

**Therapeutic Hypothermia to Reduce Cardiac Arrest-Related Neurological  
Deficits and Mortality**

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## TABLE OF CONTENTS

|                                                 |       |
|-------------------------------------------------|-------|
| ABSTRACT.....                                   | iii   |
| 1. INTRODUCTION .....                           | 1     |
| 2. BACKGROUND .....                             | 1-9   |
| 2A. HISTORY OF THERAPEUTIC HYPOTHERMIA.....     | 1-4   |
| 2B. PHYSIOLOGY OF THERAPEUTIC HYPOTHERMIA ..... | 4-9   |
| 3. METHODOLOGY.....                             | 9-10  |
| 4. REVIEW OF LITERATURE RESULTS .....           | 10-18 |
| 4A. HOLZER AT AL. ....                          | 10-13 |
| 4B. SUNDE AT AL.....                            | 13-15 |
| 4C. BERNARD AT AL .....                         | 15-18 |
| 5. DISCUSSION .....                             | 18-21 |
| 6. CONCLUSION.....                              | 21-22 |
| REFERENCES .....                                | 23-25 |
| APPENDIX                                        |       |
| A. MESH TERMS.....                              | 26    |
| B. TABLE 1.....                                 | 27-31 |
| C. RISK OF BIAS EVALUATION .....                | 32-33 |
| D. POST RESUSCITATION TREATMENT PROTOCOL.....   | 34-35 |

## **Abstract**

### **Purpose**

The purpose of this clinical review is to determine if induced therapeutic hypothermia is effective in reducing neurological deficits and mortality in cardiac arrest patients.

### **Methods**

PubMed, Cochrane Review Database, Embase, and Trip database were utilized. A common set of search terms including "induced hypothermia", "therapeutic hypothermia", "cardiovascular resuscitation", "cardiac arrest", "neurological deficits", "neurological outcome" and "mortality" guided the search. A total of three individual studies that were included for final results review.

### **Results**

Clinically based trials revealed that induced therapeutic hypothermia can improve both survival rates and neurological outcomes in cardiac arrest patients compared to cardiac arrest patients that do not receive therapeutic hypothermia.

### **Conclusion**

Although more research needs to be done to make therapeutic hypothermia implemented across all cardiac arrest patients, current research has suggested that therapeutic hypothermia implantation in cardiac arrest protocols can prove to be extremely beneficial in improving patient survival rates and neurological outcome

## **Introduction**

Death rates among patients that suffer sudden cardiac arrest out of hospital are high. In the United States alone, more than 350,000 individuals had an incidence of out of hospital cardiac arrest in 2016.<sup>10</sup> Out of these 350,000 patients that suffered cardiac arrest, ~200,000 of them resulted in death. This clinical condition affects many individuals without warning as it is difficult to predict. One adverse effect of cardiac arrest is persistent neurological deficits as a consequence of spontaneous reperfusion. Surviving with good neurological outcome is difficult to achieve and experimental evidence proposes that therapeutic hypothermia is beneficial<sup>11</sup>. Research has suggested that therapeutic hypothermia implantation in cardiac arrest protocols can prove to be extremely supportive in giving the patient the very best neurological outcome.

The concept of therapeutic hypothermia has been around for over 2000 years and while the principle has advanced since then, there is still research that needs to be done to establish guidelines for its widespread implementation. With the continuous advances in medicine there is no set limit to how it can drastically change our patients outcomes for the better. In the meantime, while we can continue to work to keep ourselves as healthy as possible, cardiac arrest can still happen. It is what happens after cardiac arrest that can be improved, and by improving that we can improve survival rates as well as quality of life.

## **Background**

### *History of Therapeutic Hypothermia*

While therapeutic hypothermia may seem futuristic, it has been around far longer than one would think. Even though it's not quite what you would think in terms of a cryocooling

chamber suspending one's animation in time while medical staff races to find a cure like a sci-fi movie would suggest, medicine still has made great advances since it was first introduced. The concept of therapeutic hypothermia has been used dating all the way back to the father of medicine himself, Hippocrates. He saw the value of it and mentioned the use of snow and ice to reduce hemorrhage in his wounded and critically ill patients.<sup>1</sup>

This treatment has emerged continually throughout history. In 1954 a study by Rosomoff and Holaday<sup>2</sup> found a surprising fall in cerebral oxygen consumption in dogs that underwent therapeutic hypothermia. They documented this decrease in oxygen consumption occurred when the dogs temperatures were lowered from 35°C to 26°C. Furthermore, it was found that there was an astonishing three-fold reduction in oxygen consumption when the dogs were cooled down to 26°C<sup>2</sup>. Through their experiments and others that followed, this helped catalyze what would then lead to predictions in how this concept could be used in human medicine. With these studies, it could predict how it could be used for cardiac arrest patients.

In 1958 the very first study on humans using therapeutic hypothermia was conducted with cardiac arrest patients<sup>3</sup>. The study suggested decreased mortality in the patients that received that therapeutic hypothermia. Although this study did not look at neurological outcome in these patients. This groundbreaking study included 19 patients that were resuscitated after suffering perioperative cardiac arrest. All patients had their thoracic cavity opened and their heart was documented to be in fibrillation or asystole. Then the subjects that were chosen for therapeutic hypothermia were cooled using a circulating coolant blanket. The subjects were cooled and maintained at approximately 31–32°C.<sup>3</sup> There was no set time that the subjects were cooled, and clinical judgment was used to determine the duration of hypothermia. Although, when improvement was noted, hypothermia was gradually stopped. The subjects were then

slowly and gradually returned to normal temperature. It was discovered that out of the 19 patients included in the study, 7 patients in the control group did not receive therapeutic hypothermia, while 12 patients in the treatment group received therapeutic hypothermia.<sup>3</sup> The conclusion showed that the survival rate was 50 percent in the treatment group compared to 14 percent in the control group.

Although the outcomes of utilizing therapeutic hypothermia to improve survival of cardiac arrest were very promising, until twenty years ago few studies on the treatment existed. The studies that were published documented favorable results and in 2002 the advisory panel from the International Liaison Committee on Resuscitation (ILCOR) implemented the recommendation of its use in common practice. In 2002, two studies were published out of Europe<sup>4</sup> and Australia<sup>5</sup> that demonstrated improved survival rates and improved neurological outcomes when using mild therapeutic hypothermia. The studies studied that effect of therapeutic hypothermia on comatose survivors of Out of Hospital Cardiac Arrest (OHCA) that were due to Ventricular Fibrillation (VF). The Hypothermia after Cardiac Arrest Study Group (HACA), including nine hospitals in five European countries, showed that mild hypothermia (cooling to 32–34°C for 24 h) in 274 OHCA patients with return of spontaneous circulation (ROSC) provided significant improvement in functional recovery and good neurological outcome after hospital discharge (55% vs. 39%).<sup>5</sup> It also led to a lower 6-month mortality rate when compared with patients who were not cooled (41% vs. 55%).<sup>5</sup> In Australia, Bernard et al. examined the endpoint of survival to hospital discharge in 77 patients.<sup>4</sup> This showed a 49% survival rate in the therapeutic hypothermia group which were cooled to 33°C for 12 hours, compared to a survival rate of 26% in the group that did not receive therapeutic hypothermia.<sup>4</sup>

Even though there were published guidelines in by the International Liaison Committee on Resuscitation (ILCOR) supporting the use of therapeutic hypothermia<sup>6</sup> in 2005, the use of hypothermia as treatment still lagged in utilization. Adoption of hypothermia in North America was even slower with far higher utilization rates in North European countries.<sup>7</sup> There were many different reasons for its delay in implementation. These reasons included insufficient knowledge of effective hypothermia techniques, lack of belief that therapeutic hypothermia would improve the outcome for individual patients, and controversies regarding the best method to reach the target temperatures<sup>6</sup>.

The ILCOR guidelines in 2005 did not clarify a set cooling protocol. In 2010, newer guidelines were published by the International Liaison Committee on Resuscitation (ILCOR)<sup>8</sup>. This progressive advancement by the ILCOR helped provide the material for the American Heart Association (AHA)<sup>9</sup> to write their new resuscitation guidelines in 2010. Now with the AHA advocating for the implementation of the use of therapeutic hypothermia, there was a higher likelihood that therapeutic hypothermia would be utilized in North America to truly see how it could impact cardiac arrest patient outcomes. While it may have started with the father of medicine more than 2000 years ago, with some modern improvisation, therapeutic hypothermia will continue to strive to benefit patient outcomes.

### *Physiology of Therapeutic Hypothermia*

The act of simply “cooling” a patient seems almost elementary in comparison to other lifesaving procedures that occur during cardiac arrest resuscitation. While it may seem that way at first, after considering what the active cooling does to the patient’s individual systems it uncovers itself to be quite complex. That is the exquisite nature of the physiology of therapeutic hypothermia. It effects each organ system and body mechanisms differently. During cardiac

arrest, there is secondary damage to the brain and other vital organs due to hypoperfusion that can ultimately lead to neurological deficits and death. Therapeutic hypothermia is being used to improve this secondary impact that causes profound damage to the brain and other organ tissue. Unfortunately, what is not yet fully understood is the complete mechanism of action of hypothermia and how it effects every organ system differently. This is due to how incredibly complex it is. Although, research has been conducted to further understand how something like hypothermia works to help individuals from this secondary damage.

Therapeutic hypothermia and its protective effects on the body, especially from secondary damage can be broken down into several pathways. A decreased metabolic state resulting in lower oxygen and energy consumption along with carbon dioxide production may prevent secondary injury when oxygen supply is interrupted or, at least, impaired.<sup>12</sup> This is especially important with patients suffering from cardiac arrest. Regardless if a patient suffers cardiac arrest out of hospital or in hospital there will almost always be a period when their oxygen supply to the brain is interrupted. When there is no oxygenation through ventilation this causes delayed perfusion to the brain and organ tissues. After the oxygen supply has been interrupted and then reintroduced this causes a rush of oxygenated blood. This rush of re oxygenated blood while necessary, can cause reperfusion injury. Therapeutic hypothermia has been speculated and studied to demonstrate protection against such reperfusion injuries through various mechanisms.<sup>13</sup> In 2003 a study was published that went to explain some of these cellular pathways.

Among the many cellular pathways that may be responsible for the beneficial effects of cooling, a central hypothesis is that hypothermia reduces cellular metabolism and oxygen demand while maintaining acceptable ATP levels.<sup>14</sup> Additionally, hypothermia attenuates



abnormal free radical production, improves cellular ion handling, and improves cellular pH balance.<sup>15</sup> Hypothermia also reduces cell death and inflammatory signaling.<sup>16</sup> Reperfusion following ischemia results in a short period of excessive free radical production. Reperfusion-induced free radical production suggests that reperfusion injury is mediated by oxidative stress.<sup>18</sup> Studies suggest that the mitochondrial electron transport chain is an important site of post-reperfusion free radical generation.<sup>13</sup> Mitochondrial free radical production is an important target mechanism during the first window of opportunity for hypothermia treatment. This window likely requires the initiation of therapeutic hypothermia during the active cardiac arrest so that when spontaneous reperfusion is finally obtained the blood that is circulating is already cooled.

A second window of opportunity for hypothermia after reperfusion injury targets the inflammatory cascade and cell death pathways known as apoptosis and necrosis. After a patient's oxygen supply is interrupted, apoptotic processes may be initiated in brain tissue and neuronal cells may start to die and become necrotic. In these earliest stages these pathways may be blocked by hypothermia.<sup>12</sup> This second window lasts several hours and is targeted by our current clinical practice of initiating therapeutic hypothermia after spontaneous reperfusion. Lampe, J. W., et al. illustrated this concept of the effects of hypothermia on reperfusion injury. As shown in

Figure 1, initiation of therapeutic hypothermia after spontaneous reperfusion occurs offers

protection but is considered to only help with

later cell death and inflammatory

signaling. The illustration also shows

that initiation of therapeutic hyperthermia

during active cardiac arrest and before

spontaneous reperfusion, is considered

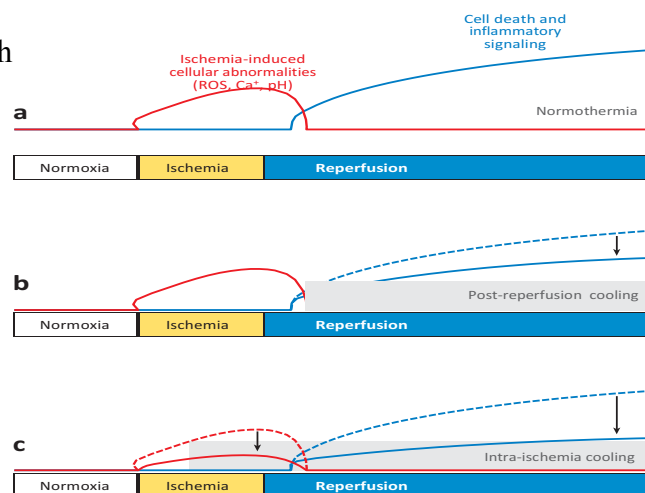


Figure 1: Lampe, J. W., & Becker, L. B. (2011). State of the art in therapeutic hypothermia. *Annual review of medicine*, 62, 79-93.

to target cellular abnormalities that are induced by ischemia as well as cell signaling after spontaneous reperfusion is obtained.

Ischemia reperfusion injury can also lead to significant disruptions in the blood-brain barrier. This disruption can initiate the development of brain edema in patients which can be problematic. The use of therapeutic hypothermia can significantly reduce the blood-brain barrier disruption, and also can decrease the vascular permeability following ischemia reperfusion. This in hand, can decrease the brain edema from forming.<sup>17</sup> Other studies such as the Eurotherm3235 Trial ISRCTN34555414 have branched off from this evidence to use therapeutic hypothermia to reduce secondary brain injury and thus the development of cerebral edema or prophylactic hypothermia.<sup>19</sup> Also, the use of rescue hypothermia as an exact treatment of raised intracranial pressure. This showed that therapies such as therapeutic hypothermia that reduce intracranial pressure also improve neurological outcome. Nevertheless, the association between controlled intracranial pressure and exactly how it can improve neurological outcome is still uncertain.<sup>20</sup> Appendix B further summarizes the changes to the blood-brain barrier and intracranial pressure related to therapeutic hypothermia.

Until the 1990s, it was presumed that the neurological protective effects of hypothermia were exclusively due to a reduction in cerebral metabolism.<sup>21</sup> Even though there is a distinct decrease in metabolism, it is now understood that this decrease is only one of numerous mechanisms behind the protective effects of hypothermia. In therapeutic hypothermia when the patients core temperature drops and the metabolic rate decreases, glucose and oxygen consumption, as well as carbon dioxide production also decrease. This helps prevent or decrease injury when oxygen supply is interrupted or limited. It is important to note that this reduction in metabolic rate due to therapeutic hypothermia may require there to be needed adjustments made

in ventilator settings to ensure a patient maintains normal arterial carbon dioxide pressures.<sup>17</sup> Since glucose consumption decreases as well as insulin sensitivity, this may also require needed adjustments in insulin infusion rates. The rate of these changes depends on how quickly a patient was cooled due to therapeutic hypothermia induction.<sup>22</sup>

A patient's electrolytes are also affected by therapeutic hypothermia due to intracellular shift and tubular dysfunction. When considering that low magnesium and potassium levels can elevate the risk of arrhythmias, and low levels of phosphate can increase the risk of infection it is important to maintain these electrolytes on the higher end of normal range during and after initiation of therapeutic hypothermia.<sup>19</sup> When potassium supplementation is administered during the cooling it is important to be aware of the possibility of rebound hyperkalaemia that is a risk during the rewarming phase. Cooling can also have effects on intracellular/extracellular acidosis and cellular metabolism. The reduction in cell membrane integrity, ion-pump failure, mitochondrial dysfunction, and cellular hyperactivity all contribute to the development of intracellular acidosis which stimulates many of these harmful processes.<sup>19</sup> The risk of these potentially harmful processes can be lessened by the use of therapeutic hypothermia. Appendix B further summarizes the changes to metabolism and electrolytes related to therapeutic hypothermia.

Cardiovascular changes and hemodynamic effects occur as well during therapeutic hypothermia. The effects of cooling on the myocardium and its contractility moderately depend on the patient's volume status and capability of sedation. This decrease in metabolic rate usually matches or exceeds the reduction in cardiac output which then maintains or improves the equilibrium between supply and demand.<sup>22</sup> After therapeutic hypothermia has been initiated there is an expected decrease in heart rate by 40-50bpm that occurs at lower core temperatures of 33°C;

it is generally advisable to allow this occur and to not attempt to increase heart rate pharmacologically. Since myocardial contractility improves when heart rate is decreased during therapeutic hypothermia, if heart rate is artificially increased it can decrease myocardial contractility.<sup>23</sup> In regards to coronary perfusion, cooling can provide protection for ischemic myocardium, although patients with preexisting coronary artery disease may not receive this protection. There is preliminary evidence available that suggests that early initiation of therapeutic hypothermia after myocardial infarction may help lessen subsequent myocardial injury.<sup>21</sup> Appendix B further summarizes the changes to heart function as well as other mechanisms of action, risks and changes to body regulations related to therapeutic hypothermia.

## **Methodology**

PubMed, Cochrane Review Database, Embase, and Trip database, were utilized. The search terms "induced hypothermia", "therapeutic hypothermia", "cardiovascular resuscitation", "cardiac arrest", "neurological deficits", "neurological outcome" and "mortality" guided the literature search. Please see appendix A for Mesh terms. Supplemental resources included JAMA evidence, Society of Emergency Medicine Physician Assistants (SEMPA), and UpToDate, utilized to provide background information and provide structure for further searches. Excluded studies in my review included those that were: not randomized clinical trials, studies that did not focus on neurological outcomes or survival rates, studies that only focused on optimal target temperature management, studies on animals, studies focusing on timing of neurologic prognostication, studies focusing solely on adverse events, studies focusing on other initial arrhythmias than ventricular in nature, and studies focusing on therapeutic hypothermia's effects on cardioprotection. To be included for final review the articles chosen were randomized clinical

trials, written in English, and published within the last 15 years. There were 3 final individual studies that were included for a final results review.

## **Review of Literature Results**

### *Holzer at al.*

Holzer at al. in association with the HACA (The Hypothermia After Cardiac Arrest Study Group) conducted a RCT study with 275 patients. They sought to understand in patients with cardiac arrest due to VF (ventricular fibrillation) or pulseless VT (ventricular tachycardia), whether mild hypothermia improve neurologic outcomes compared with standard care normothermia. Their study design was a randomized, controlled trial with blinded assessment of the outcome. The patients were then randomly assigned to either the hypothermia group or the normothermia group (received standard care after resuscitation).<sup>5</sup> 137 of the patients were randomly assigned to the hypothermia group and 138 to the normothermia group. Unfortunately, 14 patients were discontinued early in the hypothermia group due to a variety of reasons including: death, arrhythmias, hemodynamic instability, cooling device technical problems, liver rupture, and assignment/cooling errors. All of the randomized patients were included in the analysis of mortality.<sup>5</sup>

To be eligible in the study the patient had to meet the following criteria: witnessed cardiac arrest, ventricular fibrillation or pulseless ventricular tachycardia as the initial cardiac rhythm, presumed cardiac origin of the arrest, age of 18 to 75 years, estimated interval of 5 to 15 minutes from the witness of patient's collapse to the first attempt at resuscitation by emergency medical personnel, and an interval of no more than 60 minutes from collapse to restoration of spontaneous circulation. The exclusion criteria were quite extensive. Patients were excluded if

they met any of the following criteria: tympanic-membrane temperature below 30°C on admission, a comatose state before the cardiac arrest due to the administration of anesthetic medications, pregnancy, response to verbal commands after the return of spontaneous circulation and before randomization, evidence of hypotension (mean arterial pressure, less than 60 mm Hg) for more than 30 minutes after the return of spontaneous circulation and before randomization, evidence of hypoxemia (arterial oxygen saturation, less than 85 percent) for more than 15 minutes after the return of spontaneous circulation and before randomization, a terminal illness that preceded the arrest, factors that made participation in follow-up unlikely, enrollment in another study, the occurrence of cardiac arrest after the arrival of emergency medical personnel, or a known preexisting coagulopathy.<sup>5</sup>

The patients in the study that were randomly assigned to the group receiving therapeutic hypothermia, had a median interval of ~105 minutes between the return of spontaneous circulation and the initiation of cooling. The median interval between the return of spontaneous circulation and when the target temperature of between 32°C and 34°C was reached was ~8 hours. Unfortunately, the target temperature could not be reached in 19 patients.<sup>5</sup> Some of the complications that arose from the study included bleeding, pneumonia, sepsis, pancreatitis, renal failure, hemodialysis, pulmonary edema, seizures, lethal or long-lasting arrhythmias, and pressure ulcers. Despite a variety of complications that arose, the proportion of patients with complications did not greatly differ from the hypothermic group and the normothermic group. Seventy-three percent of patients in the hypothermic group suffered from complications, while 70 percent of patients in the normothermic group reported complications. The greatest difference between the two groups was related to the complication of sepsis, although not statistically

significant, with incidences reported in: 7 percent normothermic group and, 13 percent in the hypothermic group.<sup>5</sup> The risk of bias assessment is discussed in Appendix C.

### *Neurological outcome*

Good neurological outcome within 6 months was found in 55 percent of the patients that received therapeutic hypothermia. In the normothermic group that did not receive therapeutic hypothermia 39 percent of the patients had a favorable neurologic outcome within 6 months. To be considered to have a favorable neurological outcome, this meant that the patient demonstrated a cerebral performance category of 1 (good recovery) or a cerebral performance category 2 (moderate disability). They calculated a risk ratio of 1.40 (1.08-1.81), with a 95 percent confidence interval. This is shown in Table 1. It was shown that 6 patients would have to be treated with therapeutic hypothermia to prevent 1 unfavorable neurological outcome.<sup>5</sup>

### *Morbidity and Mortality*

The therapeutic hypothermia group had a mortality rate of 56 percent within 6 months, while the normothermic group had a mortality rate of 76 percent. This showed that the patients that were cooled had a mortality rate that was 14 percent lower than the patients that were not in the hypothermic group. They calculated a risk ratio for the hypothermic group of 0.74 (0.58-0.95), with a 95 percent confidence interval. This is shown in Table 1. It was shown that 7 patients would have to be treated with therapeutic hypothermia to prevent 1 death. The study also reported that most of the patients that had unfavorable neurological outcome died within 6 months after being discharged from the hospital.<sup>5</sup>

Table 1: Neurologic Outcome and Mortality at Six Months

| Outcome            | Nonrmothermic<br>No./total no.<br>(%) | Hypothermic<br>No./total no. (%) | Risk Ratio<br>95% CI | P Value |
|--------------------|---------------------------------------|----------------------------------|----------------------|---------|
| Good neuro outcome | 54/137 (39%)                          | 75/136 (55%)                     | 1.40 (1.08-1.81)     | 0.009   |
| Death              | 76/138 (55%)                          | 56/137 (41%)                     | 0.74 (0.58-0.95)     | 0.02    |

Table 1: Hypothermia after Cardiac Arrest Study Group. (2002). Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*, 2002(346), 549-556.

Sunde et al.

Sunde et al. conducted a study where they designed a standardized treatment protocol for post resuscitation care following an out of hospital cardiac arrest. The treatment protocol that they designed included therapeutic hypothermia, percutaneous coronary intervention (PCI) only if indicated, and standardized goals for factors such as blood glucose, hemodynamics, ventilation, and handling of seizures.<sup>32</sup> Since their study was a multivariate system approach, the patients could not be randomized to either select patients to receive therapeutic hypothermia or not in the emergency department and intensive care unit. Instead they compared their results to patients that were admitted to Ullevål University Hospital in a recently published study from a preceding period that Sunde was a part of.<sup>33</sup>

In this study, all patients included sustained return of spontaneous circulation (ROSC) in the emergency department after suffering out of hospital cardiac arrest (OHCA) of cardiac etiology. To be included they also had to be admitted to the ICU in the two-year interval for which they were studying. This included 61 patients in total. These patients were then compared



to the patients in Sunde's previous study which also looked at patients in a two-year interval. This included 58 patients in total.

This article's major endpoints were neurological outcome at time of discharge and survival after 1 year. With their overall goal of improving patient survival and good quality of life due to a favorable neurological outcome they created a standardized post resuscitation treatment protocol (see Appendix D) that was implemented and distributed to all involved hospital personnel. Some of the complications that arose in both the earlier control study and this study included general complications, pneumonia, sepsis, severe arrhythmias, and seizures.<sup>32</sup> They did not include bleeding complications since it was not looked at in the control study. There were no significant complication differences found between the groups. The risk of bias assessment is discussed in Appendix C.

### *Neurological outcome*

Good neurological outcome= patient demonstrated a cerebral performance category of 1 (good recovery) or a cerebral performance category 2 (moderate disability). Good neurological outcome at time of discharge was found in all patients that survived and were discharged from the hospital of the intervention group that received therapeutic hypothermia. This included 34 patients out of the initial 34 patients initially admitted to the ICU that survived. In the control group for which patients did not receive therapeutic hypothermia there was good neurological outcome at the time of discharge for 15 patients out of the 18 patients that survived and were admitted to the ICU. The intervention group initially had 69 patients that were admitted to the ER but 8 patients were excluded due to death before ICU admission. 61 patients were admitted to the ICU and 34 patients survived. In the control or normothermic group they initially had 68

patients that were admitted to the ER but 10 patients were excluded due to death before ICU admission. 58 patients were admitted to the ICU and 18 patients survived.

### *Morbidity and Mortality*

In the therapeutic hypothermia group, there were 34 patients out of the initial 69 patients with a one-year survival after discharge. Although 34 patients were alive at discharge so this means that 100 percent of the patients that survived discharge were alive a year later. The intervention group had 56 percent of their patients with one-year survival. In the control group, there were 15 out of the initial 68 patients with a one-year survival after discharge. This normothermic group had 31 percent of their patients with one-year survival.<sup>32</sup> In conclusion all survivors with a favorable neurological outcome in both groups were still alive one year after discharge. The data shows that significantly more patients survived with a favorable outcome in the therapeutic hypothermia group than the control group or normothermic group.

### *Bernard et al.*

In a highly reviewed and cited study by Bernard et al, they enrolled patients over a 3-year period to look at patient outcomes. They examined patients suffering out of hospital cardiac arrest with VF (ventricular fibrillation) as their first cardiac rhythm who were comatose after they achieved ROSC (return of spontaneous circulation). This was a randomized controlled trial that was set up with the help of Melbourne EMS and 4 adjacent emergency departments and intensive care units. To be eligible to be included in the study the patient had to meet the following criteria: VF as an initial cardiac rhythm at the arrival of EMS, successful return of spontaneous circulation, persistent coma after the return of spontaneous circulation, and transfer to one of the four approved participating emergency departments. Patients were also excluded

from the study even if they met all of the initial criteria if there was no ICU bed available at the chosen hospital. A patient would initially be excluded if they met any of the following criteria: men with age less than 18 years old, females with age less than 50 years old (due to the possibility of pregnancy), cardiogenic shock (a systolic blood pressure of less than 90 mm Hg despite epinephrine infusion), or possible causes of coma other than cardiac arrest (such as drug overdose, head trauma, or cerebrovascular accident).<sup>4</sup>

Patients were randomly assigned to either the normothermic group (control), or the therapeutic hypothermia group (treatment). After meeting inclusion criteria, there were initially 84 patients selected for this study. Seven patients were excluded from the study due to either being transferred to another hospital that was not participating in the study or due to the next of kin refusing consent for data collection. Of the remaining 77 patients that met inclusion criteria, 34 patients were assigned to the control/normothermic group, and 43 patients were assigned to the treatment/therapeutic hypothermic group. If patients were assigned to the treatment group EMS would initiate the cooling by placing ice packs around the head, neck, torso, and limbs. If patients were assigned to the control group EMS would provide standard therapy without therapeutic hypothermia. After initial stabilization of the patient in the emergency department, the patient was admitted to the ICU and a pulmonary artery catheter was inserted. The target core temperature for the treatment group was 33°C which needed to be maintained over a 24-hour period.<sup>4</sup> After the 24-hour cooling period the patients underwent a 8 hours of passive rewarming. After rewarming the treatment group patients received standard intensive care unit protocols which mirrored those patients in the control group. The risk of bias assessment is discussed in Appendix C.

### *Neurological outcome*

Examining patients in the treatment group, 21 of the 43 patients that underwent therapeutic hypothermia had good neurological outcome at the time of discharge. The control group had 9 patients out of the 34 that were discharged with good neurological outcomes. In the treatment group out of the 43 patients, 15 patients had normal or minimal disability (good ADLs/able to take care of themselves) and were discharged directly to home. 6 patients had moderate disability and were discharged to a rehab facility. In the control group, out of the 34 patients, 7 patients had normal or minimal disability (good ADLs/able to take care of themselves) and were discharged directly to home. Two patients had moderate disability and were discharged to a rehab facility, 1 patient had severe disability (awake but completely dependent) and were discharged to a long-term care facility, and 1 patient was unconscious with a severe disability and discharged to a long-term care facility. Forty-nine percent of the therapeutic hypothermic patients had good neurological outcomes in comparison to 26 percent of the normothermic patients.<sup>4</sup>

### *Morbidity and Mortality*

Examining patients in the treatment group, 21 patients survived to be discharged from the hospital that underwent therapeutic hypothermia. In the control group, 11 patients survived. Some factors that were found to have affected outcome were age, time from collapse to return of spontaneous circulation, and CPR administered by a bystander. It was found that for each 2-year increase in age there was a 9 percent decrease in likelihood of a good outcome or survival. An odds ratio was calculated: 0.91; 95 percent confidence interval, 0.84 to 0.98; P=0.014.<sup>4</sup> Consequently, for each additional 1.5 minutes from the time of collapse to the time of return of spontaneous circulation there was a 14 percent decrease in the likelihood of a good outcome or

survival. An odds ratio was calculated: 0.86; 95 percent confidence interval, 0.78 to 0.94; P=0.001. CPR administered by a bystander was found to be associated with a nonsignificant improvement in outcome as well. An adjusted analysis for base-line differences in age, time of collapse to time of return of spontaneous circulation, the odds ratio for good outcome in the treatment/ therapeutic hypothermia group compared to the control/ normothermia group was 5.25.<sup>4</sup> In the data for mortality the patients that underwent therapeutic hypothermia totaled at 51 percent and the patients that were not cooled totaled at 68% for death. This showed that the difference in mortality rates between the treatment group and the normothermia group did not reach statistical significance (P=0.145).<sup>4</sup>

## **Discussion**

Limited randomized clinical trials have been conducted to study the use of therapeutic hypothermia in the setting of cardiac arrest patients. The studies that have been performed look to determine effectiveness in reducing neurological deficits and mortality. The use of therapeutic hypothermia is not yet the standard of care among health care providers in the United States. Although, through this clinical review it has shown great promise in displaying the increased chance of survival and good neurological outcome of cardiac arrest patients that have underwent therapeutic hypothermia. Granted there are limitations of these studies along with their strengths.

The results of the Holzer at al. study showed that for the patients in their treatment group which received therapeutic hypothermia for the 24 hours did show to have an increased chance of survival as well as better neurological outcomes. These results were compared to the patients that did not receive any cooling and were treated with standard life support protocols. There also wasn't a great significant difference in rate of complications between the treatment and control group. The overall benefit of therapeutic hypothermia surpassed the possible adverse effects of

receiving the therapy. While there are many strengths of this study that is not to say that it was without limitations.

A limitation of this study was that the health care providers taking care of the patients in the study could not be blinded to whether the patient was chosen to be in the control or the treatment group. This is to be expected considering the nature of this study. Although a patient may be randomly assigned to the treatment group, the health care team could not be blinded to their treatment due to the fact that after cooling was initiated it would need to be continued in the ICU as well as the rewarming phase. Another limitation of this study was the small sample size. Due to the importance of eligibility criteria it was found that only 8 percent of all patients that were initially assessed for inclusion were actually included in the study.<sup>5</sup>

The results of the Sunde et al. study showed when using their standardized post resuscitation care treatment protocol that included therapeutic hypothermia patient outcomes improved. The authors were looking at survival to hospital discharge with favorable neurological outcomes and well as one-year survival rates. Their survival rates were high in comparison to the survival rates of the previous results reported. The reported a 56 percent<sup>32</sup> survival rate at hospital discharge with good neurological outcomes and a one-year survival among the patients that had out of hospital cardiac arrest that were admitted to the ICU. While their findings are very encouraging for the benefits of implementing therapeutic hypothermia in the standard of care for these patients, limitations were not absent.

One limitation that was found was patients that were included in the treatment group phase of the study to receive therapeutic hypothermia were found to be younger than the patients in the control phase. It was reported that the younger age could be a huge factor associated with the improved survival rates and improved neurological outcome. Although, it was calculated that

the mean age for both groups was below 70 years of age.<sup>32</sup> Another limitation was the patients in the study could not be randomized for this study. If eligible patients were admitted to the participating hospitals during the treatment phases when the new protocol had been initiated they would receive therapeutic hypothermia. Since these participating hospitals had been trained on the new protocol and may have had increased enthusiasm for this new treatment plan it was thought that this could influence good patient outcomes. While staff enthusiasm cannot be controlled this has to be included as a possible limitation of the study.

The results of the Bernard et al. study showed that not only did the patients in the treatment group that received therapeutic hypothermia have better outcomes than the patients in the control group but their results also suggested that the use of therapeutic hypothermia did not seem to show any association to significant adverse effects.<sup>4</sup> This evidence of no increased clinically significant adverse reactions is very important information to gain from the study. Since the use of therapeutic hypothermia in cardiac arrest is not entirely implemented in the United States yet, it is important to look at the evidence that shows it does not have any increased harm to patients. It is important to note that their study looked at cooling for 12 hours but nothing beyond that time frame. While there are many strengths of this study and it was a major strength to also show no increase in adverse effects, like other studies reviewed this study was not without limitations.

Much like other studies in the treatment of cardiac arrest patients, a limitation of this study was being unable to blind the health care providers from whether a patient was in the treatment or control group. Another limitation of the study was the out of hospital randomization of patients in the designated emergency medical systems.<sup>4</sup> They found this to be very challenging and their solution to this was to use the method of odd or even days to attempt to randomize the

patients into either the treatment group that received therapeutic hypothermia or the control group which received standard protocol management. Despite their studies limitations, they concluded that induced hypothermia does improve patient outcomes in those patients that are comatose after resuscitation from out of hospital cardiac arrest.<sup>4</sup>

## **Conclusion**

While patients resuscitated from cardiac arrest remain at high risk of neurologic deficits or death, huge strides are starting to be implemented to try to improve these outcomes.

Therapeutic hypothermia has been demonstrated to help improve survival rates and improve better neurological outcomes. Not only has it been shown to improve patient outcomes, it also has not been shown to cause increased adverse effects. With the use of high quality critical care during cardiac arrest and after the return of spontaneous circulation, this care based on the most recent evidence based results will improve patient outcomes. Although more studies are needed to make the use of therapeutic hypothermia evidence stronger. The optimal core temperature of cooling to result in the best possible patient outcome needs further studies and evaluations.

Along with looking into the optimal temperature, the duration of the cooling needs to also be studied more. There is not enough evidence on different durations of therapeutic hypothermia to make an evidence based decision on duration of cooling prior to the rewarming phase.

Another area of evidence that needs further studies is patients that suffer in hospital arrest and patients that suffer cardiac arrest that is not due to reasons of cardiac etiology. After more studies show good evidence for the use of therapeutic hypothermia in adults the next population that needs to be studied is the effect on children. Although more research needs to be done to make therapeutic hypothermia implemented across all cardiac arrest patients, current research has



suggested that therapeutic hypothermia implantation in cardiac arrest protocols can prove to be extremely beneficial in improving patient survival rates and neurological outcomes.

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## Appendix A

### PubMed

“hypothermia, induced; patients; heart arrest; mortality, heart arrest; hypothermia, induced; patients, heart arrest; resuscitation; cardiovascular system”

### Cochrane Review Database

“Induced hypothermia, Hypothermia, Induced, Therapeutic Hypothermia; Hypothermia, Therapeutic; Induced Hypothermia; Moderate Hypothermia, Induced; Induced Moderate Hypothermia; Induced Moderate Hypothermias; Moderate Hypothermias, Induced; Mild Hypothermia, Induced; Induced Mild Hypothermia; Induced Mild Hypothermias; Mild Hypothermias, Induced, Heart Arrest, Induced, Induced Heart Arrest; Cardiac Arrest, Induced; Induced Cardiac Arrest, Hyperthermia, Induced, Induced Hyperthermia; Therapeutic Hyperthermia; Hyperthermia, Therapeutic, Heart Arrest, Arrest, Heart; Cardiac Arrest; Arrest, Cardiac; Cardiopulmonary Arrest; Arrest, Cardiopulmonary, Neurologic Manifestations, Neurological Manifestations; Manifestations, Neurological; Manifestation, Neurological; Neurological Manifestation; Neurologic Deficits; Deficit, Neurologic; Deficits, Neurologic; Neurologic Deficit; Focal Neurologic Deficits; Deficit, Focal Neurologic; Deficits, Focal Neurologic; Focal Neurologic Deficit; Neurologic Deficit, Focal; Neurologic Deficits, Focal Death, Sudden, Cardiac, Sudden Cardiac Death; Cardiac Death, Sudden; Death, Sudden Cardiac; Cardiac Sudden Death; Death, Cardiac Sudden; Sudden Death, Cardiac; Sudden Cardiac Arrest; Arrest, Sudden Cardiac; Cardiac Arrests, Sudden; Cardiac Arrest, Sudden. Cardiopulmonary Resuscitation, Resuscitation, Cardiopulmonary; Cardio-Pulmonary Resuscitation; Cardio Pulmonary Resuscitation; Resuscitation, Cardio-Pulmonary; Mouth-to-Mouth Resuscitation; Mouth to Mouth Resuscitation; Mouth-to-Mouth Resuscitations; Resuscitation, Mouth-to-Mouth; Resuscitations, Mouth-to-Mouth; Basic Cardiac Life Support; Life Support, Basic Cardiac.”

### Embase

('induced hypothermia'/exp OR 'induced hypothermia') AND therapeutic AND ('hypothermia'/exp OR hypothermia) AND ('cardiovascular'/exp OR cardiovascular) AND ('resuscitation'/exp OR resuscitation) AND cardiac AND ('arrest'/exp OR arrest) AND deficits AND neurological AND ('outcome'/exp OR outcome) AND ('mortality'/exp OR mortality)

### Trip database

(Cardiac arrest patients)(therapeutic hypothermia)(standard icu protocol)(reduced mortality)

## Appendix B

Table 1: Potential mechanisms of action, risks and changes with hypothermia

| Mechanism/change                        | Explanation                                                                                                                                                                                                                                                                                                                                                                                                                                             | When/treatment                                                                                                                                                                                           |
|-----------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Metabolic changes                       | ↓ Cerebral metabolic rate by 6–8% per 1° C<br>↓ in core T → ↓ in O <sub>2</sub> consumption and CO <sub>2</sub> production. Excessive ↑ in CO <sub>2</sub> can ↑ cerebral edema, and excessive ↓ in CO <sub>2</sub> can ↑ ischemia.                                                                                                                                                                                                                     | Acute in induction/frequent BGs and ventilator setting adjustments to maintain normocapnia, slow rewarming                                                                                               |
| Electrolytes                            | Cooling → ↑ renal tubular dysfunction → ↑ electrolyte excretion. Cooling → intracellular electrolyte shift → ↓ K <sup>+</sup> , Mg <sup>2+</sup> , PO <sub>4</sub> <sup>-</sup> → ↑ risk for arrhythmias. Rewarming → intracellular K <sup>+</sup> released → hyperkalemia                                                                                                                                                                              | Keep electrolytes in high-normal range, slow rewarming (0.25° C/h post cardiac arrest, slower for severe TBI)                                                                                            |
| Apoptosis and mitochondrial dysfunction | Post IR injury mitochondrial dysfunction (mitochondria = cells' energy source), disturbed energy metabolism in cell, and caspase enzymes can → apoptosis<br>Hypothermia blocks apoptotic pathway early by: ↓ caspase enzyme activation, ↓ mitochondrial dysfunction, ↓ excitatory neurotransmitters, and modifying intracellular ion concentrations                                                                                                     | Starts late in post-reperfusion phase, can continue for 72 h or more → In theory wide window for treatment                                                                                               |
| Ion pumps and Neuro excitotoxicity      | IR injury → ↓ brain O <sub>2</sub> supply → quick ↓ in ATP and phosphocreatine levels. This initiates a complex cascade of events involving excessive calcium influx into brain cells, excessive glutamate receptor activation and neuronal hyperexcitability (excitotoxic cascade) which can lead to further injury and cell death even after reperfusion and normalization of glutamate levels. Hypothermia can ↓ damage from neuroexcitatory cascade | Disturbed Ca <sup>2+</sup> homeostasis begins minutes after injury and may continue for many hours → may be treatable. Animal studies suggest to initiate treatment early in the neuroexcitatory cascade |

|                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                        |
|-------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
| Inflammation                              | <p>Brain injury → Proinflammatory mediators released ++ → leukocytes drawn across BBB → ↑ inflammatory cells in brain → passage of neutrophils, phagocytic monocytes and macrophages into brain → phagocytic action and toxin production → further injury by stimulating further immune reactions. Some of this is neuroprotective, but if continual and excessive → ↑ injury. Hypothermia → ↑ ischemia-induced inflammatory and immune reactions, ↓ NO production (key agent in developing brain injury post-ischemia), ↓ neutrophil/macrophage function and ↓ WCC</p> | <p>Begins ~ 1 h after ischemia and persists for up to 5 days, suggesting a therapeutic window for these mechanisms</p> |
| Free radicals                             | <p>IR injury → ↑ free radicals that oxidize and damage cell components → brain's defense mechanisms likely overwhelmed. Hypothermia → ↑ release of free radicals → endogenous antioxidants more able to meet demand</p>                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                        |
| Blood-brain Barrier/vascular permeability | <p>Traumatic/IR injury can disrupt BBB → brain edema. Mild hypothermia ↓ BBB disruptions and vascular permeability after IR injury → ↓ brain edema. Brain edema and ICH play key role in neurological injury in severe TBI and ischemic stroke, and ICH is a marker for neurological injury → plausible that therapies to ↓ ICP may also improve neurological outcome Hypothermia has been used to ↓ ICP in neurological injury including TBI, ischemic stroke, meningitis and SAH</p>                                                                                  | <p>Brain edema peaks after 24–72 h → this mechanism could offer a wide therapeutic window</p>                          |
| Acidosis and cellular Metabolism          | <p>Ion-pump failure, mitochondrial dysfunction, cellular hyperactivity and ↓ in cell membrane integrity → intracellular acidosis → ↑ harmful processes. Hypothermia can alleviate this, may improve brain glucose metabolism and when induced early enhances speed of metabolic recovery → ↓ toxic metabolite accumulation → ↓ acidosis</p>                                                                                                                                                                                                                             |                                                                                                                        |

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|                      |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                            |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------|
| Brain temperature    | Brain temperature slightly higher than core temperature and can $\uparrow$ 0.1–2.0 °C post-injury (more with fever). Injured areas are hotter than uninjured areas due to cellular hyperactivity. Dissipation of heat by lymph/venous drainage is hampered by local brain edema (cerebral thermopooling) $\rightarrow$ $\uparrow$ hyperthermia related injury<br>Hypothermia in brain-injured patients may $\downarrow$ potential hyperthermia-related adverse effects                                                                                                                                                                                                          |                            |
| Coagulation          | Activation of coagulation seems to be involved in developing IR injury. Its reversal, whilst targeting other mechanisms, could improve outcomes<br>Hypothermia induces anticoagulatory effects: mild platelet dysfunction at 33–35° C; can affect clotting factors at $\leq$ 33° C, and a potential reduction in platelet count, may influence synthesis and kinetics of clotting enzymes and plasminogen activator inhibitors. This anticoagulation effect could provide protection, but not investigated. Cooling to 35° C – no effect on coagulation                                                                                                                         | Assess risk versus benefit |
| Vasoactive mediators | Secretion of vasoactive substances endothelin and TxA <sub>2</sub> (vasoconstrictors) and prostaglandin I <sub>2</sub> (vasodilator) is affected by hypothermia. TxA <sub>2</sub> and prostaglandin I <sub>2</sub> regulate cerebral blood flow. Their balanced production is required to maintain homeostasis. If disrupted by ischemia/trauma TxA <sub>2</sub> production increases which can $\rightarrow$ vasoconstriction and hypoperfusion in injured brain. Hypothermia $\rightarrow$ $\downarrow$ imbalance, but regulation of cerebral perfusion is complex and influenced by cerebral autoregulation and patient management. Influence of hypothermia on secretion of |                            |

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|                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                             |
|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                   | vasoactive mediator in brain-injured patients requires further investigation                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                             |
| Improved tolerance of ischemia (pre-conditioning) | In animal models ‘preconditioning’ with hypothermia improves tolerance for ischemia. As brain injury is frequently complicated by ischemic events after the initial insult, this could be a valuable neuroprotective mechanism                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                             |
| Reduction of epileptic activity                   | Epileptic activity without signs and symptoms (non-convulsive) occurs frequently in brain-injured patients and if it occurs in the acute phase of brain injury the combined effect is destructive. Evidence indicates that hypothermia # epileptic activity; another mechanism through which it could provide neuroprotection                                                                                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                             |
| Early gene activation                             | Hypothermia → ↑ early gene activation which is part of the protective cellular stress response to injury and → ↑ production of cold shock proteins that can be cryoprotective in the presence of ischemic and traumatic injury                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                             |
| Shivering                                         | ↑ metabolic rate, O <sub>2</sub> consumption, work of breathing, heart rate and myocardial O <sub>2</sub> consumption                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                             |
| Insulin sensitivity and secretion                 | ↓ with cooling → hyperglycemia or ↑ insulin required                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 34–35° C/opiates, sedation, paralysis if required, other agents                                                                                                                                                                             |
| Cardiovascular/hemodynamic effects                | Mild hypothermia: In euvoletic, adequately sedated pts ↓ HR, ↑ myocardial contractility, → or slightly ↑ BP, ↓ CO. ↓ metabolic rate matches or exceeds ↓ CO → balance maintained Initial transient ↑ HR due to ↑ venous return (↑ if sedation inadequate, shivering untreated) Stabilizes cell membranes → ↓ risk of arrhythmias, ↑ successful defibrillation. Deep hypothermia: (≤30°C) ↓ contractility, ↑ risk for arrhythmias, ↓ successful defibrillation, ↓ response to antiarrhythmics Cold diuresis: the result of ↑ venous return (due to peripheral vessel constriction), atrial natriuretic peptide activation, ↓ ADH and renal ADH receptor | Induction and rewarming/frequent BGL checks and insulin adjustments, slow rewarming<br><br>Sedate adequately<br><br>Allow ↓ HR 45–55 at 33°C (artificial ↑ HR → ↓ contractility)<br><br>Avoid and correct hypovolemia. Avoid stimulating HR |

|                    |                                                                                                                                                                                                                                                                                                                                              |                                                                                                                               |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|
|                    | levels, and tubular dysfunction → hypovolemia.                                                                                                                                                                                                                                                                                               |                                                                                                                               |
| Coronary perfusion | ↓ metabolic rate and HR protects ischemic myocardium, ↑ coronary vasodilation and perfusion. But in severely atherosclerosed coronaries, vasoconstriction can occur → may affect result of hypothermia<br><br>Shivering can ↑ myocardial O <sub>2</sub> consumption                                                                          |                                                                                                                               |
| Drug clearance     | Most enzyme-based reactions slowed → ↓ drug clearance by liver. Tubular dysfunction may also affect clearance, and response to some drugs alters e.g. ↓ effect of adrenaline and noradrenaline. BUT most drug levels ↑ → ↑strength and duration of effect                                                                                    | Sedate adequately-prevent shivering<br><br>Modify doses of certain drugs                                                      |
| Infection          | ↓ leukocyte migration and phagocytosis, ↓ proinflammatory cytokine synthesis → ↓ proinflammatory response → may protect against damaging neuroinflammation, but ↑ risk for infection (↑ risk with ↑ duration) ↑ risk for wound infection due to cutaneous vasoconstriction<br><br>Signs of infection: e.g. fever and possibly CRP and WCC ↓. | Low threshold for antibiotic treatment may be advisable<br><br>↑ in ‘cooling power’ required may indicate fever and infection |
| Gut                | ↓ gut function and gastric emptying, ↓ metabolic rate                                                                                                                                                                                                                                                                                        | Reduce feeding target in maintenance phase                                                                                    |

*Table 1: Moore, E. M., Nichol, A. D., Bernard, S. A., & Bellomo, R. (2011). Therapeutic hypothermia: benefits, mechanisms and potential clinical applications in neurological, cardiac and kidney injury. Injury, 42(9), 843-854*

↓: decrease (d), →: leads to, ↑: increase (d), T: temperature, O<sub>2</sub>: oxygen, CO<sub>2</sub>: carbon dioxide, BGs: blood gases, IR: ischemia reperfusion, ATP: adenosine triphosphate, Ca<sup>2+</sup>: calcium, BBB: blood-brain barrier, NO: nitric-oxide, WCC: white cell count, ICH: intracranial hypertension, ICP: intracranial pressure, TxA<sub>2</sub>: thromboxane A<sub>2</sub>, °C: degrees Celsius, BGL: blood glucose level, K<sup>+</sup>: potassium, Mg<sup>2+</sup>: magnesium, PO<sub>4</sub><sup>-</sup>: phosphate, TBI: traumatic brain injury, HR: heart rate, BP: blood pressure, CO: cardiac output, ADH: antidiuretic hormone, CRP: C-reactive protein.

## Appendix C

The Cochrane Risk of Bias Tool was my quality evaluation choice.

|                         | <b>Holzer at al.</b>                                                                                                                                                                                                                                                                                                                  | <b>Sunde at al.</b>                                                                                                                                                                              | <b>Bernard at al.</b>                                                                                                                                                                                            |
|-------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Selection bias</b>   | Treatment assignments were randomly generated by computer in blocks of 10                                                                                                                                                                                                                                                             | The patients in this study could not be randomized. They were either in the control group (1 <sup>st</sup> phase), or the treatment group (2 <sup>nd</sup> phase)                                | The patients were randomized using the method of odd and even days. Despite the potential for bias in randomization, it appears that the two patient groups were comparable.                                     |
| <b>Performance bias</b> | Patient care providers involved in the care of patients during the first 48 hours after cardiac arrest could not be blinded with respect to treatment assignments. Physicians responsible for assessing the neurologic outcome within the first six months after the arrest were however blinded of the patients treatment assignment | Treatment assignment could not be blinded. Medical providers were not blinded to patient treatment plans. Possible bias due to increased awareness and enthusiasm for the new treatment approach | Treatment assignment was not blinded. It was not feasible to blind medical providers to the patients' treatment group assignments. There is a possibility that bias could have affected patient care and outcome |
| <b>Detection bias</b>   | Physicians responsible for assessing the neurologic outcome within the first six months after the arrest were blinded of the patients treatment assignment                                                                                                                                                                            | Physicians responsible of patient care were not blinded of their patients outcome, however they were blinded to the patient outcomes in the control phase                                        | Patient was discharged by a rehab center physicians who was unaware of initial treatment protocols and were blinded to the outcome due to being unaware of group selection                                       |

|                       |                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                                                                                                                                                                                                                                 |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Attrition bias</b> | Minimal incomplete outcome data reported                                                                                                                                                                                                                                   | Minimal incomplete outcome data reported                                                                                                                                                                                                                                                                                                                                                                                                                           | Minimal incomplete outcome data reported                                                                                                                                                                                                        |
| <b>Reporting bias</b> | No evidence of selective outcome reporting found                                                                                                                                                                                                                           | No evidence of selective outcome reporting found                                                                                                                                                                                                                                                                                                                                                                                                                   | No evidence of selective outcome reporting found                                                                                                                                                                                                |
| <b>Other</b>          | The requirement of informed consent was waived in accordance to ethical standards and local guidelines. The patient's family was informed about the trial, and the studies protocol stated that if there were any protests, the patient would be withdrawn from the study. | Written consent to be included in this study could not be obtained from patient. Written informed consent for participation in this study was sought from the next of kin as soon as possible after the arrival of the patient at the hospital. Also there could be possible bias due to conflict of interest since Dr. Sunde received research grants from Laerdal Foundation for Acute Medicine and Professor Steen is a member of the Board of Laerdal Medical. | Written consent to be included in this study could not be obtained from patient. Written informed consent for participation in this study was sought from the next of kin as soon as possible after the arrival of the patient at the hospital. |

## Appendix D

### Standardized post resuscitation treatment protocol

In hospital standardized treatment plan after ROSC at Ullevål University Hospital Goal: to reduce the vital organ injuries (brain, heart), through:

1. Initial optimizing hemodynamics and oxygenation
2. (a) Treat the cause of arrest; reperfusion (PCI) after STEMI and  
(b) Therapeutic hypothermia (33 °C in comatose patients for 24 h) Start as early as possible after decision making in the ED Initially 1-3 l of ice-cold 0.9% NaCl i.v. together with ice bags  
Endovascular cooling/external cooling for maintenance after arrival at the ICU
3. A standardized treatment protocol for the following days

| 3.1. Factor             | Goal                                               | Strategy                                                                                                                                        |
|-------------------------|----------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
| Reperfusion             | Reperfusion                                        | PCI in STEMI                                                                                                                                    |
| Blood pressure          | MAP > 65—70 mmHg                                   | Volume, vasopressors, inotropic agents, IABP                                                                                                    |
| Central venous pressure | 8—12 mmHg                                          | Volume, glyceryl trinitrate, diuretics                                                                                                          |
| ECG, rate/ischemia      | 60—100/min                                         | Volume, sedation, glyceryl trinitrate, beta-blocker (normally not indicated when using therapeutic hypothermia because of relative bradycardia) |
| Temperature             | 33 °C for 24 h                                     | Initially ice cold (4 °C) NaCl 0.9% i.v. and icepacks, then internal/external cooling device                                                    |
| Ventilator              | SpO <sub>2</sub> 95—98<br>pCO <sub>2</sub> 5—6 kPa | Respiratory control, FiO <sub>2</sub> , PEEP (NB! Avoid hyperventilation)                                                                       |
| Blood glucose           | 5—8 mmol/l                                         | Actrapid-infusion (NB! Avoid hypoglycemia/hypokalemia)                                                                                          |
| Electrolytes            | Normal values                                      | Replacement/specific treatment                                                                                                                  |
| Hemoglobin              | >9—10 g/dl                                         | Transfusion if necessary                                                                                                                        |
| Diuresis                | >1 ml/kg/h                                         | Volume, diuretics or pressors                                                                                                                   |
| Buffers                 | pH > 7.1, BE > -10                                 | When indicated, trometamol 125—250 ml i.v.                                                                                                      |
| Seizures                | Prevent/treat seizures                             | Increase sedation, or specific anticonvulsive medication<br>EEG when indicated (early contact with a neurologist)                               |

### 3.2. Sedation

Fentanyl and propofol (paralysis when indicated with cisatracurium/pancuronium)

### 3.3. Monitoring

Arterial catheter O<sub>2</sub>-saturation  
Continuous ECG  
Central venous line with central venous pressure  
Temperature (bladder)  
Arterial blood gases (pH, BE, pCO<sub>2</sub>, pO<sub>2</sub>)  
Blood glucose and electrolytes  
Echocardiography, chest X-ray  
EEG and SEP

### 3.4. Vasopressors/inotropic agents

First choice: dopamine  
(2—10 µg/kg/min)

If tachycardia, check volume status,  
or change to noradrenaline  
(norepinephrine)  
(0.02—0.3 µg/kg/min)

If pump failure/cardiogenic shock

IABP  
Dobutamine (2—10 µg/kg/min) and if necessary adrenaline  
(epinephrine)(0.02—0.3 µg/kg/min)  
(levosimendan as last resort)

### 3.5. Awakening protocol/respirator weaning

After 24 h of cooling, patients should be slowly rewarmed (0.5 °C/h). Sedation may be stopped after the body temperature has reached 35.5 °C. Extubation using normal indications. Avoid long term ventilator treatment (if no complications are present)

Sunde, K., Pytte, M., Jacobsen, D., Mangschau, A., Jensen, L. P., Smedsrud, C., ... & Steen, P. A. (2007). Implementation of a standardised treatment protocol for post resuscitation care after out-of-hospital cardiac arrest. *Resuscitation*, 73(1), 29-39.