Chapter 1

Therapeutic Hypothermia: Adverse Events, Recognition, Prevention and Treatment Strategies

Rekha Lakshmanan, Farid Sadaka and Ashok Palagiri

Additional information is available at the end of the chapter

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1. Introduction

Therapeutic hypothermia has been around for centuries, ancient Egyptians, Greeks, and Romans have used it.

Hypothermia is any body temperature below 36 degree C.

Therapeutic Hypothermia is induced hypothermia and can be mild (34-35.9 degree C), moderate (32-33.9 degree C), moderately deep (30.1-31.9 degree C) or deep (less than 30degree C).

Cardiopulmonary resuscitation	Class-I
Traumatic brain injury (ICP CONTROL)	Class I
Traumatic brain injury (outcome)	Class IIa
Stroke	Class-III
Fever in patients with neurological injury	Class IIb
Subarachnoid hemorrhage- vasospasm prevention	Class-IV
Intraoperative hypothermia for intracerebral aneurysm surgery	Class-IIb
Intraoperative hypothermia for thoraco-abdominal aortic aneurysm	Class-III

Figure 1. Current indications for induced therapeutic hypothermia

2. Cardiac arrest

Despite advances in ICU care, cardiac arrest remains a significant cause of death in many countries. Mortality reports vary from 65 to 95% for out-of hospital cardiac arrest. I is a class –I recommendation now that after return of spontaneous circulation in out-of-hospital VF cardiac arrest , patients that remain comatose should be subjected to hypothermia at 32°C to 34°C for 12 to 24 hours. This may also be applied to comatose adult patients with spontaneous circulation after OHCA from a non VF rhythm or in-hospital cardiac arrest.[1]

Several unanswered questions however remain, due to lack of randomized studies. These in part, relate to time from initiation of therapy to achieving target temperature, and whether this is a significant predictor of outcome. The optimal rate of cooling is also an unanswered question, so is the optimal duration of TH in some settings, albeit in the setting of cardiac arrest, improved outcomes have been demonstrated with 12 and 24 hrs of TH at 32°C to 34°C. Hypothermia for neonatal asphyxia is commonly performed for 72 hrs, while hypothermia for cerebral edema associated with liver failure has been reported for as long as 5 days. [2]

3. TBI

Traumatic brain injury (TBI) is a leading cause of death and disability in young people in Western countries. The neuroprotectant effects are thought to be related to decreased metabolic rate, cerebral blood flow, decreased release of excitatory neurotransmitters, decreased apoptosis, cerebral edema, decreased cytokine response etc.[3]

While studies have shown that Hypothermia is clearly effective in controlling intracranial hypertension (level of evidence: class I); it has been difficult to show that lowering ICP definitely improves outcomes. Few positive studies with regard to survival and improved neurological outcome have been shown mainly in tertiary referral centers with experience in use of hypothermia. Here again, as in cardiac arrest, more unanswered questions remain- duration, time of cooling and rewarming, type of rewarming. Currently, most centers perform it for at least 48 hours. Rewarming is typically done slowly, over at least 24 h (level of evidence: class IIa). [4] If there is evidence of ICP elevation during rewarming, again no definite recommendations are available, but most experts will proceed with repeat cooling. It could be that in traumatic brain injury, other therapies, including cerebrospinal fluid drainage, osmolar therapies, sedation, barbiturate coma, and decompressive craniectomy may confer additional benefits that may make it more difficult to prove that Therapeutic hypothermia is superior.

4. Stroke

Similar to Cardiac arrest and TBI there is evidence from animal studies that show benefits of therapeutic hypothermia in stroke. Use of hypothermia in stroke remains experimental, until large prospective randomized human clinical trials using hypothermia in acute stroke are completed. [5]

5. MI

Hypothermia may decrease infarct size in patients with acute myocardial infarction after emergency percutaneous coronary intervention

6. Other indications

Intraoperative hypothermia is used during neurological surgery but without strong evidence from randomized controlled trials. Indications are being studied in the areas of SAH, Neurosurgery, liver failure, Spinal cord injury.

7. Induction of hypothermia

Methods [6]

Both Invasive and non invasive cooling methods have been developed and used to induce hypothermia. The ideal cooling technique should offer efficacy, speed of cooling for target organs, and offer ease of use and transport. It should also have the ability to provide controlled rewarming.

Surface cooling: Dine et al

Surface cooling as a noninvasive method to induce hypothermia is easy to use, on the other hand requires more time to achieve the target temperature. There are two described methods: generalized cooling, and selective brain cooling.

Generalized cooling is achieved through the use of cooling blankets, ice packs, and cooling pads. Care should be paid to prevent cold injury to the patient's skin. This method has variability in time to cooling, ranging from 0.03 to 0.98 °C per hour and difficulty in titration of temperature.

Pads that provide direct thermal conduction through the skin are also used; these are unlike conventional water blankets or wraps where heat transfer is by convection. The cooling rate is reported to be 1.5°C/hour or more. Hydrogel-coated pads in these circulate temperature-controlled water under negative pressure, and are placed usually on the patient's abdomen, back and thighs.

Selective brain cooling is another non invasive method. The most commonly used methods are cooling caps and helmets that contain a solution of aqueous glycerol to facilitate heat exchange. Helmet devices do not appear to provide particularly significant protection to the brain, but they reduce core temperature slowly.

Several other limitations exist in surface cooling methods. Through vasoconstriction, shivering, redirection of blood flow away from extremities, they create thermal energy. Overcooling occurs. In a study involving 32 patients where surface cooling was used to induce hypothermia, 63% of patients were overcooled, increasing the risk for adverse events. Another problem with surface cooling is cold injury, causing pressure ulcers and

skin breakdown. Surface cooling is less efficient in reducing the temperature of target organs, such as the brain and heart[6]

Invasive cooling

30 ml/kg Lactated Ringers solution that has been chilled to 4°C can be infused over 30 minutes. No adverse effects of the rapid infusion of this volume of IV crystalloid fluid in a study by Bernard. This is followed by another method to maintain hypothermia. Different types of fluids can be used, including 0.9% sodium chloride injection, lactated Ringer's injection, and albumin. Studies have reported cooling rates of 0.8–1.2 °C per liter of fluid infused. Some experts caution that in patients unable to handle the fluid challenge, infusion of large volumes of intravenous fluids in the presence of pulmonary edema or chronic renal failure requiring dialysis may increase adverse events. However , several studies have shown that this process has not been associated with worsening pulmonary edema.[7]

Endovascular cooling is another invasive method used. This is achieved by inserting central venous catheters, with an external heat exchange-control device that circulates cold intravenous fluid. The user sets a target temperature, and the device appropriately adjusts the fluid /water temperature. These devices can reduce temperatures at rates close to 4 °C per hour. In a study by Holzer and colleagues, looking at post cardiac arrest patients, endovascular cooling was found to improve survival and short-term neurologic recovery without higher rates of adverse events, compared with standard treatment. Furthermore, the constant rate of rewarming prevents elevations in ICP. As with any central venous catheters, insertion risks and infectious, bleeding complications may occur. The placement of catheters with associated risks and, and costs of placing them need to be factored. [8]

Other methods for invasive cooling that are reported include cold carotid infusions, single carotid artery perfusion with extracorporeal cooled blood, ice water nasal lavage, cold peritoneal and lung lavage and nasogastric and rectal lavage

Monitoring temperature

Temperature must be monitored continuously and accurately during TH. Peripheral and core temperatures may not always correlate, so two methods of monitoring are usually recommended. A true core temperature is obtained from a pulmonary artery catheter. Tympanic temperatures poorly reflect core temperature. Bladder temperatures are easily obtained by temperature-sensing indwelling urinary catheters. Studies have shown that bladder temperatures are continuous, safe and reliable, correlate well with fluctuations in core temperature. Clinicians must be mindful that in oliguric patients, bladder temperature may poorly reflect core temperature, and other monitoring sites should be used. There is also a delay in reflecting core temperature changes, before bladder temperature also changes, especially the more rapid the cooling rate. This is more of a problem with rectal temperatures. Education of the caregivers about this helps prevent undercooling or overcooling the patient, thereby helps to mitigate the risk of adverse events. Stone, Gilbert J et al

8. Phases of temperature modulation in therapeutic hypothermia[2]

Temperature modulation during therapeutic hypothermia may be broken down into four phases: induction, maintenance, rewarming/ decooling, and normothermia. Each of these phases requires monitoring for and prevention of associated complications.(please refer to Figure 2 for an example of a therapeutic hypothermia protocol used in our institution for cardiac arrest patients).

DO NOT SUBSTITUTE **STAT MEDICATION ORDER**

PLEASE INCLUDE: PHYSICIAN NAME, NUMBER AND SIGNATURE

✓	DATE	TIME	**Hypothermia Induction Order Set** **Page 1 of 2**
			Indication: **Patient weight: kg**
			☒ NS - 30 mL/kg IV of cold injection at a target of 4° Celsius **STAT**
			☒ Initiate cooling with the appropriate hypothermia induction device according to Hypothermia Induction policy
			☒ Apply pads appropriate for patient weight(Apply Universal pads if Wt>= 220 LBs)
			☒ The Arctic Sun is preset to 33° Celsius
			☒ Start Magnesium Sulphate 4 Gm IV (in 100 ml injectable water) over 4 hours
			Nursing
			☒ Continuous cardiac monitoring with pulse oximetry - monitor vital signs and record every hour
			☒ Consider target MAP ≥ 90mmHg or mmHg to maintain Cerebral Perfusion Pressure (CPP) of ____
			☒ Goal CVP 8-12mmHg or mmHg ☒ Maintain ScvO2 > 70%.(if available)
			☒ Obtain bedside glucose every 1 hour. (See Adult Insulin order sheet if already initiated.)Maintain Accuchecks q 1 Hr until T=37° Celsius.(maintain BS=110-150)
			☒ ABG every hour(s)
			☒ CBC, BMP, Magnesium, Phosphorus, PT/PTT every 6 hours
			☒ Consider blood cultures 12 hours after initiation of cooling
			☒ Initiate VAP Bundle Order Set, if not already begun
			☒ No sedation vacation if patient is receiving neuromuscular blockade infusion or in cooling phase
			☒ Consider Empiric Antimicrobial therapy if sepsis or immunosuppression is suspected(ex: neutropenia..)
			Activity
			☒ Bedrest
			☒ Skin assessment should be performed and documented every 4 hours
			☒ Turn patient every two hours unless contraindicated and ordered
			☒ PT/OT consults and treatment if not already ordered
			Sedation/Analgesia/Control of Shivering
			☒ Propofol (DIPRIVAN) drip initiated at 10mcg/kg/min. - titrate by 5mcg/kg/min for Ramsay of _____ to a max. of 80mcg/kg/min
			☒ Midazolam (VERSED) drip initiated at mg/hour - titrate by 1mg/hr for Ramsay of _____
			☒ Fentanyl infusion at mcg/hour - titrate to mcg/hour
			☒ Morphine infusion at mg/hour - titrate to mg/hour
			If still shivering (physical assessment or trend indicator) give:
			☒Buspar 10mg/ 20mg PT TID(circle dose)
✓	DATE	TIME	**Hypothermia Induction Order Set** **Page 2 of 2**
			If still shivering, consider neuromuscular blockade:
			☒ Start with PRN dosing as ordered for shivering ☒ If patient still shivering, consider continuous infusion. ☒ Place "Neuromuscular Blockade in use" sign at head of bed.
			☒ Atracurium ☒ Intermittent dosing_____(dose/route/interval) ☒ Loading dose (0.5 mg/kg) = _____ mg IV x one dose now ☒ Infusion – begin at 4 mcg/kg/min IV to a max. of 12 mcg/kg/min
			☒ Vecuronium ☒ Intermittent dosing_____(dose/route/interval) ☒ Loading dose (0.1 mg/kg) = _____ mg IV x one dose now ☒ Infusion – begin at 1 mcg/kg/min IV to a max. of 2 mcg/kg/min

			Paralytic Titration
			☒ Monitor patient for ventilator compliance and shivering
			Continuous EEG(please choose one of the following):
			☒ Start now and D/C when patient is rewarmed to 37° Celsius - page EEG tech
			☒ Start in am and D/C when patient is rewarmed to 37° Celsius - page EEG tech
			Respiratory: ☒ Maintain O2 Sats=95% ☒ Maintain pCO2=40mmHg
			Medications
			☒ Artificial tears ophthalmic ointment (LACRILUBE or equivalent) – one ribbon in each eye every 12 hours.
			☒ Maintenance IV Fluids: at ml/hr.-**Titrate to maintain equal to UO.**
			Rewarming - To start 24 hours after temperature of 33° Celsius is attained
			☒ Continuous EKG for dysrhythmias
			☒ Stop all potassium infusions
			☒ Rewarm at 0.25° Celsius to 0.33° Celsius per hour - ☒ Keep patient in goal temperature range of 36° Celsius to 37° Celsius for next 48 hours
			☒ May discontinue paralytic(if used) once goal temperature is obtained
			☒ Begin daily sedation vacation once paralytic has been discontinued
			Once rewarmed, please maintain EUTHERMIA(~37° Celsius).

Figure 2. Mercy Hospital St Louis In-HOSPITAL Therapeutic Hypothermia Protocol

In the setting of cardiac arrest, based on animal and human data, initiation of cooling should be done as soon as possible after return of spontaneous circulation (ROSC). The induction phase can be initiated in the prehospital or in hospital setting. There are ongoing studies involving prehospital cooling. One should be mindful that if prehospital cooling is not followed by in hospital cooing, outcomes could be considerably worse, especially if patients are rewarmed quickly

The maintenance phase usually occurs in an intensive care unit and hemodynamic parameters, electrolytes should be watched closely. For example, hypokalemia is a common occurrence, and can precipitate further arrests, so replacement is essential. Secondary insults such as hypercarbia, hypoxemia, glycemic shifts should be avoided. It is important to recognize that drug metabolism is altered in hypothermia, meticulous attention to medication dosing is needed and aggressive treatment of shivering, with sedation and neuromuscular blockade is often needed

Fever in the first 72 hrs after ROSC is associated with poor outcome. Although unproven, an increasing body of evidence supports the cautious prevention and treatment of fever in the setting of critical neurological illness, and many clinicians attempt to maintain a core temperature of 36°C to 37.5°C until at least 72 hrs after ROSC

Rewarming /Decooling is associated with electrolyte shifts, vasodilation, and the "post resuscitation" syndrome, many deaths occur in this phase due to hemodynamic instability and other complications. Rewarming / Decooling should not be treated casually.

The "post resuscitation" syndrome which is characterized by elevated inflammatory cytokine levels, vasodilatory shock, intracranial hypertension, and thereby decreased cerebral perfusion pressure often compounds the myocardial dysfunction related to acute myocardial infarction, defibrillation injury or cardiomyopathy. The duration of cooling and

rewarming may vary depending on the indication, for instance, in post cardiac arrest, rewarming is usually begun 24 hours after the initiation of cooling, in intracranial hypertension, this is typically done later, after 48 hours. Patients should be rewarmed slowly so that it avoids rapid hemodynamic alterations, while preserving the neuroprotectant effects of hypothermia. The usual rate of rewarming is a goal rate of 0.2°C to 0.33°C per hour, in ICP elevations; the rate is sometimes slower, at 0.05 to 0.1 degrees C per hour. While the optimal rewarming rate remains unknown; the process usually takes about 8 hours. Careful hemodynamic monitoring is needed, patients may require additional hemodynamic support with fluid boluses, inotropes, and vasopressors to maintain adequate cerebral perfusion pressures, and mean arterial pressures during decooling, Sometimes, if significant hemodynamic instability or signs of elevated ICP occur, it may become necessary to slow or stop the temperature decooling process. Rewarming is typically achieved through active or passive means through the use of heated-air blankets, or the removal of cooling methods allowing the patient's body temperature to increase over time. Paralysis and sedation should be maintained until the patient's temperature reaches 35 °C. Patients must be monitored closely, and all electrolyte infusions must be discontinued to avoid dangerous electrolyte shifts

Physiological effects of hypothermia

Hypothermia affects many intracellular processes. While some of these are directly related to its protective effects, hypothermia therapy is also known to be associated with a number of potential adverse events. These adverse effects generally do not pose a problem until core body temperatures are< 35°C.

Many physiological, laboratory changes occur with induction of hypothermia. Education of caregivers is key, so there is not only timely recognition of adverse events, but unnecessary interventions are minimized in case of routine changes that are seen. It is possible that in many studies especially in traumatic brain injury and hypothermia, the results may have been negatively impacted by adverse events related to hypothermia and /or failure to recognize and treat the physiological effects.

Example, mild hypothermia is associated leucopenia, thrombocytopenia. Hyperglycemia is common due to decreased insulin sensitivity and increased insulin resistance. Decreases in cardiac output may be seen, also an increase in lactate levels and levels of serum transaminases, amylase. A common occurrence is increased urinary output (cold diuresis). These effects of hypothermia depend on the degree of hypothermia, age, comorbidities. A significant risk for severe arrhythmias occurs at temperatures below 28–30°C. These low temperatures are not typically used in current practice; the target temperature is usually mild –moderate hypothermia, although they are still practiced in major vascular and other neurosurgical procedures.[4]

Hypothermia leads to a decrease in the metabolic rate. Metabolism is reduced by between 5% and 7% per Celsius degree reduction in body temperature. Cerebral blood flow is decreased, but, this is offset by the decrease in metabolism. It decreases cerebral edema,

decreases the excessive influx of Ca2+ into the cell, decreases the accumulation of glutamate, an excitatory neurotransmitter. It thereby is thought to decrease apoptosis.

Hypothermia inhibits neutrophil and macrophage function, suppresses inflammatory reactions and inhibits the release of pro-inflammatory cytokines. While this may help contribute to hypothermia's neuroprotective effects, this may occur at the expense of an increased the risk of infections.

Shivering	Increased muscle activity, increased oxygen consumption, increased rate of metabolism
Drug metabolism	Altered clearance of various medications
Cardiovascular EKG **Manifestations**	prolonged P-R and Q-T intervals and widening of the QRS
Arrhythmias	tachycardia, and then bradycardia, atrial fibrillation
Infection	inhibits the release of various pro-inflammatory cytokines, inhibit neutrophil and macrophage function
Coagulopathy	increased bleeding time, increased APTT/CT, thrombocytopenia
Electrolyte disorders	Hypokalemia, Hypomagnesemia during cooling, hyperkalemia during rewarming
Insulin resistance	hyperglycemia

Figure 3. Adverse events of Hypothermia, prevention and management strategies:

Shivering

Shivering is the body's physiological response to hypothermia. Both in the induction and maintenance of hypothermia, this can pose challenges, and shivering is sometimes more an issue when normothermia is the goal temperature. Shivering generates heat and increases the oxygen consumption and metabolic demands of tissues.

Shivering is especially important in the extremes of age. It has been associated with a higher risk of adverse cardiac events and poor outcomes in the perioperative setting. The threshold for shivering is slightly higher in females. The process is regulated via the preoptic nucleus of the anterior hypothalamus. Through positive and negative feedback loops this helps minimize fluctuations, maintains core body temperature within 0.1°C– 0.2°C. [4]

Typically a shivering response is seen when core temperature decreases below 35.5°C, the "shivering threshold." However, in febrile patients, and in brain injured patients, this regulation is altered and both the temperature "set point" and the shivering threshold increase. The hypothalamus then makes attempts to maintain the higher temperatures as it

does to maintain normal temperature or normothermia. This causes an increase in oxygen consumption, metabolic rate, and increases carbon dioxide production. At temperatures lower than 33-34°C, the shivering response decreases, therefore sedation and paralytics can be decreased at this point, if the clinical situation allows it.

The Bedside Shivering Assessment Scale (BSAS) is a simple scale that was developed as a means to detect and quantify shivering and guide therapeutic interventions. The scale has 4 levels. [9]

Score	Description or observation	Severity
0	Absence of shivering on palpation of neck or pectoralis muscles	None
1	Localized to the neck and/or thorax	Mild
2	Involvement of the upper extremities with or without neck	Moderate
3	Generalized, whole-body involvement	Severe

Table 1. Bedside Shivering assessment Scale

A non pharmacologic measure that has been shown to decrease shivering in some studies, mainly in healthy volunteers is called Surface counter warming. Studies have shown decreased shivering and improved metabolic profiles, and that is safe and effective, easy to use. Theoretically, an increase of 4°C in skin temperature could compensate for a 1°C decrease in core temperature, reducing the shivering response.[9]

Numerous pharmacologic strategies have been used to control shivering. In the operating room, volatile anesthetics, including halothane, isoflurane and enflurane, are used to control post anesthetic shivering. In the intensive care unit, other agents are of more practical use. These agents are thought to be effective by various mechanisms. The agents act though serotonin manipulation, or are N-methyl-D-aspartate Antagonists, α_2-agonists, Opioids, and others. Most studies involving these agents have been conducted in healthy volunteers.

Buspirone is a serotonin (5-HT) 1A partial agonist that has been shown to be a good anti shivering agent. At a 60-mg dose, buspirone – a 5-HT1a partial agonist – reduced the shivering threshold by 0.7°C. A study in volunteers found that a 30-mg dose combined with low-dose meperidine produced a similar reduction in shivering threshold compared to a large dose of meperidine alone (2.3°C).Buspirone provides a good synergistic therapy when combined with other antishivering interventions. The main disadvantage of buspirone is that it needs to be administered enterally, no IV formulation is available. Bioavailability in the critically ill may not be reliable.[10]

Meperidine is an opioid analgesic. Meperidine is probably the single most useful antishivering drug, but has significant adverse events. Meperidine acts on both mu and kappa receptors, is considered the most effective antishivering agent among the opioids. The mechanism behind meperidine's antishivering action is not clearly known. It is thought that activation of [kappa]-opioid receptors, anticholinergic action, and N-methyl-d-aspartate antagonism all play a role. In studies, plasma concentrations near 1.3 μg/mL have been required to induce moderate hypothermia with meperidine alone, which could increase the

risk of side effects. Meperidine is effective for postoperative shivering and, it inhibits shivering twice as much as vasoconstriction.

Meperidine has major side effects; the more significant of them is lowering of seizure threshold. Other reported adverse events include arrhythmias, hyperreflexia, and myoclonus. The metabolite Normeperidine accumulates in patients with renal failure and could potentiate these adverse events.

Fentanyl, morphine are pure mu opioid receptor agonists, and have had mixed results in studies. High doses may be needed to achieve this effect, and this may potentiate side effects[11].

The alpha$_2$-receptor agonists are another important class of drugs used as pharmacologic measures to control shivering. Bradycardia and hypotension are the main adverse events with this class of drugs. Important to remember, they may also exacerbate the bradycardia induced by hypothermia.

Clonidine decreases the vasoconstriction and shivering thresholds. Prophylactic use of clonidine lowered the threshold of vasoconstriction in healthy volunteers. [12, 13] In a trial comparing clonidine and meperidine, the average onset of action for meperidine and clonidine were 2.7 and 3.1 minutes, respectively. At least from these data, clonidine appears to be as effective as meperidine for postanesthetic shivering[14]

Dexmedetomidine is another agent that has been shown to decrease postanesthetic shivering when compared to both placebo and Meperidine. In studies with dexmedetomidine in healthy volunteers, it showed a decrease in the vasoconstriction and shivering thresholds by similar amounts.[15]

A small study looked at healthy volunteers and found that Meperidine and Dexmedetomidine were synergistic as well. [16, 17]

Magnesium is another anti shivering agent. It is thought to act as an antagonist of the NMDA receptors. In addition, hypothermia causes hypomagnesaemia commonly, and magnesium replacement is often required. Results on magnesium as a neuroprotectant have been variable. In a study of healthy volunteers, despite reducing the shivering threshold, the authors concluded that it was not clinically significant in counteracting the shivering effect of therapeutic hypothermia. [18] In another study, magnesium shortened the time to achieve target temperature and improved patient comfort.

In this small study, 22 volunteers were randomly assigned to one of four therapies: meperidine monotherapy; meperidine plus buspirone; meperidine plus ondansetron; or meperidine, ondansetron, and magnesium sulfate. In this study, Magnesium was shown to decrease time to target temperature and increase patient comfort. Although the presence of shivering was recorded in this investigation, these data were not reported. [19]

Dantrolene is another agent that has been used for malignant hyperthermia. It acts on the skeletal muscle and interferes with the release of calcium from the sarcoplasmic reticulum, and inhibits the excitation-contraction coupling of skeletal muscles. It is a good adjunctive

antishivering agent. In a study with healthy volunteers, dantrolene decreased the gain of shivering. Dantrolene had no effect on the vasoconstriction threshold. Hepatitis is a complication of dantrolene, especially in people older than 35 years. The reaction can be dose dependent or idiosyncratic.[20]

Propofol has been widely studied in Shivering control. It has been compared to Thiopental and isoflurane. Patients on propofol experienced less shivering compared to thiopental alone or thiopental plus isoflurane. Like other drugs, during hypothermia, the plasma concentration of propofol is increased by 30% due to reduced clearance. Clinicians should also be aware of propofol infusion syndrome.[21] [22] Propofol infusion syndrome is a rare complication of propofol infusion. Risk factors include administration of high doses (greater than 3-5 mg/kg per) and prolonged use, more than 48 hours, patients on catecholamines for vasopressor support, steroids. Additional proposed risk factors include a young age, critical illness, high fat and low carbohydrate intake, inborn errors of mitochondrial fatty acid oxidation. Patients present with cardiac dysrhythmias, metabolic acidosis, rhabdomyolysis, and renal failure. It can be associated with a high mortality.

There is limited data on the use of other agents such as Ketamine, methylphenidate and doxapram as anti shivering agents in hypothermia.

Drug metabolism

By redistributing blood flow away from muscle, skin, and fat, hypothermia alters drug pharmacokinetics. Drugs with a large volume of distribution, in the setting of hypothermia distribute to reduced volume and thereby produce higher plasma concentrations. Due to reduced blood flow, these drugs may initially be sequestered in tissue, but subsequently with rewarming and vasodilation, these drugs now redistribute from tissues, leading to high plasma concentrations, thereby increasing the risk of toxicity.[23]

Cardiovascular manifestations

Cardiac output decreases, but this is offset by the decreased metabolic rate

Common electrocardiographic findings during hypothermia include prolonged P-R and Q-T intervals and widening of the QRS complex as well as altered T waves and appearance of the J wave. (Osborne). These usually do not require interventions.

Arrhythmias: Initially, hypothermia causes tachycardia, and then bradycardia ensues. The arrhythmias depend on the severity of hypothermia, more severe commonly occur at temperatures of < 28C. The bradycardia may be severe enough to warrant discontinuing hypothermia. This is compounded by the fact that the anti arrhythmics become less effective, and so does electrical defibrillation. Attempts at electrical defibrillation can initiate malignant arrhythmias.

In the setting of a cardiac arrest, the myocardium in a deeply hypothermic patient is easily susceptible to manipulations such as CPR, defibrillation, and can predispose to arrhythmias.

While mild hypothermia can be protective by stabilizing membranes, severe hypothermia increases risk of malignant arrhythmias.

Limited data exist on the efficacy of various antiarrhythmics. Bretylium, the most commonly studied agent, has been recommended as the drug of choice during moderate-to-severe hypothermia

Observational data from humans and experimental animal models have looked at Bretylium. Bretylium is a parenteral Class III antiarrhythmic agent. However, Bretylium is no longer available in the US secondary to lack of availability of raw materials needed to produce the drug, as well as declining usage in clinical practice. Amiodarone has been studied in an animal model. Stoner et al looked at thirty anesthetized dogs and induced hypothermic VF. They compared defibrillation rates after drug therapy with amiodarone, bretylium, and placebo. In this study, neither amiodarone nor bretylium was significantly better than placebo in improving the resuscitation rate.[24, 25]The benefits of amiodarone during hypothermia have not been clearly established in humans. In the Bernard study looking at hypothermia after cardiac arrest, Lidocaine was administered for 24 hrs. Clinically significant cardiac arrhythmias occurred with less frequency in the Australian study compared to the European study, where no lidocaine was employed. [6]

Coronary blood flow has been shown to decrease during mild hypothermia in patients with coronary artery disease. Evidence from animal studies has shown a 10% reduction in myocardial infarct size for every 1°C decrease in body temperature. [26]

Dixon et al looked at a randomized study of 42 patients with acute myocardial infarction and where cooling was maintained for 3 hours after reperfusion (core temperature target 33 degrees C.)There were no significant adverse hemodynamic events with cooling; however, the median infarct size was not significantly smaller in those that were cooled compared with the control group[27]

Other clinical studies of therapeutic hypothermia in patients with acute myocardial infarction who are undergoing primary PCI have not shown any beneficial effects.

Despite these data, hypothermia can potentially cause hypotension and myocardial dysfunction. It induces a cold diuresis and induces hypovolemia. This is through increased venous return, stimulation of atrial natriuretic peptide, decreased anti diuretic hormone levels, and renal tubular dysfunction.

Patients with severe Traumatic brain injury may also receive mannitol for hyperosmolar therapy for raised intracranial pressures or may have diabetes insipidus, which can further contribute to hypovolemia.[4]

Infection

Infectious complications occur frequently in ICU patients, especially after cardiac arrest. The increasing use of therapeutic hypothermia has raised awareness about increased infectious complications. In a retrospective review of a single institution cohort, Mongardon et al

found that pneumonia as the most common source, and Staphylococcus aureus was the main causative agent. Duration of hypothermia was associated with increased infection rates. ICU survival and neurologic outcome were not affected. [28]A numbers of studies, especially in patients with stroke or TBI, have reported higher risks of pneumonia when therapeutic hypothermia is used over longer periods of time (48–72 h) However, other studies using hypothermia for prolonged periods in patients with TBI reported no increase in infection rates.

Evidence from clinical and in vitro studies shows that hypothermia can impair immune function. Hypothermia inhibits the release of various pro-inflammatory cytokines, inhibit neutrophil and macrophage function. Kimura and colleagues found that the peak release of interleukin-6, interleukin-1, and other proinflammatory cytokines was significantly delayed at 33 °C compared with 37 °C [29, 30] Hypothermia reduces gastrointestinal motility, and cardiac dysfunction in post arrest patients, therefore, it may increase risk of mucosal ischemia and breakdown. This may cause bacterial translocation. The insulin resistance and hyperglycemia associated with hypothermia may further predispose the patient to infection. The normal host responses to infection like leukocytosis may not be noted in hypothermic patients, so careful surveillance is needed. The threshold to initiate antibiotic treatment should be low. Fever in these patients should be treated aggressively to prevent further neurologic injury.

Many institutions perform blood cultures and sputum cultures at the time of initiation of hypothermia, and periodic surveillance cultures to detect early bacteremia. In patients developing infections after hypothermia treatment, fever should be treated aggressively, to mitigate new or additional neurological injuries

Seizures

In a retrospective observational study involving neonates, moderate cooling decreased seizures recorded by EEG.[31] Seizures after cardiac arrest and TBI are common; the detection of seizures is an important aspect of a neurointensivist in the care of therapeutic hypothermia patients. Many of these patients are under neuromuscular blockade, and convulsive movements are absent. The incidence of seizures after cardiac arrest is around 24%, with some studies showing a higher incidence than others. Continuous EEG monitoring should be used when available over intermittent EEG, because seizures could be no convulsive as well as convulsive in these patients. The disadvantage of continuous EEG is that is not always available, is expensive, labor intensive, and subject to misinterpretation. No clear guidelines exist to guide therapy of EEG findings like PLEDS.

Intravenous benzodiazepines are used the initial medical treatment of status epilepticus. If the patient fails first line therapy and is considered to be in refractory status epilepticus, there is no firm data to guide subsequent management. The VA cooperative study showed that early control with a first line agent is important, because, if the first line agent fails, the success of subsequent second and third line agents is marginal. In the VA cooperative trial, the treatment success rate with the first drug was 55% in the overt status group and 15% in the subtle status group.[32, 33]

Many experts recommend continuous intravenous antiepileptic drugs at this stage. Midazolam is the safest anesthetic agent in treating SE. Doses as high as 3 to 5 mg/kg/h may be necessary to maintain seizure suppression in the most refractory cases. Tachyphylaxis is often encountered when prolonged infusions are used. The other agents used to treat SE are propofol, and barbiturates (Thiopental or pentobarbital). Barbiturates produce hypotension, and myocardial depression, this may pose further challenges in the post cardiac arrest setting. Other side effects include ileus, hepatotoxicity, increased susceptibility to infections and very prolonged sedation. Propofol can be associated with propofol infusion syndrome as discussed earlier. Valproic acid, levetiracetam, are emerging as alternative agents. Fosphenytoin is an antiepileptic that is often added in these patients. Fosphenytoin is a prodrug of phenytoin and its preparation does not include propylene glycol. It can be administered faster than IV phenytoin, and has less adverse cardiac events with IV infusion compared to phenytoin. It is much less likely to produce local tissue reactions, and it can be infused faster than phenytoin.[34] As with status epilepticus from other causes, it is not clear whether burst suppression on EEG is superior to seizure suppression. No data on seizure prophylaxis after hypoxic ischemic encephalopathy are available

9. Coagulation

Bleeding diatheses occur in the setting of mild therapeutic hypothermia. For every 1 °C decrease in temperature, coagulation-factor function is decreased by 10%. Watts et al showed that in trauma patients, enzyme activity alteration, platelet dysfunction and changes in fibrin pathways occur. Clinically significant bleeding is rarely a significant problem, even in traumatic brain injury patients. Schefold et al. in a prospective observational study of 31 patients with AMI and mild induced hypothermia and primary PCI found no excessive bleeding risk with cooling/PCI.[35,36]

Values of standard coagulation tests such as prothrombin time and partial thromboplastin times are usually normal, because these tests are usually performed at 37°C in the lab. Tests will be prolonged only if they are performed at the patient's actual core temperature

10. Pressure ulcers

Skin integrity should be assessed carefully and frequently. The surface cooling, vasoconstrictive response to cooling can increase skin breakdown in hypothermic patients.[6]

11. Gastrointestinal dysfunction

Hypothermia patients have GI dysmotility, ileus. Caution needs to be exercised with promotility agents like Erythromycin, metoclopramide, neostigmine, as they can induce arrhythmias. Increased serum amylase levels are common, but patients rarely have significant pancreatitis. Enteral nutrition can help decrease risk of bacterial translocation. Gaussorgues P, et al. Bacteremia following cardiac arrest and cardiopulmonary resuscitation. *Intensive Care Med* 1988; 14(5):575-7.

12. Hypovolemia, fluid balance and electrolytes, glycemia

A common problem is severe electrolyte disorders hypokalemia, hypomagnesemia, hypophosphatemia during induction of cooling. These may cause further arrhythmias in post-arrest patients. Hypothermia decreases insulin sensitivity and insulin secretion, which often leads to hyperglycemia. Tight control of glucose levels may decrease morbidity and mortality in ICU patients, but the exact levels at which glycemia needs to be maintained is controversial. During rewarming, glucose levels tend to drop, and therefore, insulin may need to be decreased or discontinued. Likewise, hyperkalemia and hypermagnesemia are common during rewarming, and cardiac arrests have occurred when the clinician s unaware of this phenomenon. Hypothermia also induces a metabolic acidosis by increased synthesis of glycerol, free fatty acids, ketones and lactate. These changes are normal metabolic consequences of hypothermia and should not be attributed to complications such as bowel ischemia.[4]

Hypotension can occur through hypovolemia, the cold diuresis, that occurs in hypothermia, and the use of agents like mannitol in TBI or diuretics in the setting of cardiomyopathies can further exacerbate this. If this is unrecognized, the problem is worse in the rewarming phase when vasodilatation often occurs, and profound shock ensues. Cueni-Villoz N, et al.

13. Summary

In conclusion, hypothermia is becoming increasingly used across many intensive care units, and the applications could expand well beyond the current indications. It is important to use safe, effective cooling methods, recognize, prevent and treat various adverse events that could occur, so we can improve the survival of these patients.

Author details

Rekha Lakshmanan, Farid Sadaka and Ashok Palagiri
Mercy Hospital St. Louis, Missouri, USA

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