three steps: induction, maintenance and rewarming, and each phase produces several changes in normal physiology.

Hypothermia induction should be started as soon as possible to minimize neurologic damage. Infusing cold fluids, e.g., Ringer's lactate >25 mL/kg at 4°C, is the easiest and most effective method for inducing hypothermia [8]. Mild cooling was shown to be beneficial without many of the feared side effects. Nonetheless, TH requires an intensive care unit setting with protocolized implementation and close monitoring [9]. It is likely that both survivors of arrest by itself and with the addition of TH procedure increase risk of complications from the hypothermia [10].

Substantial amount of literature data are available although there is a need to culminate these in a systematic and orderly fashion to guide monitoring the patients to avoid these in the procedure. This article

reviews the current literature to provide systematic data regarding adverse and untoward effects attributed to the procedure of TH in the emergency setting.

### Side/Adverse Effects/Complications Attributed to TH

Decrement in body temperature virtually affects all biological processes. Therefore, hypothermia can cause serious complications (Table 1). Although many respond to standard measures, some may end up with important morbidity and mortality. MacLaren et al. compared the incidences of adverse events and predictors of good versus poor neurological recovery after TH in a review of medical records of 91 patients who received TH for  $\geq 6$  hours [11]. They reported that common adverse events were hypoglycemia (99%), shivering (84.6%), bradycardia (58.2%), electrolyte abnormalities (up to 91.2%), acute kidney injury (52.8%), infection (48.4%), and coagulopathy (40.7%).

### Cardiovascular effects

Induction of mild TH causes sinus tachycardia in order to increase oxygenation of the vital organs. Compartmental shifting from peripheral vasoconstriction to the core vasculature follows. Vasoconstriction-related increase in systemic vascular resistance ensues which, in turn, result in an increase in mean arterial pressure concomitant with a drop in heart rate and cardiac output [12,13]. Hypothermia has a positive inotropic effect which results from improved left ventricular filling

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Organ system	Adverse effects	Specific measures
<b>Cardiovascular</b>	Sinus tachycardia Peripheral vasoconstriction Bradycardia Increased contractility 'Cold diuresis' Prolonged action potential duration J (Osborn) waves, prolonged PR, QRS, and QT intervals Hypertension Ventricular dysrhythmias Coronary vasoconstriction	Fluid boluses Bedside monitoring of the rhythm, right heart filling, vena cava inferior index etc. (via Swan-Ganz catheter) Beware of fluid depletion Dysrhythmias are typically managed conventionally
<b>Pulmonary</b>	Neurologic pulmonary edema ARDS Pneumonia	Pneumonia incidence is not increased if TH <48 hours Suctioning, head elevation, sedation breaks reduce ventilator associated pneumonia incidences
<b>Infections</b>	Suppression of the immune system, Meningitis, Pneumonia, Wound infections	Cultures, prophylactic antibiotics, and removal of unnecessary catheters may decrease the incidence of infection. Extra caution must be exercised to prevent bedsores and monitor any catheter insertion sites closely
<b>Hematological</b>	Low platelet count, Increased blood loss and transfusions with surgery, Coagulopathy	Close monitoring is warranted. Analyses may be masked if performed after rewarming
<b>Renal</b>	Diuresis, Renal tubular dysfunction, Reduced creatinine clearance Depletion of electrolytes	Returns to normal after rewarming
<b>Fluid and electrolyte disorders</b>	Hypokalemia, Hypomagnesemia, Hypophosphatemia, hypo- and hyperglycemia	Frequent measurement and repletion of deficient serum magnesium and other electrolytes
<b>Acid-base</b>	Increased serum lactate Ketonemia, Metabolic acidosis	
<b>Endocrine effects</b>	Hyperglycemia, Hypoinsulinemia	Although still debated, tight control of blood glucose might be beneficial
<b>Gastrointestinal</b>	Ileus, Delayed gastric emptying	Early enteral nutrition is feasible in those without ileus
<b>Liver Function and Drug Metabolism</b>	Reduced P450 activity Reduced plasma clearance of drugs Propofol, fentanyl, and acetaminophen are commonly associated with ADRs	Reversed after rewarming Adding a bolus as opposed to increasing the drip rate is advised to achieve more sedation Judicious use and close monitoring of drugs
<b>Neurological</b>	Seizures EEG abnormalities / Malignant EEG	Decreased incidence with a target temperature of 32°C EEG monitoring to prevent seizures.
<b>Others-miscellaneous</b>	Shivering	Buspirone (PO) and/or meperidine (IV), skin warming work for treatment

**Table 1:** Distribution of adverse effects and/or complications attributed to TH.

due to bradycardia. Heart rate is mostly reduced up to 40 to 45 beats/min at 32°C which does not warrant any specific treatment per se [13]. Jacobshagen et al. reported hemodynamic data from 200 survivors of arrest who underwent mild TH and showed increased contractility in the failing human myocardium, due to augmented sensitivity to calcium which suggested that mild TH stabilizes hemodynamics [14].

Hypothermia is known to decrease spontaneous repolarization of cardiac myocytes and prolongs action potential duration and impulse conduction which is translated to ECG abnormalities as J (Osborn) waves concurrent with prolonged PR, QRS, and QT intervals. Fortunately, J waves are rarely seen in mild (32°C-34°C) hypothermia [13]. Accordingly, the most frequent ECG changes in patients receiving mild TH are prolonged PR intervals, widening of the QRS complex, and increased QT interval [15,16].

Augmented venous return leads to an overt activation of atrial natriuretic peptide and decreased levels of antidiuretic hormone creating the so-called 'cold diuresis' [12]. Therefore, patients treated with TH is recommended to receive fluid boluses with bedside monitoring of right heart filling, vena cava inferior index etc. to beware of fluid depletion.

Hypothermia induction is associated with an increase in heart rate, cardiac output, systemic vascular resistance, which result in augmented reading of blood pressure [17].

- In the range of 32°C to 35°C, decreases in heart rate, blood

pressure, and cardiac output are seen along with an increase in central venous pressure.

- Around 32°C to 33°C, there is an increased risk of cardiac dysrhythmias, and J waves, first-degree heart block, and prolonged QT [17].
- Below 28°C, ventricular dysrhythmias may first appear but are mostly encountered in case of more severe hypothermia.

The risk of dysrhythmias generally does not increase at temperatures more than 30°C [13,18]. Dysrhythmias have typically been manageable with standard interventions and in some researches of mild-to-moderate TH, they were not any more common than in normothermic settings [19,20]. Bernard et al. pointed out that TH was not associated with a substantial proarrhythmic effect in the group treated with 33°C [7].

It is shown that hypothermia may cause coronary vasoconstriction especially during induction phase (PSJT, MGJSG) [21,22]. This may result in acute myocardial ischemia and finally, ventricular fibrillation or ventricular tachycardia. Hypothermia causes an elevation in endothelial-derived release factor, a vasodilator to prevent vasospasm. On the other hand, magnesium deficiency has been shown to be an inciting event for coronary spasm. Another interesting point is whether these patients suffered from cardiovascular complications related to coronary interventions after resuscitation and TH. Chisholm et al. identified 68 unconscious patients between 2010 and 2013, who were

resuscitated after OHCA and underwent acute percutaneous coronary intervention (PCI) with stent implantation and immediate TH, and followed these for 30 days via Western Denmark Heart Registry [23]. The authors observed only one stent thrombosis in this cohort and concluded that PCI with stent implantation could be performed with acceptable safety in these patients.

It is recommended to manage the patient treated with mild TH with close monitoring via Swan-Ganz catheter if shock is suspected. It is of utmost importance to ensure proper mixed venous oxygenation to provide necessary hemodynamic support. Indeed, TH may provide beneficial effects in patients with cardiogenic shock, as the profound bradycardia may act as a beta-blockade to reduce work and therefore oxygen demand of the heart [24].

### Pulmonary effects

It is sometimes hard to discern untoward effects of TH from those caused by the disease of the patient itself and metabolic complications of these. For example, we know that up to one-third of intubated neurologic patients may develop acute respiratory distress syndrome (ARDS) [25]. Neurologic pulmonary edema is also common in patients treated with TH [26]. Interestingly, the reported incidence of ARDS in patients undergoing even prolonged TH is half of that for normothermic population [27]. Reports cited that increased incidence of pneumonia was reported only when hypothermia is maintained for longer than 48 hours [28,29]. Some researchers pointed out that the barbiturate use may be a significant risk factor [19]. On the other hand, the most recent Cochrane systematic review of TH for TBI found that TH was associated with an increased incidence of pneumonia, but that this was not statistically significant for trials with good allocation concealment [30].

Solutions suggested to reduce the risks include strict implementation of protocols known to reduce ventilator associated pneumonia (vigorous suctioning, head elevation, sedation breaks), minimizing the use of barbiturates, and keeping the duration of hypothermia as short as possible [31].

### Infectious complications

Increased rates of bacteremia were encountered after prophylactic hypothermia in the operative setting [32]. Other studies showed a significantly increased incidence of meningitis [29]. Likewise, pneumonia and wound infections risks are significantly increased. In a large, multicenter, international registry of patients receiving mild TH, pneumonia and sepsis were not associated with increased mortality, and there was an inverse relationship between infection and mortality [33]. On the other hand, a sample of patients undergoing prolonged TH has been shown to exhibit a significantly lower rate of infection in the hypothermia group compared to controls [34]. Culture of the bodily fluid, use of prophylactic antibiotics, and removal of unnecessary catheters may decrease the incidence of infection [24].

TH is reported to boost the risk of wound infections; therefore, extra caution must be exercised to prevent bedsores and monitor any catheter insertion sites closely [13]. Wound infection rates are found to be higher because of local vasoconstriction and tissue hypoxia, as well as suppression of the immune system [35-37]. To reduce the risk of infections augmented by TH, Polderman and colleagues used both antibiotic prophylaxis and selective decontamination of the digestive tract, which may have had some protective effect [31].

### Effects on hematologic function

“The more hypothermic the patient is, the more likely hemorrhage will occur” [38]. Some researchers declared that TH causes a decrease in platelet count and function which is reversible with rewarming [38-41], although hemoglobin levels remain the same [27,42,43]. Specifically, platelet function may be decreased to less than 35°C, while the coagulation cascade is affected at below 33°C [13]. Note that technically the adverse effects on coagulation studies in the clinical setting may be masked if analyses are performed on rewarmed blood [18].

There is ongoing debate on whether significant prolongation of activated partial thromboplastin time (aPTT) can be expected or not [34,43]. A meta-analysis of high-quality clinical trials of TH for TBI showed that overall, PTT was only slightly increased with TH [44]. One study of TH on neonatal infants with hypoxic-ischemic encephalopathy reported higher PT, lower platelets, and more requirements for platelet and plasma transfusion in the hypothermia group [45].

In the surgical setting, hypothermia was reportedly associated with increased blood loss and transfusions [46]. Coagulopathy may be of more concern in trauma where there is more likely to be ongoing hemorrhage [47]. On the other hand, large clinical trials in patients with subarachnoid hemorrhage, TBI, and stroke did not report an increased risk of bleeding with hypothermia.

There seems to be an increased risk for coagulopathy in the treatment with TH and thus the procedure warrants close monitoring for this. The risks of coagulopathy are to be weighed against the advantages of TH. For instance, a reversible period of coagulopathy may be an acceptable risk if the treatment increase the chances of survival in an otherwise fatal condition.

### Renal effects

Known effects of hypothermia include urinary diuresis, renal tubular dysfunction, reduced creatinine clearance and increased excretion of electrolytes which result in depletion of important elements [17,31,48-51]. Zane et al. recently published data on the differences in vancomycin disposition in pediatric patients following cardiac arrest treated with either TH or normothermia [52]. They noted that children receiving hypothermia and/or with decreased renal function had lower vancomycin clearances based on a retrospectively fitted two-compartment model in children who experience cardiac arrest. Metz et al. pointed out that serum creatinine levels had returned to normal in all participants after 24 hours of rewarming [51].

### Fluid and electrolyte disorders

Electrolyte disorders are common in TH, especially in the induction phase. Electrolyte abnormalities such as hypokalemia, hypomagnesemia, hypophosphatemia, hypo- and hyperglycemia have been described during TH [11,53-56]. TH typically causes a decrease in almost all electrolyte except sodium: magnesium, potassium, phosphate, and calcium which can be translated into many clinical conditions [49,57,58]. Of note, a reduction in magnesium level may impair neurological functions [13].

Potassium levels decline with hypothermia and hyperkalemia may be encountered if a patient is rewarmed rapidly. Serum sodium levels are usually unaffected [42,43]. Higher prevalences of hyponatremia and hypokalemia were reported by Shiozaki et al. in patients undergoing TH in one study [29]. Thus, frequent measurement and repletion of deficit serum magnesium and other electrolytes should be instituted.

Electrolytes have been recommended to be maintained in the high normal range during TH [15], although it is necessary to replace only proven losses of most electrolytes, e.g., potassium. Reports indicated that patients who had only documented losses replaced remained normokalemic upon rewarming and thus dysrhythmias are beware of [59].

### Acid-base disorders

Hypothermia has been shown to increase serum lactate levels (5-7 mmol/L) and augment the synthesis of glycerol, free fatty acids, ketonic acids and lactate, leading to mild metabolic acidosis [15]. On the other hand, a respiratory compensation occurs and pH measured in the hypothermic state will be higher than that measured at 37°C, parallel with a decrease in PaCO<sub>2</sub> [17]. During the induction of TH procedure, patients receiving mild TH had an average pH decrease from 7.37 to 7.31 [49]. Hypothermia decreases both oxygen consumption and the production of carbon dioxide, thereby diminishing metabolic demands (+8% per °C drop in core temperature) [60].

### Endocrine effects and glycemic control

MTH commonly induces hyperglycemia due to insulin sensitivity because of decreased insulin secretion by the pancreas not only resulting in increased insulin requirements but also may further increase the risk of infection [13,15,60]. During TH procedure, hyperglycemia can be seen with temperatures in the mildly hypothermic range [17]. Several studies showed benefit to tight control [61-64] whereas some other trials and a meta-analysis found no benefit and potential harm [65-67] especially in patients with TBI. Hypothermic patients may require more insulin administration, which seems to be associated with increased mortality [62].

Glycemic variability may play a role in morbidity regardless of the blood glucose levels [68]. Therefore, optimal glycemic control in TH warrants more studies and changes with the nature of trauma. Nevertheless, significant differences in glycemia or insulin requirements were not reported in trials comparing patients undergoing hypothermia to controls monitored closely [34,42,43].

### Shivering

Shivering occurs with a decrease in core temperature below 35.5°C and ceases at temperatures less than 30°C; it increases metabolic rate and oxygen consumption [18]. The process is viewed as the body's adaptive mechanism against cooling. It may increase metabolic heat production along with oxygen consumption by 50% to 400%. Data have shown that oxygen consumption is linearly related to shivering. However, one study found that hypoxia reduced oxygen consumption more in cold than in thermoneutral environments and concluded that the decrease in metabolic rate was in part due to the hypoxic suppression on shivering [69]. Of note, shivering increase hemodynamic stress through tachycardia, vasoconstriction, and hypertension. Some studies indicated that shivering may be an important surrogate for good neurologic outcome [70].

Most researchers do not favour shivering in patients survived resuscitation via TH. A study by Mokhtarani, et al. found that treatment with buspirone 30 mg prior to initiation of mild TH decreased the shivering threshold 2°C to 4°C while working synergistically with meperidine [71]. Skin warming and intermittent administration of IV meperidine 25 to 75 mg can help achieve adequate suppression of shivering. Likewise, IV magnesium sulfate 2 mg, IV dexmedetomidine 0.2 to 1.5 mg/kg/h, IV propofol, and IV vecuronium 0.1 mg/kg attenuate shivering [24].

### Gastrointestinal effects

TH is known to precipitate or worsen ileus and delay gastric emptying. Furthermore, ileus is common and thus gastric decompression may be beneficial. Incidence of stress ulcers are also boosted and standard care measures thereof should be instituted [17]. Dobak et al. conducted a comparison study of small sample size focusing on feeding in patients with spontaneous intracerebral hemorrhage and treated with mild TH [72]. They reported that three patients (50%) with mild TH experienced high gastric residuals prior to prokinetic agents, and one (16.6%) had mild ileus. No gastrointestinal-related adverse events were reported in those treated with mild TH. They also concluded that early enteral nutrition is feasible, although delayed early enteral nutrition initiation, high gastric residuals, and less early enteral nutrition provision are common in the clinical practice.

### Liver function and drug metabolism

TH has the potential to alter physiological processes and thus several classes of drugs may become affected by the process. Functional activity of cytochrome P450 system is reduced in patients treated with TH [73]. A systematic review found that P450 activity was reduced between 7% and 22% per °C below 37°C [74]. Reactions dependent to these enzymes can be inhibited, which means that plasma levels of drugs will mostly be higher than expected and prolonged effects can be seen. Fortunately, these are effects which are usually reversed after rewarming [17,51].

TH modify drug function via changes in drug absorption, metabolism, and excretion, resulting in possible underperformance of the drug or reduced plasma clearance with potential adverse drug reactions (ADRs) and toxicity. The essential mechanism of altered metabolism is diminution of cytochrome P 450 enzyme activity secondary to reduced hepatic blood flow and decreased gastrointestinal absorption [73]. Clearance of commonly used medications such as vasopressors, opiates, sedatives, volatile anesthetics, neuromuscular blockers, and phenytoin was shown to be reduced with TH in studies [13]. Since this can increase drug potency, adding a bolus as opposed to increasing the drip rate may be advised in cases that require more sedation.

Witcher, et al. have recently conducted a retrospective chart review of 229 patients admitted to an intensive care unit after cardiac arrest and treated with TH [75]. There were 670 possible ADRs i.e., an average of 3 for each patient treated with TH- and 69 probable ADRs identified. Of the 670 possible ADRs, propofol, fentanyl, and acetaminophen were the most common drugs associated with ADRs, while fentanyl, insulin, and propofol were the most common drugs associated with a probable ADR. There is a need for judicious use and close monitoring of drugs in the setting of TH until recommendations on dosing are available to help prevent ADRs.

### Neurological disorders: seizures, EEG features

Seizures are also encountered in survivors of CA treated with mild TH up to 12% to 44% [76,77]. Seizures after CA are associated with poor outcome [77] with prolonged seizures likely contributing to secondary brain injury. A trial from Lopez-de-Sa, et al. found a decrease in seizure incidence with a target temperature of 32°C and may yield better protection than cooling at 34°C (1 vs. 11) [78]. EEG monitoring may help prevent this complication in victims of arrest undergoing mild TH. Kim et al. suggested that increased interictal epileptiform discharges with rewarming in post-CA patients undergoing TH may suggest poor prognosis [79]. There was a trend toward the emergence

of interictal epileptiform discharges upon rewarming and mortality, but it was not statistically significant.

Westhall et al. reported that highly malignant EEG after rewarming reliably predicted poor outcome in half of patients without false predictions [80]. An isolated finding of a single malignant feature did not predict poor outcome whereas a benign EEG was highly predictive of a good outcome.

## Conclusion

TH may render patients with successful recovery from CA situations prone to a myriad of complications or untoward effects on virtually all organ systems of the human being. For example, adverse drug reactions may be encountered more commonly following use of medications which mandate close monitoring and necessary measures be taken. Potentially beneficial effects of TH on neuronal recovery must be balanced against the adverse effects, such as infections, impaired blood coagulation, electrolyte disorders, and hyperglycemia.

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