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Hypothermia in Return of Spontaneous Circulation (Rosc): Acute Management Option

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Hypothermic therapy dates back 5000 years [1]. The narrative of Anne Green, hung on a cold December day; in1650, showing signs of recovery within an hour of an external cardiac massage and natural hypothermia incited interest in the practice's therapeutic potential [2]. The neuroprotective potential of mild hypothermia was comprehensively investigated in post-cardiac arrest, cerebral ischemia and infectious brain diseases.

RECOMMENDATION BY AMERICAN HEART ASSOCIATION (AHA)

The AHA 2015 practice guidelines, define a temperature range of 32°C to 36°C for hypothermic therapy (Targeted Temperature Management: TTM) [3,4] (Class I, LOE B-R). AHA recommends therapeutic hypothermia in post-cardiac arrest,comatose adult patients, after return of spontaneous circulation. The comatose were generally defined as patients lacking meaningful verbal responses. AHA reports no contraindication to such temperature ranges in post-cardiac arrest,with return of spontaneous circulation patients.

They identify patients with higher level of benefits from the upper or lower values in the temperature range (Class I, LOE B-R for Ventricular Fibrillation (VF) and pulse less Ventricular Tachycardia in out-of-hospital cardiac arrest; for non-VF/pVT (i.e., "nonshockable") and in-hospital cardiac arrest. The time period recommended is at least 24 hours after achieving target temperature [3,6]. (Class IIa, LOE C-EO).The recommendation advises against the use of rapid

cold intravenous infusions for routine pre-hospital induction of hypothermia after return of spontaneous circulation [7,8] (Class III: No Benefit, LOE A) while active steps for preventing fever in such patients is advocated [9,10]. (Class IIb, LOE C-LD).

THERAPEUTIC HYPOTHERMIA (TARGETED TEMPERATURE TREATMENT: TTM)

Induction of hypothermia is initiated after the return of spontaneous circulation, as soon possible. It has remain effective in cases of four to six hours, delay in its induction since return of spontaneous circulation with cardiopulmonary resuscitation **(CPR)**. The patient's body is actively cooled to a temperature range of 32˚C-36˚C, under institutionalized induced hypothermia protocol for a period of twenty four hours (Figure 2) [3,4].

Most animal studies favor early induction of hypothermia after reperfusion, usually within three to four hours of the initiation of the process, while others show good results despite delay several hours. A prospective European trial has shown beneficial results with the return of spontaneous circulation to attainment time of desired temperature (32˚-34˚C) in the interquartile range of 4 to 16 hours [5].

PROTOCOL FOR THERAPEUTIC HYPOTHERMIA

Therapeutic hypothermia consists of four stages: induction, maintenance, re-warming, and maintaining normothermia (Figure 1) [11].

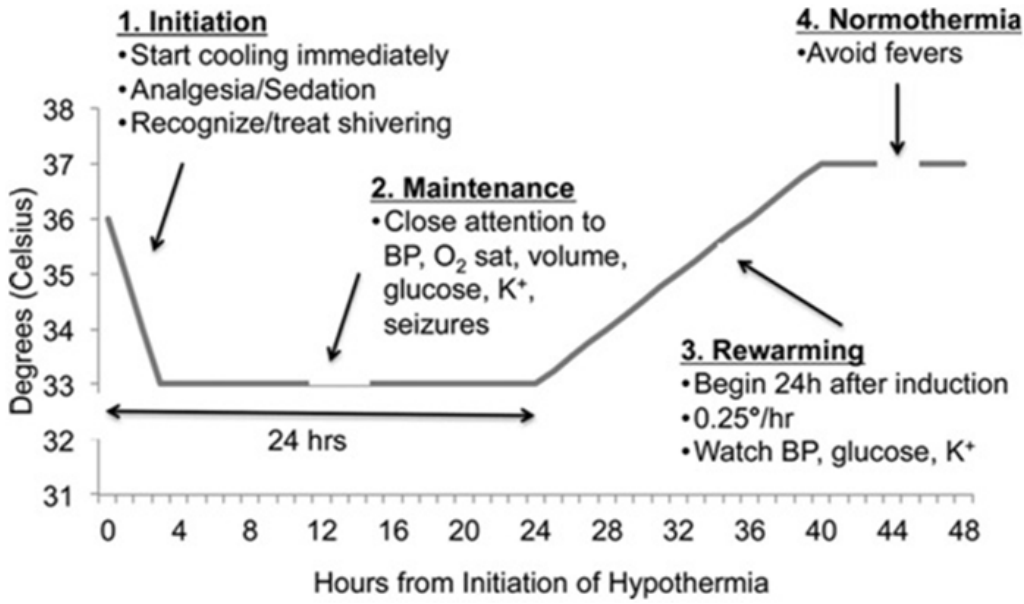

Figure 1: TTM stage.

BP: Blood Pressure; K+: Serum Potassium Concentrations; O2 sat: Oxygen Saturation; and SBP: Systolic Blood Pressure.

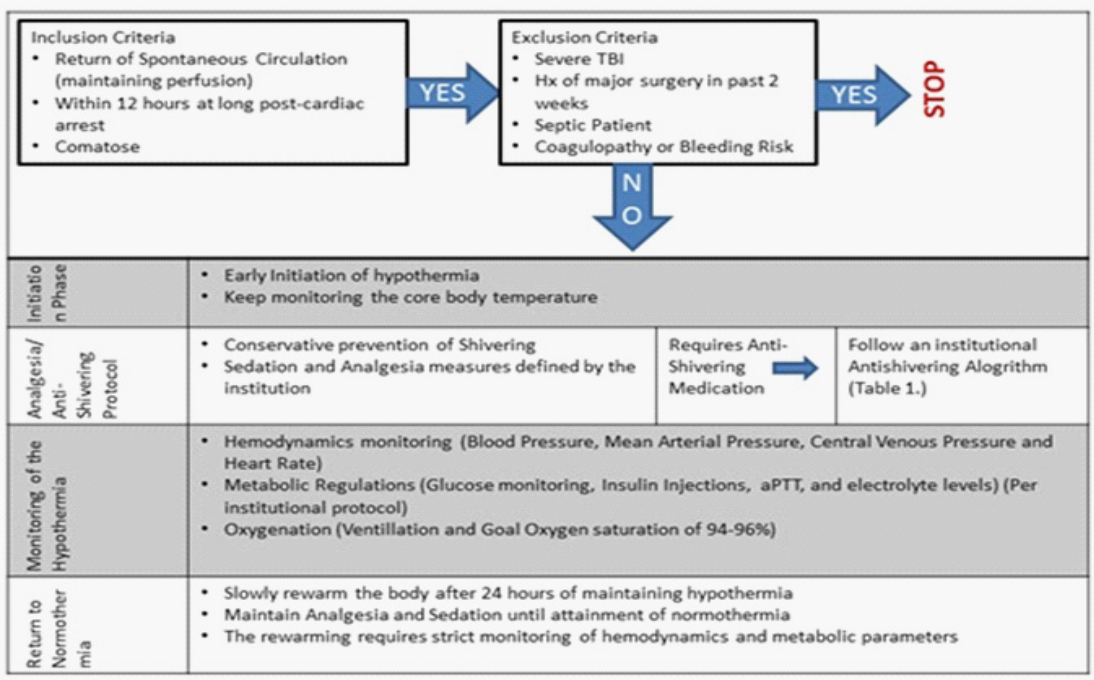

Figure 2: Exemplifying a hospital-based protocol for Therapeutic Hypothermia **(TH)** with summary of key steps.

The best possible duration of hypothermia is controversial, with animal models restricting the effective duration to less than twenty four hours in cases of rapid initiation after return of spontaneous circulation [9,10]. In other such models, the longer duration of cardiac arrest and delay in therapy initiation can prolong the duration of hypothermia to forty eight hours in order to achieve better neurological outcomes.

Various cooling techniques are utilized however, none combines use with efficacy. External cooling techniques include application of icepacks to neck, axillae and groin. Cooling blankets, fans, wet towels, and cooling helmets take longer at cooling core temperature [12] (Figure 2). The Arctic Sun utilizes cooling-pads applied external to the body). In a study by Bernard et al. intravenous infusion of crystalloid at 4˚C was utilized in achieving the targeted core temperature without the risk of pulmonary edema [13]. Cooling with a peritoneal and pleural lavage [14] and extracorporeal methods [15] are not generally used for their invasiveness.

Recently, two intravenous devices named *Thermoguard XP temperature management system (Zoll)* and *Inner CoolRTx with Accutrol catheter* have become popular (Philips) [16]. The Thermoguad XP uses percutaneous central venous catheters placed in subclavian, internal jugular or femoral vein. The catheter balloon circulates cool or warm saline in a closed loop to attain temperature control. The InnerCoolRTx with its Accutrol integrated temperature sensor controls the temperature precisely without lag in core temperature measurement. The

intravenous devices use a programmed feedback control during maintenance and rewarming phases of the management, with fewer incidences of shivering, overcooling or failure compared to other systems [17]. Nevertheless there is supplementary risk of infection, thrombosis and other complications related to intravenous lines.

The body rewarming is begun Twenty four hours after the hypothermia initiation [3] (Figure 2). In order to prevent rebound hyperthermia, the normothermia is restored with a slow pace [18].

Neuro-protective mechanisms and neurologic outcome with hypothermia after return of spontaneous circulation ROSC

The cardiac arrest leads to decreased neuronal perfusion. The anoxia compromises neuronal function in seconds, specifically the most vulnerable brain areas. Within minutes of cardiac arrest, cellular glucose and ATP are depleted, neurons start losing their cellular integrity. Mitochondrial damage and loss of calcium hemostasis follow [19]. In addition to the damage caused by the higher intracellular calcium levels, the persistent release of glutamate triggers acute cellular necrosis and apoptosis.

The anoxic injury can be alleviated by reperfusion with cardiac resuscitation, while the inflammatory cellular damage from anoxia and reperfusion continues for the coming hours and days.

The reoxygenation of the oxygen deprived brain parenchyma leads to a higher level of reactive oxygen species **(ROS)** formation. Injury from ROS complements the inflammatory process and exacerbates the endothelial and vasomotor dysfunction compromising the blood brain barrier, enhancing the edema and neuronal damage [20]. The ischemic event interferes with the equilibrium of endothelin, thromboxane A_2 **(TxA_2)**, prostaglandin I_2 and other cytokines, increasing the risk of vasospasm, decreased perfusion and thrombogenesis in an anoxic brain parenchyma [21,22].

Hypothermic management in such patients has shown a better equilibrium of these cytokines [23]. The ischemic-reperfusion injury interferes with the brain glucose utilization, whereas hypothermia has proven benefit in better cerebral utilization of glucose [24]. Hypothermia has shown improved lactate compared to higher levels in post-ischemic brain regulated at normothermic management [25].

Hypothermic management lowers the inflammatory torrent, and halts the apoptosis by lessening the release of pro-inflammatory cytokines, excitatory neurotransmitters, and diminishing the formation of reactive oxygen species **(ROS)** [26,27]. 1°C reduction in brain parenchymal temperature reduces the cerebral metabolic rate for oxygen **(CMRO2)** by six percent, thus hypothermia decreases the metabolic demand of oxygen [28,29]. The post-ischemic patients have a higher risk of epileptic activity, whereas the hypothermic management has shown decline in the convulsions, providing satisfactory neuro-protection [30].

Hypothermia escalates the expression of the stress response genes and enhances the induction of cold shock proteins enhancing the protective mechanisms for post-ischemia [31].

A prospective study was conducted in five European countries, including 136 patients who underwent TTM (32˚C to 34˚C) [3]. The hypothermic temperature was achieved within four hours of return of spontaneous circulation, and maintained for 24 hours. At a six months follow up 55 percent of the patients in TTM showed better neurological outcome compared to 39 percent in the non-hypothermia group (Relative Risk, RR 1.40, 95 percent CI 1.08 to 1.81). The mortality in the former group was noticed at 41 percent while 55 percent for the later (RR 0.74, 95 percent CI 0.58 to 0.95). Another prospective trial was undergone in Australia, where the hypothermia group was managed at 33˚C versus 37˚C in the control group [4]. The targeted temperature was retained for 12 hours and rewarming was commenced at 18 hours of hospital admission. 49 percent (21 of total 43) patients in the hypothermic group had better neurologic outcome at hospital discharge compare to 26 percent (9 of total 34) patients in the control group (RR 1.85, 95 percent CI 0.97 to 3.49). Mortality at discharge was 22 of 43 (51 percent) in the treatment group compared to 23 of 34 (68 percent) in the control group (RR 0.76, 95 percent CI 0.52 to 1.10).

PHYSIOLOGIC EFFECTS OF HYPOTHERMIA ON ORGAN SYSTEMS

Temperature is one of the three determinants, (other two: pH and substrate) of biochemical metabolic rate. Hypothermia thus decreases the metabolic rates in different organ system. Each stage in the therapeutic hypothermia [32] has its own physiologic effects on the organ systems.

a. Musculoskeletal system

Decreasing temperature during the induction part of hypothermia leads to temperature below 35.5˚C. The body counteracts this drop in temperature by trying to regain the normothermic temperature range and hence start shivering [33]. Shivering increases the metabolic rate and oxygen consumption, while the hypothermia protocol uses active steps to control and prevent shivering.

Table 1: The Columbia Anti-Shivering Protocol [34].

Step	Intervention	Dose
0 Baseline	Acetaminophen	650-1000 mg Q 4-6 h
	Buspirone	30 mg Q 8 h
	Magnesium sulfate	0.5-1 mg/h IV Goal (3-4 mg/dl)
	Skin counter warming	43C/MAX Temp
1 Mild sedation	Dexmedetomidine	0.2–1.5 mcg/kg/h
	Or Fentanyl	starting dose 25 mcg/h
	Opioid Meperidine	50-100 mg IM or IV
2 Moderate sedation	Dexmedetomidine and Opioid Doses as above	
3 Deep sedation	Propofol	50-75 mcg/kg/min
4 Neuromuscular blockade	Vecuronium	0.1 mg/kg IV

b. Cardiovascular system

The decreasing temperature leads to a lower heart rate, with reported heart rates of 40-45 beats per minute at 32˚C [32]. The lowering heart rate unburdens the compromised myocardium, decreasing the metabolic oxygen demand improving left ventricular filling with regard to the required effect, no active steps are taken to enhance the heart rate. As the temperature is retained higher than 30˚C, the risk of arrhythmia does not increase [13,33,35].

Hypothermia affects the myocardium by decreasing the spontaneous repolarization, leading to a prolonged duration of action potential. The ECG identifies this affect as Osborn (J) waves in addition to prolonged PR, QRS and QT intervals. J waves are usually seen at temperatures lower than 32˚C [32]. The findings of interval prolongation and J waves can be seen in normothermic patients with brain injuries and aneurysmal subarachnoid hemorrhage [36,37]. In addition Takotsubo cardiomyopathy, associated with various neurologic conditions can explain similar ECG changes [38]. During hypothermia one must be aware of the different ECG changes and the etiologic pathologies, to explain any myocardial derangements.

Despite the drop in heart rate, the mean arterial pressure increases due to the hypothermia induced peripheral vasoconstriction [32,39]. Cold-diuresis occurs, as a result of increased cardiac return leading to higher atrial natriuretic peptide and a lower anti-diuretic hormone [39]. This effect is pronounced in patient who receives mannitol and can benefit from fluid challenge.

c. Hematologic changes

The decreasing core body temperature induces a state of hypercoagulability [40]. In hypothermic patients activated partial thrombopastin time **(aPTT)** is closely monitored while subcutaneous heparin is given during the therapy. Some studies have reported prolongation of aPTT [41], and lower platelet count [42] while others report no change in either [41,43,44].

Hypothermia has not been reported with increased risk of bleeding, whereas patients with hereditary bleeding disorders or active bleeding may need careful monitoring of blood counts and coagulation factors assay specifically in temperatures lower than 35˚C [32].

d. Pulmonary System

In the earliest of literature, in an animal study hypothermia was found to increase the pulmonary vascular resistance [45]. This can translate to the half number of patients developing acute respiratory distress syndrome **(ARDS)** during hypothermic management compared to normothermic management [42].

In addition every 1˚C drop in core body temperature causes the overall body metabolism to decrease by 8 percent and hence decrease oxygen consumption and carbon dioxide production [32]. This necessitates adjustments of the ventilator settings in order to prevent hyperventilation which can worsen the damage by cerebral vasoconstriction.

e. Gastrointestinal and Renal System

Hypothermia can lead to ileus and delayed gastric emptying [33]. Gastrointestinal **(GI)** tract decontamination has been reportedly associated with lower infectious rate during hypothermia, while a higher risk of wound infection has been reported [44]. This demands care in order to prevent bedsores and catheter site infections [32].

Hypokalemia has been reported with hypothermia, mandating its close monitoring in regard to myocardial and GI sensitivity to potassium levels [43]. A rapid rewarming has higher associated risk of hyperkalemia, which can further lead to arrhythmias thus a slow rewarming is advocated.

The severe electrolyte depletion has been reported partly due to the hypothermia induced polyuria. Hypomagnesemia increases brain injury, and thus prophylactic electrolyte supplementation and frequent monitoring is employed through the hypothermic management [46].

The albumin levels remain in the normal range whereas the drug metabolism can be affected as per the route of elimination [47]. Reduced cytochrome p450 activity and renal tubular secretion and reabsorption lead to lower plasma clearing rates of various medications [32].

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