Chapter 2

# Therapeutic Hypothermia for Cardiac Arrest

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## 1. Introduction

In the era before Therapeutic Hypothermia (TH) was recommended and used as a therapeutic modality for out-of-hospital cardiac arrest (OHCA) patients, reported data suggests in-hospital mortality exceeded 58%.[1,2,3,4,5,6] Mortality after a sudden and unexpected cardiac arrest (CA) is high, and the chance of survival to hospital discharge has, until recently, remained unchanged.[7] In one report, OHCA in the U.S. has a mortality rate greater than 90% which results in more than 300,000 deaths per year.[8] Those who survive the devastating event, often retain a hypoxic brain injury and a permanently incapacitating neurologic deficit.[9] Studies of patients who survived to ICU admission but subsequently died in the hospital, brain injury was the cause of death in 68% after out-of-hospital cardiac arrest and in 23% after in-hospital cardiac arrest.[10,11] Therapeutic hypothermia, or targeted temperature management, is a therapeutic intervention that is intended to limit neurologic injury after a patient's resuscitation from cardiac arrest.

## 2. Mechanisms of neuroprotection

A cascade of destructive events and processes begins at the cellular level in the minutes to hours following an initial injury. These processes, the result of ischemia and reperfusion, may continue for hours to many days after the initial injury.[12] It is crucial to note that all of these processes after ischemic-reperfusion injury in the brain are temperature dependent; they are all stimulated by fever, and can all be mitigated or blocked by hypothermia. Since most of these processes start within minutes to hours after the injury, then application of hypothermia earlier might be even more beneficial than conventional later application.

### 2.1. Slowing of brain metabolism

When hypothermia was first used in a clinical setting it was presumed that its protective effects were due purely to a slowing of cerebral metabolism, leading to reduced glucose and

oxygen consumption. Cerebral metabolism decreases by 6% to 10% for each 1°C reduction in body temperature during cooling.[13,14] This could play a therapeutic effect, but only partially. This mechanism is not the only explanation for the dramatic difference seen despite the positive role of metabolic slowing in neuroprotection.

## 2.2. Inhibition of apoptosis

Therapeutic hypothermia can also effectively inhibit apoptosis [15-17 ]Hypothermia inhibits the early stages of the programmed cell death process.[16] Thus, inhibiting apoptosis is another mechanism by which therapeutic hypothermia could influence the ischemia reperfusion injury or secondary injury early on in the disease process.

## 2.3. Inhibition of excitotoxicity

Excitatory processes play a major role in the pathophysiology of secondary injury post-cardiac arrest.[13] Evidence suggests that hypothermia inhibits these harmful excitatory processes occurring in brain cells during ischemia–reperfusion. Ischemic insult to the brain leads to decrease in Adenosine triphosphate (ATP) supplies.[13] This culminates into an influx of calcium (Ca) into the cell through prolonged glutamate exposure inducing a permanent state of hyperexcitability in the neurons (*excitotoxicity*). All these processes are inhibited by hypothermia very early after injury. Some animal experiments suggest that neuroexcitotoxicity can be blocked or reversed only if the treatment is initiated in the very early stages of the neuroexcitatory cascade.[18-24]

## 2.4. Antiinflammatory role and decrease in free radical formation

Acute inflammation early after return of spontaneous circulation (ROSC) plays a harmful role in postcardiac arrest, including cytokines, macrophages, neutrophils, and complement activation , leading to free radical formation. Multiple animal experiments and few clinical studies have shown that hypothermia suppresses all these ischemia-induced inflammatory reactions, leading to a significant reduction in free radical formation. [25-28]

## 2.5. Protection of blood-brain barrier

Ischemia–reperfusion can also lead to significant disruptions in the blood– brain barrier, which can facilitate the subsequent development of brain edema. Mild hypothermia significantly reduces blood– brain barrier disruptions, and also decreases vascular permeability following ischemia–reperfusion, further decreasing edema formation.[29-31]

## 2.6. Antithrombotic role

The coagulation cascade is also activated with ischemia-reperfusion injury leading to intravascular clot formation resulting in microvascular thrombosis in the brain.[32,33] Therapeutic Hypothermia could be beneficial in this instance since platelets number and

function are decreased with temperatures <35°C, and some inhibition of the coagulation cascade develops at temperatures <33°C.[34,35] Vasoconstriction , mediated mainly by thromboxane and endothelin plays a pivotal role in the secondary injury as well. This could also be mitigated by hypothermia [36-38]

## 3. Clinical evidence

### 3.1. Out of hospital and ventricular fibrillation cardiac arrest

The first major clinical trials that provided direct evidence of a benefit of therapeutic hypothermia were published in 2002. These studies have indicated that TH with a reduction of body core temperature (T) to 33 °C over 12 to 24 hours has improved survival and neurologic outcome in OHCA patients. The European Hypothermia after Cardiac Arrest Study Group demonstrated an improvement in survival from witnessed V-fib cardiac arrest from 41% to 55% and an improvement in favorable neurologic outcome among survivors from 39% to 55% when TH of 32-34°C was maintained for the first 24 hours post cardiac arrest.39 Bernard demonstrated similar neurologic outcome benefits from 12 hours of TH at 32-34°C induced on the same patient population in Australia.40 Recently, a meta-analysis showed that therapeutic hypothermia is associated with a risk ratio of 1.68 (95% CI,1.29-2.07) favoring a good neurologic outcome when compared with normothermia. The meta-analysis concluded the number needed to treat (NNT) to produce one favorable neurological recovery was 6.41 This would translate to improved neurological recovery in > 10,000 patients per year in the U.S.41 Findings were also reviewed from recent literature on the postresuscitation care of cardiac arrest patients using therapeutic hypothermia as part of nontrial treatment. Although varied in their protocols and outcome reporting, results from published investigations confirmed the findings from the landmark randomized controlled trials, in that the use of therapeutic hypothermia increased survival and favorable neurologic outcome.[42]

### 3.2. In hospital and non-ventricular fibrillation cardiac arrest

Although ROSC rates are higher in patients with VF and these represent the majority of patients transported to the hospital, many patients still present to the hospital comatose after resuscitation from non-VF arrest. Patients with an initial cardiac rhythm of asystole have a lower rate of survival than patients with VF, because total absence of rhythm is associated with worse underlying causes. Some evidence has now shown that the treatment may be beneficial in cases with non-VF initial rhythm.[43-47] However, other studies involving this patient population did not show outcome benefit. In a recent study of TH after inhospital cardiac arrest (IHCA), 91%of patients had an arrest rhythm of asystole or pulseless electrical activity. No difference in neurological outcome at discharge was detected in these non-shockable IHCA patients treated with TH.[48] Given this increased severity of neurological injury in non-VF arrest patients, the possible role of TH remains uncertain. Given such low rates of recovery after non-VF arrest with the use of TH, a prospective study

comparing TH with normothermia in patients with an initial cardiac rhythm asystole or PEA would require very large numbers of patients to get enough power to show improved outcomes, and thus is unlikely that such trials will be conducted.

### 3.3. Asphyxial causes of cardiac arrest

Suffocation is the second leading cause of death from suicide in the United States, accounting for 22.5% of the 33 300 suicide-related deaths.[49] Victims of near-hanging may carry a poor prognosis even if cardiac arrest has not occurred. Those who suffer cardiac arrest, present with a Glasgow Coma Scale (GCS) of 5 or less, and experience a longer hanging time have the worst prognosis.[50,51]Nearhanging is defined as an unsuccessful attempt at hanging. Victims of near-hanging suffer from strangulation with cerebral ischemia-reperfusion injury rather than a fatal cervical spine injury. Therapeutic Hypothermia has not been prospectively studied in this patient population, and it is doubtful that large randomized, controlled trials comparing TH with normothermia will be conducted. There are few retrospective reviews and case reports and case series on asphyxiated patients with or without cardiac arrests who had good neurologic recovery after therapeutic hypothermia.[52-55] Although it would be difficult to conduct good prospective studies, the compiling case studies, anecdotal evidence, and extrapolated data support the use of therapeutic hypothermia for asphyxial cardiac arrest until more evidence can be obtained.

## 4. Guidelines

In 2005, guidelines for resuscitation and emergency cardiac care of the European Resuscitation Council and the American Heart Association recommended that the core body temperature of unconscious adult patients with spontaneous circulation after a VF OHCA should be lowered to 32 to 34°C (Class IIA recommendation).[56] Cooling should be started as soon as possible after the arrest and should be continued for at least 12 to 24 hours.

The guidelines note that patients who have had a cardiac arrest due to nonshockable rhythms and patients who have had a cardiac arrest in the hospital may also benefit from induced hypothermia (Class IIB recommendation).[56]

With more evidence and trials showing the feasibility and the evidence supporting TH for cardiac arrest patients, the new guidelines by European Resuscitation Council and the American Heart Association in **2010** recommend that comatose (ie, lack of meaningful response to verbal commands) adult patients with ROSC after out-of-hospital VF cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours (**Class I**).[57] Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electrical activity or asystole (**Class IIb**).[57] Active rewarming should be avoided in comatose patients who spontaneously develop a mild degree of

hypothermia (32°C [89.6°F]) after resuscitation from cardiac arrest during the first 48 hours after ROSC. (**Class III**).[57]

## 5. Cooling methods

### 5.1. Methods for induction of therapeutic hypothermia

Bernard et al., reported the results of a clinical trial of the rapid infusion of large-volume (30 ml/kg), ice-cold (4°C) lactated ringer's solution in comatose survivors of OHCA. This study found that this approach decreased core temperature by 1.6°C over 25 minutes with no adverse events.[58] Polderman, et al., used in addition to surface cooling, 30ml/kg (mean 2.3 liters) of cold normal saline over 50 minutes that showed similar results.[59] Several small randomized trials, and nonrandomized observational and retrospective trials, looked at pre-hospital cooling initiation for patients with OHCA with large-volume ice-cold (4°C) fluids (discussed in more detail in a separate chapter: **Prehospital Therapeutic Hypothermia for Cardiac Arrest).**[60-68] All these studies documented the safety and feasibility if ice-cold fluids for the rapid induction of therapeutic hypothermia. Other promising methods for induction of hypothermia include transnasal cooling device [69], self-adhesive cooling pads [70], and cranial cooling caps.[71]

### 5.2. Methods for maintenance of therapeutic hypothermia

An ideal cooling method would be one that will help with rapid induction of cooling, cost-effective, easily implemented, safe, effective, and able to maintain the temperature with minimal variations.

#### *5.2.1. Surface cooling*

Ice packs are still used in some centers for induction and maintenance of hypothermia, by applying them to the head, neck, torso and extremities. Disadvantages of this method include slow cooling rate, labor-intensive for the nurses, and wide fluctuations with overshooting and undercooling or unintentional rewarming.[40,72,73]

An effective surface cooling system uses cooling blanket (Arctic Sun, Medivance, Louisville, CO, USA). This technology can cool as fast as 1.2°C per hour through especially designed pads, is radiolucent (can be used during cardiac catheterization), has minimal temperature variation (operates with feedback control), and can perform active controlled rewarming. The pads can be applied easily by the nurses. Disadvantages include expense, possible skin sloughing, and slower cooling rates in very obese people.[72,74]

A promising technology is the Thermosuit System (Life Recovery Systems, Kinnelon, NJ, USA), which surrounds patients directly with cool water and also possesses a feedback control mechanism. Animal studies suggest that it provides a cooling rate of 9.7°C per hour in 30-kg pigs, versus 3.0°C per hour in humans. Disadvantages include expense and hindering appropriate physical exams.[75,76]

### *5.2.2. Intravascular cooling*

The CoolGard System (Alsius, Irvine, CA, USA) is one of the products that uses Intravascular devices. This technology works by exchanging heat through a catheter containing circulating saline at a controlled temperature with a feedback of patient temperature. This technology can cool as fast as 1 to 1.5 °C per hour, is very good at maintaining goal temperature (feedback mechanism) and cal also provide active controlled rewarming. Disadvantages are those of central venous catheters (risks of bleeding, vessel thrombosis, and catheter-related infection). It also requires placement by a physician, which if not readily available, may delay initiation of this important and timely therapy.[77.78]

Although many devices are available to achieve and maintain therapeutic hypothermia, there are no current data recommending one method over another, or comparing them against each other. Several factors need to be taken into consideration, such as patient factors, nursing factors and nurse to patient ratios, and institutional factors when making a decision regarding the optimal method.

## 6. Conclusion

On the basis of current evidence, comatose (ie, lack of meaningful response to verbal commands) adult patients with ROSC after out-of-hospital VF cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours, as fast as possible. Therapeutic Hypothermia should be strongly considered for other rhythms, for inhospital arrests, and for cardiac arrest secondary to asphyxia. Intensivists should be familiar with techniques to induce, maintain, and rewarm from therapeutic hypothermia, and select the most appropriate method for a given patient, and institution. Research questions for the future are whether very early cooling, or longer cooling periods (eg, 72 h), or both can further improve outcome.

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## Conflicts of interest

The author reports no conflicts of interest.
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