



## EMERGENCY THERAPEUTIC HYPOTHERMIA FOLLOWING CARDIAC ARREST; LITERATURE REVIEW

Osama Adel Marta<sup>1\*</sup>, Hassan Ali Alyousef<sup>2</sup>, Walid Tawfig Osman<sup>3</sup>, Abdullatif Mohammed Alabdullatif<sup>4</sup>, Dana Sulaiman Alsayyari<sup>5</sup>, Abdulaziz Ibrahim Alhonaizil<sup>5</sup>, Doaa Abdulaziz Aljohani<sup>6</sup>, Murtadha Hussain Ali Alameer<sup>7</sup>, Abdullah Ali Alstrawi<sup>7</sup>, Alhanouf Ibrahim Alzanitan<sup>8</sup>, Sultan Ibrahim Abu Tayli<sup>9</sup>

1. King Khalid Hospital, Tabuk, KSA.
2. Faculty of Medicine, Alfaisal University, Riyadh, KSA.
3. Faculty of Medicine, University of Khartoum, Khartoum, Sudan.
4. Faculty of Medicine, King Saud University, Riyadh, KSA.
5. Faculty of Medicine, Almaarefa University, Riyadh, KSA.
6. Faculty of Medicine, Taibah University, Madinah, KSA.
7. Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan.
8. Faculty of Medicine, Vision Colleges, Riyadh, KSA.
9. Department of Emergency, Imam Abdulrahman Alfaisal hospital, Riyadh, KSA.

### ARTICLE INFO

**Received:**

10 Nov 2020

**Received in revised form:**

17 Feb 2021

**Accepted:**

23 Feb 2021

**Available online:**

28 Feb 2021

**Keywords:** Therapeutic hypothermia, Hypothermia, Cardiac arrest, Targeted temperature management, Ventricular fibrillation

### ABSTRACT

Sudden cardiac death represents a significant global health issue. Despite advanced resuscitation procedures, post-cardiac arrest consequences, especially neurological outcomes, remain a health burden. Several methods were conducted to improve survival rate and prevent post-arrest neurological outcomes, including therapeutic hypothermia. This narrative review aims to assess the latest update on therapeutic hypothermia effect in post-cardiac arrest syndrome, either out-of-hospital arrest or inside-hospital arrest. We tried to summarize the impact of therapeutic hypothermia in both shockable and non-shockable rhythms. A 20 references were searched in the PubMed database using relevant Mesh words: Therapeutic hypothermia, Cardiac arrest, Resuscitation, post-cardiac arrest syndrome. Therapeutic hypothermia with targeted temperature measurement (32° to 36°C) has beneficial effects in post-cardiac arrest patients. The better outcomes were reported in patients with shockable rhythm upon presentation and/or out-of-hospital arrest. The other non-shockable rhythm and in-side hospital arrest conditions require further clinical trials to establish therapeutic hypothermia efficacy and safety among these groups. Overall, therapeutic hypothermia provides a safe profile with controllable side effects in the intensive care setting.

This is an **open-access** article distributed under the terms of the [Creative Commons Attribution-Non Commercial-Share Alike 4.0 License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows others to remix, tweak, and build upon the work non commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**To Cite This Article:** Marta OA, Alyousef HA, Osman WT, Alabdullatif AM, Alsayyari DS, Alhonaizil AI, et al. Emergency Therapeutic Hypothermia Following Cardiac Arrest; Literature Review. Pharmacophore. 2021;12(1):97-101. <https://doi.org/10.51847/Bzq7DvQYfa>

### Introduction

Sudden cardiac death (SCD) remains a global epidemic with an estimated annual incidence of 250,000 related to coronary artery disease (CAD) and over 450,000 when all mortality causes are included in the US [1]. Almost 50% of all deaths associated with heart disease are sudden and unexpected. Further, up to 50% of all SCDs represent the initial presentation of coronary artery disease or another structural heart disease that might be SCD [1]. SCD leads to immediate cessation of organ blood flow, particularly cerebral blood flow. Neurological ischemic injury is consequently resulted in oxygen deprivation after minutes, leading to brain damage and death if not promptly resuscitated [2, 3]. Cardiopulmonary resuscitation (CPR) must be immediately implemented to restore blood perfusion, and a defibrillator must be employed post-CPR if the rhythm is shockable (ventricular fibrillation and pulseless ventricular tachycardia) [3].

If restoration of spontaneous circulation (ROSC) resulted from adequate resuscitation, further reperfusion injury might occur [2]. The following are the major component of the post-cardiac arrest syndrome: neurologic, myocardial, hemodynamic, arrhythmic, and ischemic that impair the cardiac, neurologic, and other organ systems. The sufficient management of post-cardiac arrest syndrome is not only to maximize survival but also to optimize and rather normalize neurological function [1]. The complex and multifactorial are etiology of reperfusion injury and brain anoxia but mainly related to toxic metabolites generation in high concentration that causes neuronal injuries. Notably, permanent neurological damage occurs 5 to 10 minutes after complete cessation of cerebral blood flow in normothermic circumstances [2]. Clinical outcomes post SCD remains poor, and the best result is obtained when ROSC is achieved quickly as soon as possible. Malignant arrhythmias like ventricular fibrillation (VF) or ventricular tachycardia (VT) are significant differences in outcomes usually if there is SCD or due to witnessed of cardiac origin. On the contrary, unwitnessed arrest and/or those with pulseless electrical activity or asystole [4]. Congestive heart failure (CHF), and other heart diseases advanced intercessions for detection, prevention, and therapy of CAD had resulted in a decrease in the incidence of SCD. However, in the era of a growing and aging population, SCD remains a major health issue [1]. The recent therapeutic advances, such as implantable cardioverter-defibrillator (ICDs), a significant reduction of VT and VF incidence have been outlined, and although >70% of out-of-hospital cardiac arrest (OHCA) were similar to VT/VF, it represents less than 30% of the initial rhythm identified amid OHCA [1]. Importantly, the clinical scenarios, pathophysiology, and outcomes of OHCA are significantly different from In-Hospital Cardiac Arrest (IHCA), given that IHCA is usually different in origin from OHCA, such as sepsis, respiratory failure, and malignancy [4]. Incidence of 95 to 98/100,000 in North America, 52.5 in Asia, 86.4 in Europe, and 112.9 in Australia overall Emergency medical service (EMS)-assessed OHCA incidence varies globally. Variations among reporting practices and EMS systems compared to others could be attributed to the variation around the globe [4]. Nevertheless, OHCA carries a 90% to 96% mortality rate (90% in Europe and 92.2% in North America) and 93% worldwide. Meta-analyses have concluded that a patient's survival would be higher if OHCA is witnessed by a bystander or by emergency staff, especially if a bystander immediately starts CPR or emergency staff [4]. However, health providers implemented several methods to improve neurological outcomes and survival of patients post-cardiac arrest. These include hemodynamics optimization, glycemic control, coronary reperfusion, providing ventilation, electrolytes and temperature management, and seizure control [5].

#### *Historical Aspect of Therapeutic Hypothermia*

One of the earliest therapeutic hypothermia (TH) use came from Hippocrates in the mid-5th century, who reportedly control bleeding by packing patients in the snow [3]. In 1814, Baron Dominique-Jean Larrey, a battlefield surgeon for Napoleon, noticed that the rapid rewarming of injured soldiers placed near the fireside resulted in death [3]. Later, he produced a strategy of gradual rewarming that was associated with improved soldiers' condition [3]. A few decades ago, TH has been utilized to provide anesthesia amid amputations, prevent cancer cells from proliferation, and reduce complications amid heart surgery. To achieve ROSC described in 1803, the Russian method of resuscitation consisted in covering a patient with snow [6]. Besides, Baron de Larrey Russian surgeon attempted to preserve injured limbs and for anesthesia during amputation by utilizing TH amid Napoleon's Russian campaign in 1812 [6].

Nonetheless, the clinical TH was first to use in 1937, hoping to prevent cancer cells from further proliferation at lower temperatures, when Fay "cooled" a woman to 32°C for 24 h. Years later, Fay and his collaborators investigated the anesthetic properties of TH, particularly in cancer and febrile patients with head injuries [6]. Smith and Fay reported that TH enhanced the recovery of the conscious state of patients with brain injury in 1914, reporting the findings in a large series of patients with severe head injury [6]. Recently, TH gained its interest concerning clinical relevance; for instance, small-scale trials were conducted between 1958 and 1959 to investigate the benefits of hypothermia after cardiac arrest. This trial was associated with severe complications, later attributed to inadequate hypothermia levels (ca. 30°C, lower than currently implemented) and lack of complications management capacities [3].

Furthermore, in 1999, a woman was accidentally left to critically cold conditions for about 1.5 h, during which her body temperature dropped below 14°C, followed by cardiac arrest. Nonetheless, after intensive medical resuscitation effort, she survived, demonstrating the human body's inherent ability to tolerate and recover such an extreme thermal trauma [3]. Interestingly, recently a case report was published of a 42-year-old male pulseless at an outdoor temperature of 1°C and was found unresponsive to external stimuli. EMS, upon arrival, recorded a VF rhythm, which persisted despite repeated defibrillation. Luckily, his rhythm was restored to sinus rhythm at a core temperature of 30°C. He was discharged successfully three weeks later to the rehabilitation center after further receiving a 24 h of TH at 32-34°C and [7]. Three months later, he was fully recovered and back to his normal life [7]. The accidental hypothermia has suggested an attribution to his complete cardio and neurogenic recovery.

## **Results and Discussion**

#### *Pathophysiological Effect of Hypothermia*

Small changes in body and brain temperature can influence a critical role in neuronal vulnerability after ischemia, hypoxia, or traumatic injury. Slight variation in intra-ischemic brain temperature ranging from only a few degrees is Initial observations that reported in transient global ischemia played a significant role in hippocampal CA1 neurons vulnerability [8]. Blood flow to the core and penumbra is reduced to 20% and 50% of the baseline in focal ischemic injury. Hypothermia does not induce

decreased cerebral blood flow (CBF) but reduces metabolism, improves collateral reperfusion through increased blood pressure, and induces sympathetic responses by cooling and shivering [9].

The mechanism that lowers the metabolic rate for oxygen by 15-20% in 32°C is primarily the mechanism by which hypothermia provides neuroprotection by a marked reduction in cerebral metabolism. In addition, TH provides delay adenosine triphosphate (ATP), lactate, and pyruvate expenditure but does not prevent it. However, TH improves the recovery of high-energy phosphate metabolisms and reverses acidosis produced by lactate accumulation during reperfusion [9]. Although ischemic cell injury, mild temperature increments aggravate histopathology, and increased mortality against relatively mild temperature reduction provides significant protection [8].

Regarding the TH effect on the myocardium, a reversible post-resuscitation myocardial dysfunction has been reported early after cardiac arrest. Kelly and Nolan [10] report the impact of TH on the myocardium in a recent review. TH in animal models provides cardio-protection effects and participates in myocardial dysfunction improvement. Recent rats and pigs studies have revealed that TH improves contractility in the failing human myocardium. This protection was attributed to probably increasing Ca<sup>2+</sup> sensitivity and inhibition of reperfusion injury [10].

Besides, TH provides a beta-blocker effect and lowers general metabolism and oxygen demand, demonstrating reduction of the heart strain, which overall improved the outcome in the post-resuscitation status. While acute myocardial infarction is the single most common cause of SCD, a recent cardiogenic pig model demonstrates that cooling before reperfusion reduces mortality and improved myocardial function. Moreover, human studies demonstrated decreased infarction size if cooling was induced before reperfusion [10]. Notably, cardiogenic shock does not seem to be contraindicated for TH now [10].

#### *The Clinical Relevance of Therapeutic Hypothermia Following SCD*

Several studies regarding neurological function after brain injury have shown that increased body temperature was associated with poor outcomes. Following SCD, there are several body responses, such as elevated levels of cytokines and anti-inflammatory mediators, named "sepsis-like" syndrome. Furthermore, the cerebral metabolic rate dropped by almost 7% for each 1°C drop in body temperature which few investigators have shown [11]. In addition, hypothermia has played a part in the principle protection of the blood-brain barrier, leading to a decline in cerebral edema that follows ischemic brain injury. TH has been categorized into three phases:

1. The induction phase, the period where actively decreased in the core of body temperature
2. The maintenance phase
3. The rewarming phase, the period where the body temperature returns into normothermia

Various ways while demonstrating all three phases of cooling in renal function, and mild hypothermia affects normal cardiac, pulmonary, endocrine [11].

Temperatures between 32°C to 34°C, demonstrate an increment in myocardial contractility and decreased heart rate. The latter was secondary to a decrease in the spontaneous depolarization of pacemaker cells [11]. Nevertheless, mortality and neurological outcomes with different temperatures concluded that no differences in outcomes across 23°C, 33°C, and 34°C after 24 studies that evaluated the differences [12]. Besides, a pilot randomized clinical trial (RCT) had concluded improvement in 6-months mortality following 32°C. After analysis restriction to patients with a shockable rhythm, it showed improved outcomes with 32°C. The 34°C groups received less CPR by bystanders, more extended downtimes, and worse admission GCS [12]. The largest RCT of 275 individuals with ROSC following VF OHCA to either TH (32°C-34°C) over 23 h compared with standard therapy. As a result, the TH group demonstrated favorable neurological outcomes at 39% in the control group) vs. 6-month (55% in the TH group [13].

The 77 patients following ROSC with VF OHCA initial RCT were evaluated compared to the standard therapy and other TH (33°C within 2 h of ROSC) over 12 h. Likewise, the control group (26%) compared TH group exhibited a higher rate of better neurological outcomes (49%) [13]. Nonetheless, an international RCT had conducted for 950 comatose adults following OHCA assuming cardiac-related to targeted temperature management (TTM) with 33°C or 36°C. The result showed no difference in the 32°C groups compared to the 34°C groups in terms of all-cause mortality [14]. The American Heart Association (AHA) has recently updated the recommendations following ROSC with VF or pulse-less VT OHCA to be initiated with TTM with a target temperature of 33-36°C for at least 24 h with remaining comatose patients [13].

Approximately 225.000 new OHCA occur annually in Europe and the US. Despite extensive improvement in resuscitation modalities, the survival rate of those populations has not markedly changed over the last half-century (21% to 33%) [15]. The most important clinical features of post-cardiac arrest syndrome in neurological outcomes. Still, post-SCD survivors admitted to the hospital have an excellent neurological full recovery in less than half. Most of the survivors remain comatose or in a vegetative state, with a high burden to the health cost [15]. The International Committee of Resuscitation suggested that comatose adult patients following ROSC-OHCA must be recommended with TH at a temperature of 23°C to 34°C over 12-24 h if the initial rhythm was VT, in October 2002. Besides, the AHA recommended mild TH for OHCA survivors with VF or VT [14]. Interestingly, Dr. Yildiz and colleagues presented a case report of cardiac arrested patients who survived after propofol and adequate TH [16].

Regarding patients following ROSC-OHCA with non-shockable rhythm (asystole or pulseless electrical activity "PEA"), they have significantly poor outcomes versus patients with shockable rhythm (VF or VT). While non-shockable rhythm often results from progressing ventricular fibrillation over time, TH demonstrated a beneficial effect in the non-shockable rhythm

group in several studies [15]. Up to our knowledge, no RCT for this specific group now. In regards to pre-hospital TH following OHCA, a systematic review and meta-analyses for RCTs comparing patients who received pre-hospital TH vs. no pre-hospital TH. The outcome showed that pre-hospital TH was successfully decreased body temperature at the time of hospital arrival but does not enhance survival rates, increased risk of re-arrest, and was associated with neurological outcome, or overall survival rate [17].

Additionally, while TH is recommended for patients following SCD IHCA or OHCA, Chan S *et al.* had conducted a cohort study for IHCA patients secondary to cardiac and non-cardiac causes. The result found that IHCA who received TH had significantly lower in-hospital survival rates (29.2% vs. 27.4%, respectively) and rates of favorable neurological outcomes [17]. Besides, TH was potentially harmful to those patients, and TH among IHCA may require further trials [17].

#### *Methods and Complications of Therapeutic Hypothermia*

Non-invasive methods including ice packs, cold blankets, helmets or caps, immersion in cold water, and self-adhesive; few methods had been conducted for TH [6]. The invasive methods include rectal lavage, intraventricular cerebral hypothermia, and peritoneal lavage with cold exchanges/cold IV fluids infusion, retrograde jugular vein flush, extracorporeal circulating cooled blood, nasal or nasogastric [6]. Ice packs are considered safe with limitations to slow cooling rate or Surface cooling with cold blankets, particularly among obese patients. Although it is a convenient and easy device, it can lead to severe sepsis in coagulopathic patients. In addition, the transnasal evaporating cooling method is liquid spray coolant-oxygen mixed into the nasal passage and the brain [18]. Nevertheless, respiratory-related complications, such as volume-overload and lower ejection fraction Besides, intravenous cold saline infusion (4°C) archives fast cooling at one hour with large volume infusion [18].

Few possible TH complications were reported. For instance, hemodynamics instability, bleeding, thrombocytopenia, pneumonia, sepsis, pancreatitis, renal failure, hypokalemia, hypomagnesemia, pulmonary edema, seizures, and arrhythmias [19]. However, a systematic review comparing post-SCD complications between hypothermic and normothermic groups showed no significant difference between the two groups, except for arrhythmias and hypokalemia [19].

In overcooling conditions (<30°C), the mortality rate was lower survival rate (30%) vs. 58% without overcooling. In addition, device-related complications were reported, such as bleeding, infection, deep vein thrombosis, and pulmonary edema. Pneumonia is a significant health problem in ventilated post-SCD patients, leading to a higher mortality rate. Around 65% of such patients suffered from early-onset pneumonia. However, possible prophylactic measures were successfully conducted, such as IV antibiotic administration, but multivariate analyses showed that antibiotic use was an independent survival predictor [19]. Overall, TH-related complications were mild and easily controllable in the ICU settings [19].

#### **Conclusion**

Sudden cardiac death represents a global health issue, especially the neurological outcomes following resuscitation. Therapeutic hypothermia had demonstrated better outcomes, particularly in patients who experienced out-of-hospital cardiac arrest. However, further clinical trials are recommended to establish the efficacy of therapeutic hypothermia following in-hospital cardiac arrest, especially if cardiac origin. Overall, therapeutic hypothermia is a safe and controllable procedure with well-known side effects. We encourage the implementation of the latest AHA guidelines regarding the use of hypothermia worldwide.

**Acknowledgments:** None

**Conflict of interest:** None

**Financial support:** None

**Ethics statement:** None

#### **References**

1. Mitrani RD, Myerburg RJ. Editorial Commentary: The cold facts: Role of therapeutic hypothermia in cardiac arrest survivors. *Trends Cardiovasc Med.* 2016;26(4):345-7. doi:10.1016/j.tcm.2015.10.005
2. Bernard S. Hypothermia after cardiac arrest: expanding the therapeutic scope. *Crit Care Med.* 2009;37(7 Suppl): S227-33. doi:10.1097/CCM.0b013e3181aa5d0c
3. Alshimeri A. Therapeutic hypothermia after cardiac arrest. *Ann Card Anaesth.* 2014;17(4):285-91. doi:10.4103/0971-9784.142065
4. Cobas MA, Vera-Arroyo A. Hypothermia: Update on Risks and Therapeutic and Prophylactic Applications. *Adv Anesth.* 2017;35(1):25-45. doi:10.1016/j.aan.2017.07.002
5. Arrich J, Holzer M, Havel C, Müllner M, Herkner H. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. *Cochrane Database Syst Rev.* 2016;2(2):CD004128.

6. Alzaga AG, Cerdan M, Varon J. Therapeutic hypothermia. *Resuscitation*. 2006;70(3):369-80. doi:10.1016/j.resuscitation.2006.01.017
7. Nordberg P, Ivert T, Dalén M, Forsberg S, Hedman A. Surviving two hours of ventricular fibrillation in accidental hypothermia. *Prehosp Emerg Care*. 2014;18(3):446-9. doi:10.3109/10903127.2014.891066
8. Dietrich WD, Bramlett HM. Therapeutic hypothermia and targeted temperature management in traumatic brain injury: Clinical challenges for successful translation. *Brain Res*. 2016;1640(Pt A):94-103. doi:10.1016/j.brainres.2015.12.034
9. Badjatia N. Therapeutic hypothermia protocols. *Handb Clin Neurol*. 2017;141:619-632. doi:10.1016/B978-0-444-63599-0.00033-8
10. Sunde K, Søreide E. Therapeutic hypothermia after cardiac arrest: where are we now? *Curr Opin Crit Care*. 2011;17(3):247-53. doi:10.1097/MCC.0b013e3283453210
11. Lay C, Badjatia N. Therapeutic Hypothermia After Cardiac Arrest. *Current Atherosclerosis Reports*. *Curr Atheroscler Rep*. 2010;12(5):336-42.
12. Schenone AL, Cohen A, Patarroyo G, Harper L, Wang X, Shishehbor MH, et al. Therapeutic hypothermia after cardiac arrest: A systematic review/meta-analysis exploring the impact of expanded criteria and targeted temperature. *Resuscitation*. 2016;108:102-10. doi:10.1016/j.resuscitation.2016.07.238
13. Silverman MG, Scirica BM. Cardiac arrest and therapeutic hypothermia. *Trends Cardiovasc Med*. 2016;26(4):337-44. doi:10.1016/j.tcm.2015.10.002
14. Nielsen N, Wetterslev J, Cronberg T, Erlinge D, Gasche Y, Hassager C, et al. Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest. *New England Journal of Medicine*. *N Engl J Med*. 2013;369(23):2197-206.
15. Picchi A, Valente S, Gensini G. Therapeutic hypothermia in the intensive cardiac care unit. *J Cardiovasc Med (Hagerstown)*. 2015;16(5):363-71. doi:10.2459/JCM.000000000000108
16. Dietrich WD. Therapeutic Hypothermia. *Ther Hypothermia Temp Manag*. 2018;8(4):187. doi:10.1089/ther.2018.29053.wdd
17. Lindsay PJ, Buell D, Scales DC. The efficacy and safety of pre-hospital cooling after out-of-hospital cardiac arrest: a systematic review and meta-analysis. *Crit Care*. 2018;22(1):1-9. doi:10.1186/s13054-018-1984-2
18. Kang IS, Fumiaki I, Pyun WB. Therapeutic Hypothermia for Cardioprotection in Acute Myocardial Infarction. *Yonsei Med J*. 2016;57(2):291. doi:10.3349/ymj.2016.57.2.291
19. Holzer M. Therapeutic hypothermia following cardiac arrest. *Best Pract Res Clin Anaesthesiol*. 2013;27(3):335-46. doi:10.1016/j.bpa.2013.07.003