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# The benefits of therapeutic hypothermia in post-cardiac arrest victims

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BOSTON UNIVERSITY  
SCHOOL OF MEDICINE

Thesis

**THE BENEFITS OF THERAPEUTIC HYPOTHERMIA IN POST-CARDIAC  
ARREST VICTIMS**

by

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B.S., University of California, Los Angeles, 2015

Submitted in partial fulfillment of the  
requirements for the degree of  
Master of Science

2016

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## **DEDICATION**

I would like to dedicate this work to Sarah Sourialle, Timmy Zaki, and Christine  
Aboseif.

## **ACKNOWLEDGMENTS**

Thank you to Dr. Uthara Mohan and Dr. Isabel Dominguez.

# **THE BENEFITS OF THERAPEUTIC HYPOTHERMIA IN POST-CARDIAC**

## **ARREST VICTIMS**

**MIRIAM FAHIM**

### **ABSTRACT**

Cardiac arrest is a phenomenon in which a sudden loss of heart function leads to cessation of blood delivery to the rest of the body. It is one of the leading causes of natural death in the United States. Because its onset cannot be predicted, therapy for post-cardiac arrest victims focuses on management of moderate organ failure and neurological injury. The mortality rate of out-of-hospital cardiac arrest victims remains about 90%, but currently, there are several management techniques that reduce the incidence of sudden cardiac death. My goal is to argue that despite some of the negative effects of therapeutic hypothermia, it holds the most promise to sustain organ and neurological recovery.

This study focuses on evaluating the pathophysiology of post-cardiac arrest syndrome, and referencing literature that documents the reversal techniques of therapeutic hypothermia. Despite the side effects and unwanted consequences that come with targeted temperature management, there is an imbalance between the benefits and consequences, resulting in enhanced recovery when this technique is carefully administered shortly after the cardiac arrest episode.

## TABLE OF CONTENTS

TITLE.....	i
COPYRIGHT PAGE.....	ii
READER APPROVAL PAGE.....	iii
DEDICATION (optional) .....	iv
ACKNOWLEDGMENTS (optional) .....	v
ABSTRACT .....	vi
TABLE OF CONTENTS .....	vii
LIST OF TABLES.....	ix
LIST OF FIGURES.....	x
LIST OF ABBREVIATIONS .....	xi
INTRODUCTION .....	1
Implications of Cardiac Arrest.....	1
Diagnosis and Mechanisms of Cardiac Arrest.....	2
Resuscitation.....	8
Pathophysiology of Post-Cardiac Arrest Syndrome.....	10
Treatments and Management of Post-Cardiac Arrest.....	21
SPECIFIC AIMS.....	28
PUBLISHED STUDIES .....	29

DISCUSSION AND CONCLUSION.....	44
APPENDIX.....	47
REFERENCES.....	48
CURRICULUM VITAE .....	54

## LIST OF TABLES

Table	Title	Page
1	CPC and mRS comparison of TTM 36°C v. 36°C	41

## LIST OF FIGURES

Figure	Title	Page
1	Normal ECG	3
2	ECG of Ventricular Fibrillation	4
3	SA Node and the Heart's Electrical Impulses	6
4	Normal v. Long QT Syndrome	7
5	Ca <sup>2+</sup> Entry into Cells	12
6	Consequences of impaired blood flow	13
7	Blood Coagulation in vivo	16
8	APC Concentration change after resuscitation	18
9	The Fibrinolytic Cascade	24
10	TH improves survival after cardiac arrest	30
11	Long term outcomes of TTM	30
12	Modulation of Apoptosis by Hypothermia	32
13	Leukocyte count: TTM v. No TTM	33
14	Cytokine and Chemokine profiles of patients during cooling (0-72 hours) and rewarming phases (72-114 hours)	34
15	Hemoglobin-oxygen affinity increases under hypothermic conditions	38
16	Probability of Survival for TTM 33°C v. 36°C	42

## LIST OF ABBREVIATIONS

APC.....	Activated Protein C
BBB.....	Blood Brain Barrier
CPC.....	Cerebral Performance Category
CPR.....	Cardiopulmonary Resuscitation
ECG.....	Electrocardiogram
GST.....	Glutathione S-transferase
ICD.....	Implantable Cardioventricular Defibrillator
IL-1.....	Interleukin-1
IL-6.....	Interleukin-6
MCP-1.....	Monocyte Chemoattractant Protein-1
MOF.....	Multiple Organ Failure
NMDA.....	N-methyl-D-Aspartate
OHCA.....	Out of Hospital Cardiac Arrest
ROS.....	Reactive Oxygen Species
ROSC.....	Return of Spontaneous Circulation
TH.....	Therapeutic Hypothermia
TNF.....	Tumor Necrosis Factor
TTM.....	Targeted Temperature Management

## INTRODUCTION

Cardiac arrest is among the leading causes of natural death in the U.S. It is responsible for approximately half of all heart disease related deaths, and nearly 325,000 adults deaths in the U.S. each year. Sudden death due to cardiac arrest is typically the result of organ failure or neurological damage, therefore cardiac-arrest management following successful resuscitation focuses on limiting the progression of these consequences.

In the first part of this thesis, we will describe the implications of cardiac arrest, its mechanisms, and its consequences. We will discuss the pathophysiology of post-cardiac arrest syndrome, and various treatment modalities. Second, we will explore the history and the clinical relevance of targeted temperature management (TTM), our choice of treatment modality, and review previous studies documenting its therapeutic uses. Finally, we will assess the efficacy of therapeutic hypothermia in reversing the effects of post-cardiac arrest syndrome following successful resuscitation efforts.

### **Implications of Cardiac Arrest**

Cardiac arrest is defined as an impaired cardiac output and failure of the heart to adequately pump blood to the rest of the body, leaving vital organs impaired of oxygen. During cardiac arrest, blood circulation ceases and oxygen delivery to vital organs is reduced. This has the greatest effect on the brain, and the victim immediately loses consciousness as their breathing shallows. The

longer cardiac arrest remains untreated, the more permanent the brain damage that results, and the more severe the degree of sepsis and vital organ failure. Approximately 95% of patients that suffer from out-of-hospital cardiac arrest die from sudden cardiac death either because resuscitation efforts such as CPR and were unavailable at the time of cardiac arrest, or due to ineffective post-cardiac management following successful resuscitation.

### **Diagnosis and Mechanisms of Cardiac Arrest**

Arrhythmias, hypertrophic cardiomyopathy, structural heart disease, and undiagnosed coronary artery disease lead to ventricular fibrillation, and are among the leading causes of cardiac arrest. If the victim is successfully resuscitated by cardiopulmonary resuscitation and use of a defibrillator, the resulting extent of damage in victims is dependent on the amount of time the patient goes untreated i.e., the amount of time that vital organs are deprived of oxygen. Immediate consequences range from shock, high fever, and biological disorders, to severe brain injury and poor neurological prognosis.

Fatigue, syncope, chest pain, and palpitations are among the many symptoms that may indicate and precede cardiac arrest. Because the onset of cardiac arrest cannot be predicted, diagnostic tests are instead performed to assess patients at risk for cardiac arrest, or following the attack to investigate the underlying cause and to help prevent future episodes. Investigations performed

to diagnose cardiac arrest include coronary catheterization, electrocardiograms (ECG), and echocardiogram.

Ventricular fibrillation (VF) is the most commonly identified arrhythmia, and can result in cardiac arrest. Ventricular fibrillation is a cardiac rhythm disturbance in which the ventricles contract in a rapid unsynchronized pattern. These erratic electrical impulses cause the ventricles to quiver, rather than pump blood to the rest of the body. Figures 1 and 2 show ECG examples of normal and atrial fibrillation.

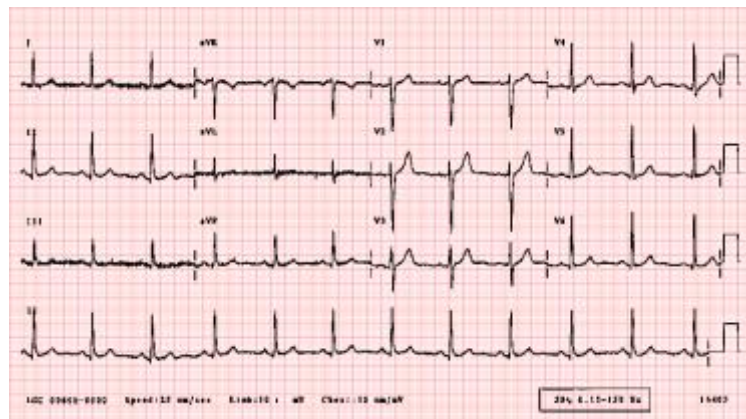


Figure 1 – Normal ECG

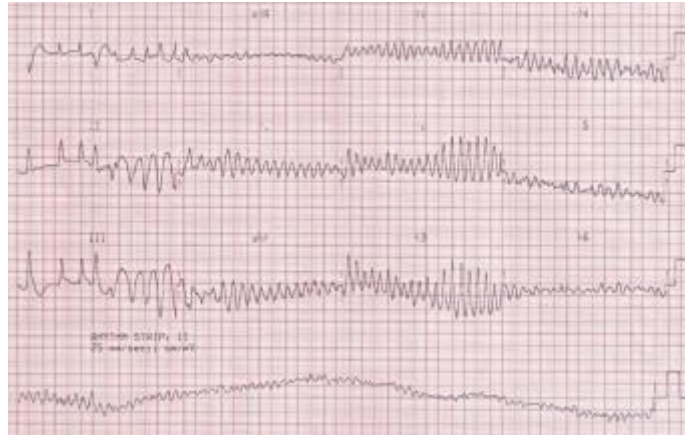
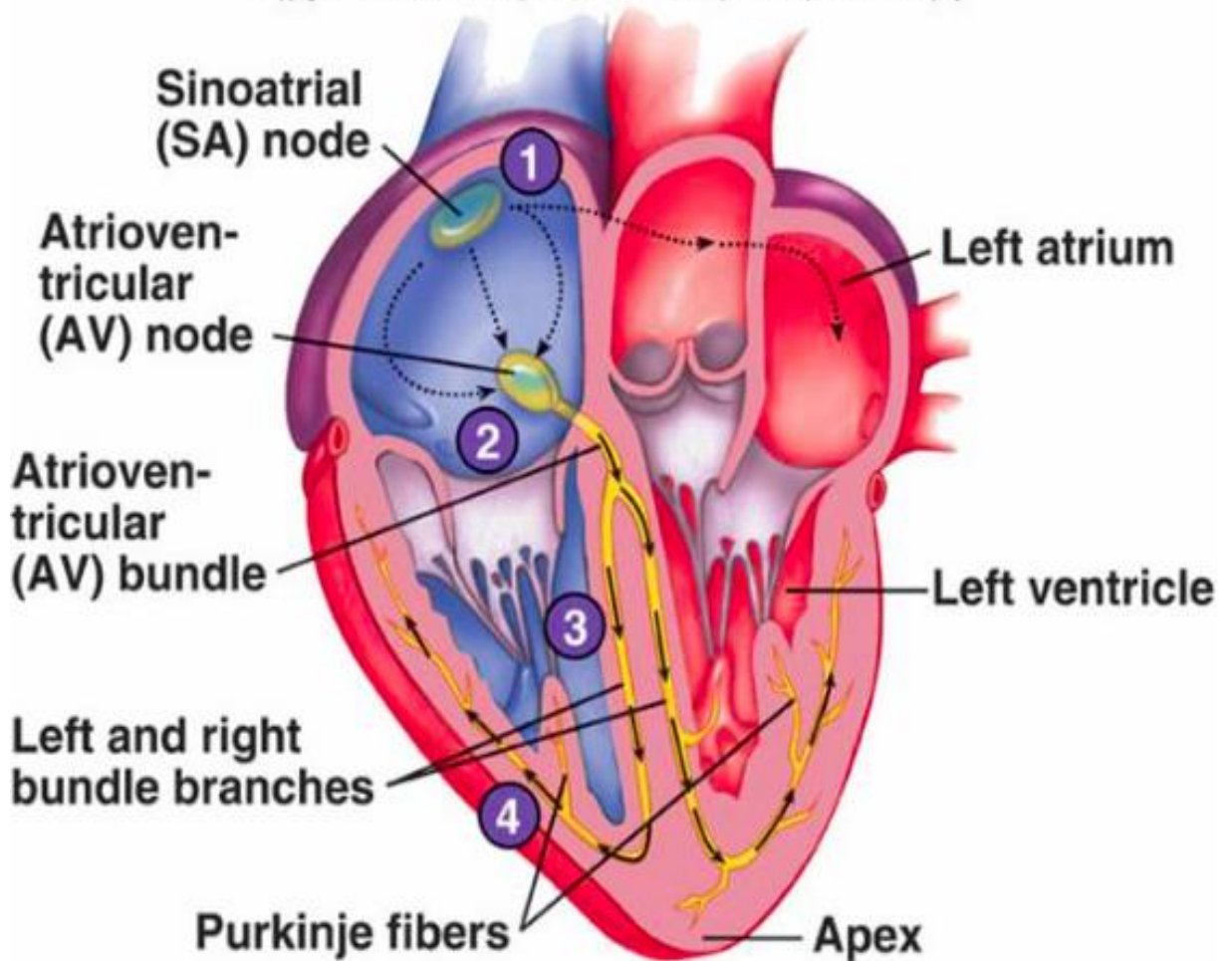


Figure 2 ECG of Ventricular Fibrillation

Myocardial infarction (MI) is among the leading causes of ventricular fibrillation and occurs when the flow of oxygenated blood to a section of the heart's muscle is blocked and consequently, the heart muscle begins to die. Typically the result of coronary artery disease, an MI can occur and trigger ventricular fibrillation and sudden cardiac arrest by causing tissue infarction. The tissue dies due to irreversible necrosis of heart muscle secondary to prolonged oxygen deprivation. The infarction caused by MI leaves behind areas of scar tissue that causes electrical short circuits around the scar – resulting in abnormalities in the heart rhythm. Diagnosis of MI is based on the patient's symptoms such as discomfort and pressure in the chest, ECG to assess heart rhythm, and blood tests to monitor levels of heart enzymes and troponins.

Disturbances that occur within the sinus node are clinically reflected as arrhythmias. The sinus node is the heart's natural pacemaker, and contraction of

the heart muscles is a result of electrical impulses generated by the cluster of sinus node cells in the right atrium of the heart (Figure 3). These electrical impulses flow through the heart - synchronizing the contractions of the ventricular muscular wall. This machinery controls the coordinated pumping of blood from the heart to the rest of the body. When the flow of electrical impulses through the heart is hindered, the delivery of oxygenated blood to vital organs of the body is impaired and cardiac arrest results.



**Figure 3 Sinoatrial Node and the Heart's Electrical Impulses**

The heart's electrical rhythm originates from the sinoatrial node in its right apex, and travels to the atrioventricular node, to the AV bundle, to the L. and R. bundle branches, through the Perkinje fibers, and towards the left ventricle. The generates the rhythmic contraction of the heart and when this does not work correct, heart arrhythmias results and lead to cardiac arrest and often times, sudden cardiac death.

Primary heart rhythm abnormalities are intrinsic electrical problems in the heart that do not involve the heart muscle or valves. Brugada syndrome and long QT syndrome are ion channelopathoies that cause ventricular fibrillation, which

leads to cardiac arrest. Patients with Brugada syndrome have an increased risk of abnormal heart rhythms from the lower chambers of the heart, ie. ventricular arrhythmias, which exhibit a type 1 Brugada ECG pattern. Similarly, long QT syndrome is an electrical abnormality that causes fast and irregular heartbeats. When the heart beats erratically for a long period of time, results in cardiac arrest and sudden cardiac death. An electrocardiogram (ECG) is typically given following cardiac arrest to reveal disturbances in heart rhythm or detect prolonged QT syndrome and other arrhythmias.

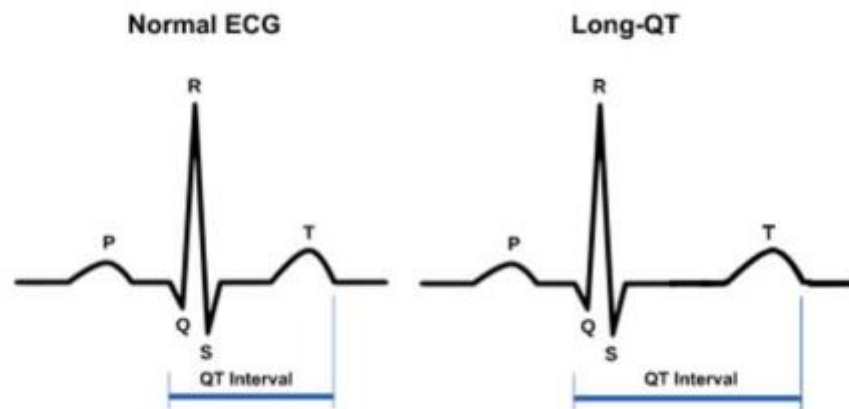


Figure 4 **Normal v. Long QT Syndrome**

Hypertrophic cardiomyopathy occurs when the cells of heart's muscular walls undergo hyperplasia and/or hypertrophy. As the muscular walls thicken, the ability of the heart to pump blood is impaired due to the weakening of the left ventricular wall. Cardiac arrest results when the ejection fraction of the left

ventricle is reduced, and the heart is unable to adequately pump blood to the rest of the body. Diagnosis of cardiomyopathy can be made by an ECG or echocardiogram, which is the gold standard for diagnosis.

Blood vessel abnormalities also contribute to ventricular fibrillation and as a result, may lead to cardiac arrest. The stretching or enlargement of heart valves causes a tightening or weakening of the valves characteristic of valvular heart disease. This increases the risk of developing arrhythmia and ultimately, cardiac arrest and sudden cardiac death result due to poor oxygenation to the body's vital organs.

Coronary artery disease is the most prevalent heart disease and is the most common cause of death in the United States. When the coronary arteries that supply blood to the heart muscle become hardened and narrowed due to a buildup of materials such as fatty deposits and scar tissue, they form atheromas on the heart wall. As plaque accumulates within the vessel, less blood is able to flow through the arteries. As a result, the heart muscles are deprived of oxygen which may lead to chest pain and myocardial infarction. If coronary heart disease remains untreated, heart failure and arrhythmias results and may also lead to cardiac arrest and sudden cardiac death.

## **Resuscitation**

Although death can result within minutes of cardiac arrest and loss of

heart function, cardiopulmonary resuscitation (CPR) may reverse early pathologies associated with cardiac arrest. CPR procedure involves restoration of blood circulation, clearance of the victim's airway, and breathing for the victim. Use of a defibrillator following CPR commonly increases patient prognosis due to the reversal of ventricular fibrillation, as discussed below.

Chest compressions help resolve impaired blood circulation, thus restoring oxygenation of vital organs and the brain. Although restoring cerebral perfusion is crucial for brain function, it is important to note that restoration of spontaneous circulation to the brain worsens neurological prognosis, as described in the Pathophysiology of Post-Cardiac Arrest Syndrome section.

Clearing of the victim's airways is achieved by using the head-tilt, chin-lift maneuver, and breathing for the victim is achieved by mouth-to-mouth breathing. Mouth-to-mouth breathing involves applying a positive pressure to the airway to ensure oxygenation of the blood. The purpose of CPR is to keep oxygenated blood flowing, and to preserve brain function until a more definitive medical treatment can restore the normal heart rhythm. The use of an automated external defibrillator (AED) applied to the chest is an electrical therapy that stops the arrhythmia and allows the heart to reestablish its normal rhythm.

Less than eight percent of out-of-hospital cardiac arrest (OHCA) victims survive to hospital discharge. This depends on whether CPR and defibrillation were provided within 5-7 minutes following the attack. If bystander CPR is available, the survival rate following cardiac arrest increases by approximately

40%. Achieving earlier defibrillation also results in a greater percentage of survivors in cardiac arrest victims with shockable rhythms (Kern, 2015).

### **Pathophysiology of Post-Cardiac Arrest**

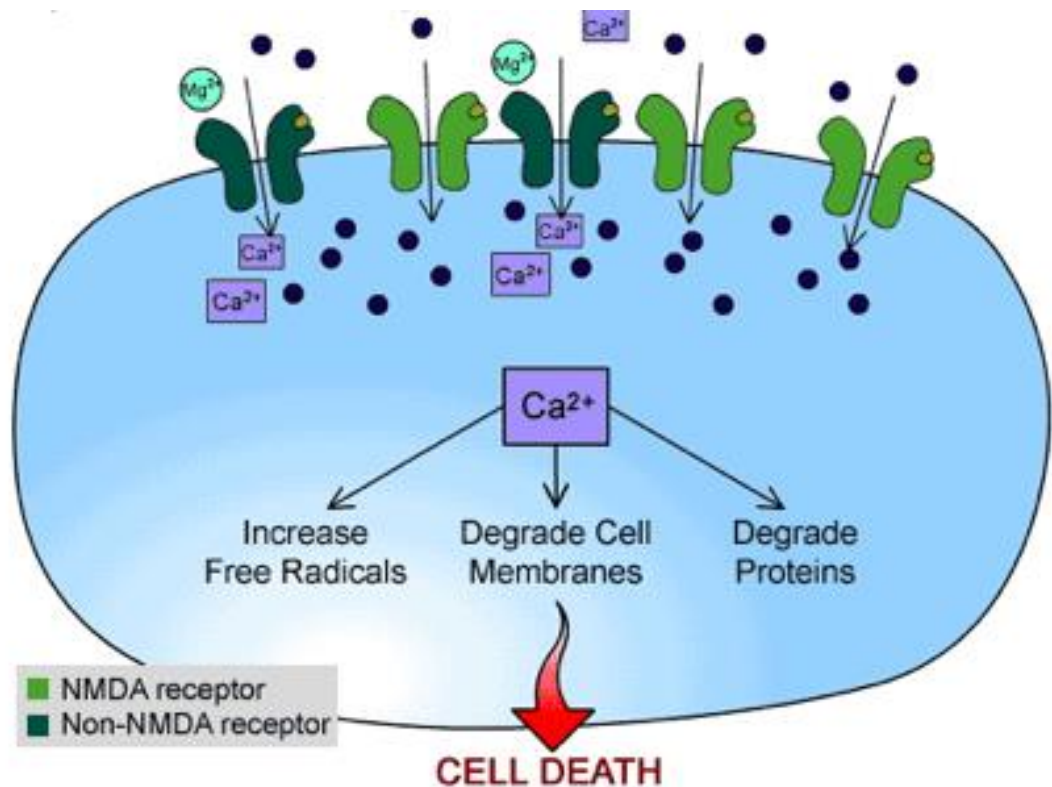
The extent of the complications experienced by post-cardiac arrest victims who have been successfully resuscitated depends on the delay of the initial resuscitation treatment, the efficacy of resuscitation, and the time elapsed between collapse and return of spontaneous circulation (Mongardon et al., 2011). Due to the profound impact of CPR, the survival rates to hospital discharge has improved drastically over the past several decades.

The pathophysiology of post-cardiac arrest syndrome involves the initial loss of blood flow followed by a global ischemia reperfusion phenomenon, and a nonspecific activation of the systemic inflammatory response. The intensity of events experienced during post-cardiac arrest syndrome depends on the duration of “no flow” and “low flow” phases. Resulting multiple organ failure, post-cardiac arrest shock, and neurological failure dominate the clinical picture in patients who are successfully resuscitated from cardiac arrest.

The ischemic phase of post-cardiac arrest syndrome involves a brief period of no flow, and is followed by longer reperfusion, or low flow period (Figure 6). The initial "no flow" phase is primarily responsible for the cellular and tissue damage that occurs during post-cardiac arrest syndrome. Reduced oxygen

delivery is typically offset by lower systemic metabolic needs. However, if there is no compensated reduction of both oxygen delivery and metabolic requirement, e.g. when cell metabolism requirements remain high or when the ischemic period is prolonged, there is reduced ATP synthesis relative to what is required by individual cells, and cellular function is interrupted.

Reperfusion occurs 4-6 minutes following the "no flow" phase (Figure 6). Blood flow and O<sub>2</sub> delivery may be spontaneously restored, or may be the result of resuscitation efforts such as CPR. During this period, ATP stores are completely depleted which leads to plasma membrane depolarization and the opening of voltage-gated calcium channels. Ultimately, this calcium influx into the cytoplasm that causes cellular and tissue damage (Figure 5). A prolonged depletion of cellular O<sub>2</sub> delivery results in anaerobic respiration and oxidative stress, characterized by lactic acid and free fatty acid accumulation. Loss of ATP stores and the resulting oxidative stress further damages cellular membranes and impairs pump function within cells.

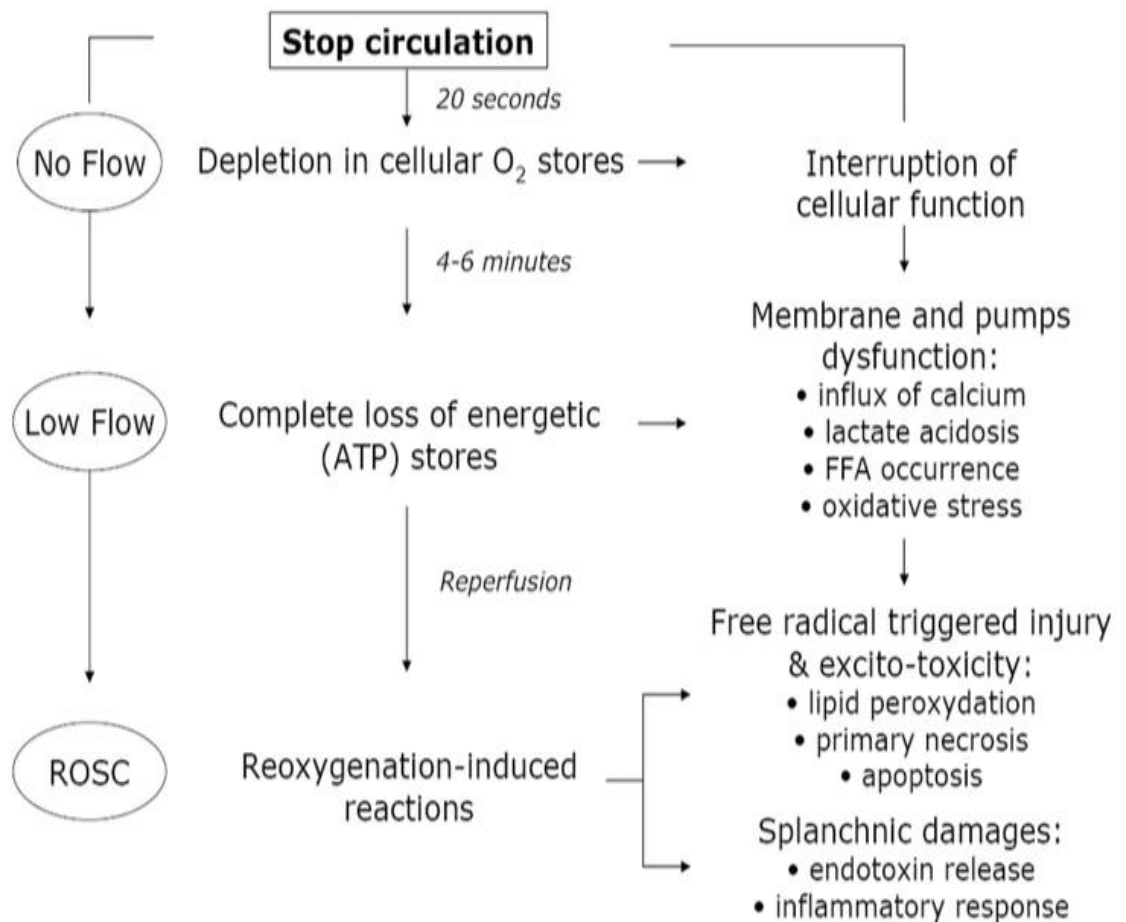


### Figure 5 Ca<sup>2+</sup> Entry into the Cell

Ca<sup>2+</sup> flow into cells through open NMDA receptors results in the degradation of cell membranes and proteins, as well as an increase in ROS.

Increased calcium concentration, hypoxia and the subsequent recovery of blood flow during reperfusion events results in the formation of radical oxygen species (ROS) (Figure 6). Hydroxyl radical ( $\cdot\text{OH}$ ) is the most destructive free radical as it causes cell death by inactivating cytochromes, introducing lipid peroxidation, and altering membrane transport proteins. Inactivation of cytochromes reduces cellular respiration, resulting in reduced ATP production and further impairing cellular function. Lipid peroxidation is the process by which

free radicals remove electrons from lipids in cell membranes - directly causing cellular damage, primary necrosis, and apoptosis. Alteration of membrane transport proteins leads to neurological damage and impairment of cognitive abilities. Other free radicals such as hydrogen peroxide ( $H_2O_2$ ) and superoxide anion ( $\bullet O_2^-$ ) also cause functional and structural lesions within cells.



**Figure 6 Consequences of impaired blood flow**

ROS also aggravate the clinical consequences of post-cardiac arrest syndrome by reducing anti-oxidant activity and enhancing a pro-oxidant state, thereby causing major endothelial toxicity. The damaged endothelium shifts the pathological state towards one of systemic inflammation as cytokines are produced, complement is activated, and chemotaxis of neutrophils occurs and initiates the inflammatory cascade. Clinical features of the systemic inflammatory response includes increased heart and respiratory rate, and an elevated white blood count. Severe sepsis is characterized by organ dysfunction, hypotension or hypo perfusion, and involves lactic acidosis, oliguria, and acute mental status changes.

Post-cardiac arrest shock is characterized by low cardiac output and a normal to low left filling pressure, leading to multiple organ failure. When a victim is in shock, his or her organs are deprived of blood and oxygen due to an overall reduction in ejection fraction from the left ventricle. If untreated, this can lead to permanent organ damage or death, caused by cardiocirculatory dysfunction.

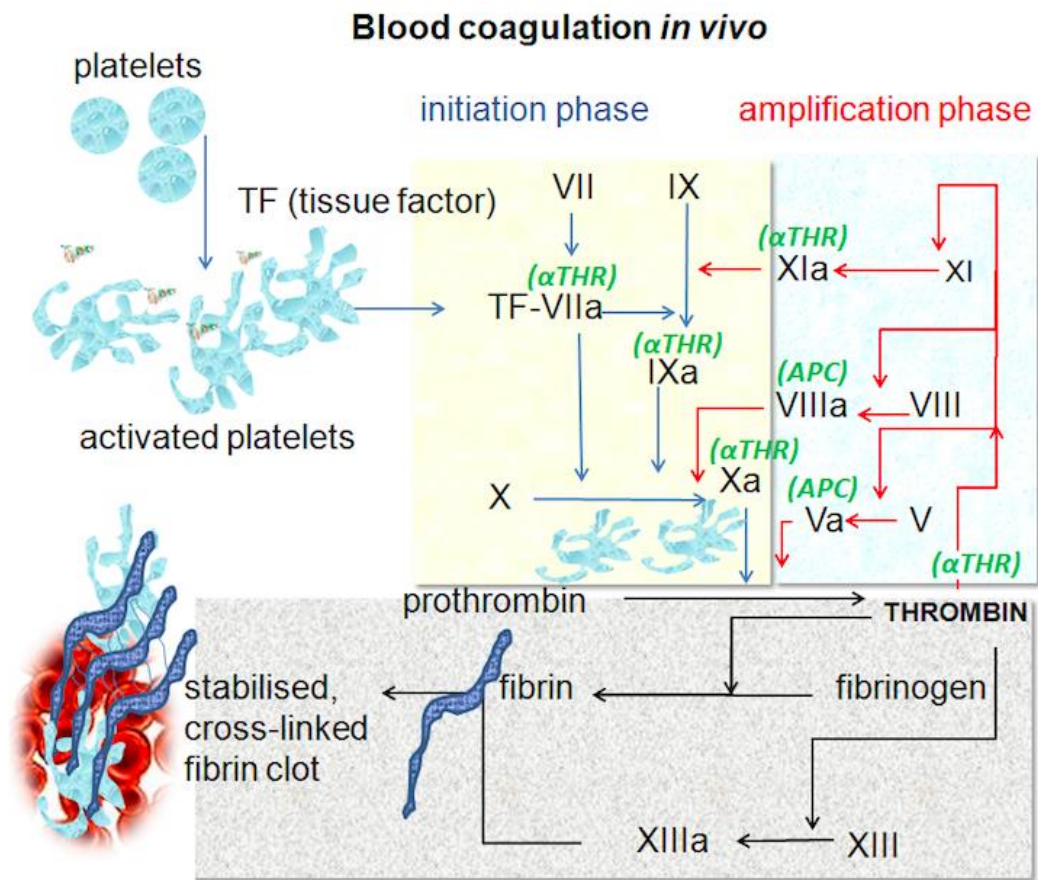
Multiple organ failure (MOF) is the direct result of post-cardiac arrest shock, caused by sequestration of activated neutrophils in organs such as the lungs, liver, kidney, and the brain. Inappropriate activation of neutrophils within the microvasculature results in the pathological manifestations of multiple organ failure. Infiltrating neutrophils produce ROS and release additional pro-inflammatory cytokines such as IL-6, TNF-alpha, and chemokines such as monocyte chemoattractant protein-1 (MCP-1). Increases in these factors

amplifies the inflammatory response in these organs. For example, inflammation of the lungs following cardiac arrest indicates respiratory failure as characterized by (Nielsen, 2010) pulmonary edema, lung contusion, atelectasis, or aspiration. This results in hypoxia, cardiogenic shock, acute renal failure, and liver failure. (Adrie, 2005) Acute kidney injury occurs in approximately 40% of cardiac arrest victims, while respiratory dysfunction occurs in approximately half of patients resuscitated from cardiac arrest.

Ultimately, the ischemic-reperfusion phenomenon is responsible for the activation of the systemic inflammatory response as plasma cytokine levels and circulating endotoxins are increased, and the clinical picture is markedly similar to what is observed in septic patients. In fact, there has been found to be a marked activation of coagulation in patients following cardiopulmonary resuscitation and restoration of blood flow. Activation of the systemic inflammatory response and the coagulation cascade leads to multiple organ failure and puts victims at risk for delayed neurological recovery by enhancing coagulation, thrombosis, and capillary permeability (Moran, 2006).

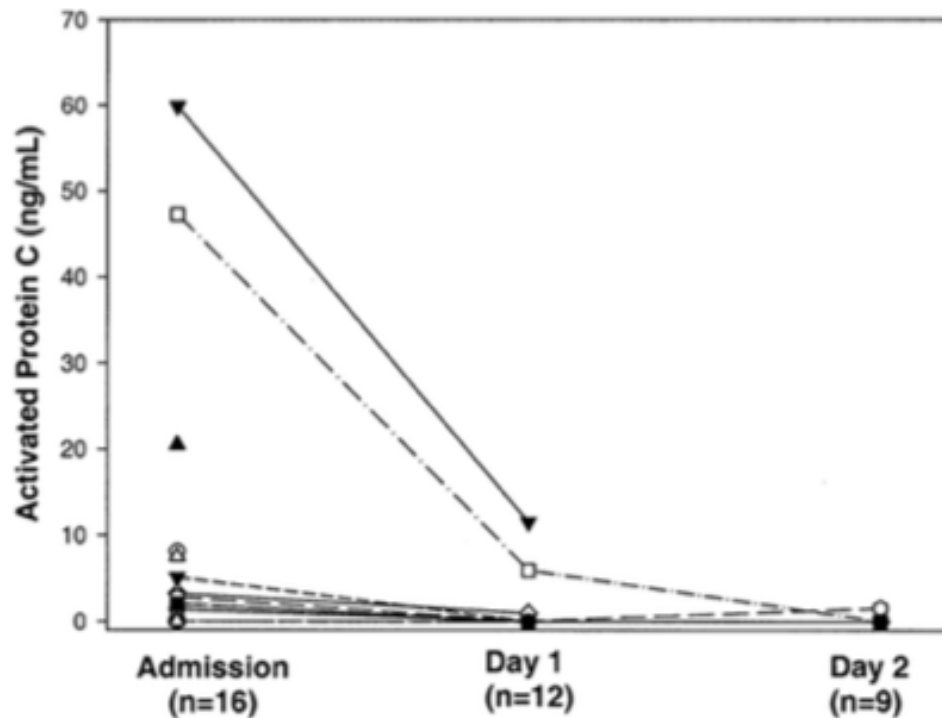
The systemic inflammatory response contributes to shock and multiple organ failure via the activation of the pro-inflammatory cytokines interleukin-1 (IL-1), interleukin-6 (IL-6), and tumor necrosis factor (TNF). The inflammatory response is associated with increased coagulation activity, reduced anticoagulation, and inhibited fibrinolysis (Adrie, 2005). Thrombin is generated, which converts fibrinogen to a fibrin clot - impairing blood flow and further

aggravating oxygen delivery to vital organs. These abnormalities are more severe in victims who die within two days of cardiac arrest, and even more pronounced in patients who die from early refractory shock— thus indicating the causative nature of coagulation in aggravating post-cardiac arrest shock and sudden cardiac death (Moran, 2006).



**Figure 7 Blood Coagulation in vivo**

Shock is associated with reduced levels of anticoagulation factors Protein C and Protein S, and increases in thrombomodulin, which is a cofactor for thrombin. Reduced anticoagulation factors and increased coagulation factor availability upregulates the coagulation cascade - further contributing to the stagnant blood flow experienced during post-cardiac arrest syndrome. Major coagulation abnormalities are consistent with secondary down-regulation of the protein C receptor pathway - via the down-regulation of protein C receptors, thereby reducing levels of Activated Protein C (APC). At a molecular level, APC is responsible for activation of anti-coagulation by proteolytically activating Factor Va and Factor VIIIa so that prothrombin is converted into thrombin. Thrombin then converts fibrinogen into fibrin, which stabilizes the cross-linked fibrin clot (Figure 7). Protein C is an endogenous protein which enhances fibrinolysis, limits thrombin generation, and modulates the inflammatory response. However, during reperfusion and the resulting state of shock, protein C levels are reduced, and coagulation is enhanced (Figure 8).



**Figure 8 APC Concentration change following resuscitation**

Upon admission, victims of cardiac have normal concentrations of APC. As reperfusion occurs, the APC concentration decreases, which results in decreased fibrinolysis and increased coagulation.

The mortality observed following cardiopulmonary resuscitation is likely linked to downregulation of the activated protein C anticoagulant pathway, secondary to protein C depletion and increased thrombosis, as well as an increased systemic inflammatory response. While shock related deaths are common, neurological failure remains the most common cause of death in patients resuscitated from post-cardiac arrest. In fact, organ failure caused by

systemic inflammation can also delay neurological recovery due to resulting reduced cerebral perfusion.

Neurological injury is characterized by neurocognitive deficits, learning, and memory impairment (Xiang, 2016). Specifically, neurological damage is caused by ischemic injury initiated during the “no flow” phase, and is aggravated further during reperfusion periods and CPR. During the no flow phase, cerebral activities are compromised. During the reperfusion period, neurological damage increases drastically and becomes permanent if not reversed soon after trauma. Fewer than 10% of patients admitted to the hospital after successfully resuscitated OHCA are discharged without severe neurological impairments. These impairments progress to a post-anoxic vegetative state and ultimately, sudden cardiac death if the underlying pathogenic mechanisms causing neurological damage are not addressed. (Bernard, 1997) Specifically, it is the activation of the inflammatory cascade and the immune response that is responsible for neurological damage during reperfusion phases. As cerebral oxygen delivery is reduced and demand is increased, cerebral edema and increased intracranial pressure worsen, resulting neurological ischemia.

The mechanisms causing neurological injury parallel that of organ failure and subsequent shock, including cell membrane and pump dysfunction, leukocyte and inflammatory cell infiltration, high concentrations of ROS, and release of cytokines and proinflammatory mediators (Bernard, 1997). Membrane and pump dysfunction is caused by depleted ATP stores secondary to calcium

influx, lactic acidosis, and oxidative stress. During oxygen deprivation, ATP production is unable to keep up with ATP consumption, which initiates biochemical cascades that lead to cell necrosis. Specifically, an ATP deficit leads to Na<sup>+</sup>/K<sup>+</sup> pump dysfunction and mitochondrial damage, which leads to increased intracellular calcium levels. This contributes to immediate cellular necrosis and apoptosis due to the triggered release of glutamate, an excitatory neurotransmitter. Glutamate binds the NMDA receptors in the brain, which triggers an even greater calcium overload by opening more calcium channels. Excessive calcium entry also directly generates ROS and excitotoxic enzymes such as endonucleases, ATPases, and phospholipases. These enzymes further contribute to cell membrane damage and pump dysfunction. As phospholipase breaks down the cell membrane, the cell becomes more permeable to harmful chemicals and ions flow into the cell.

The reperfusion period also directly results in the generation of oxygen free radicals from oxidative metabolism - thus reducing iron Fe<sup>3+</sup> to Fe<sup>2+</sup>. Reduced iron participates in the formation of more oxidizers, which injures cellular membranes even further. As the production of ROS increases within brain cells such as microglia and astrocytes, sequestration of neutrophils results and pro-inflammatory mediators are released.

Victims successfully resuscitated from post-cardiac arrest are also at an increased risk for infectious issues, secondary to complications caused by the cardiac arrest during the reperfusion period (Levi, 2003). Two thirds of cardiac

arrest survivors present with infectious complications - likely caused by loss of airway protection, pulmonary contusion, mechanical ventilation, BBB interruption, and ischemia-reperfusion injury during cardiac arrest. Neurons are damaged by the upregulation of cytokines and adhesion molecules, which results in the disruption of the blood brain barrier (BBB) (Kvietys, 2012). The brain becomes increasingly susceptible to infection, which can result in further neurological damage. Cerebral edema also results due to the leakage of large proteins through the damaged BBB. The swollen brain causes compression, and further damages the brain tissue.

### **Treatments and Management of Post-Cardiac Arrest**

Following successful resuscitation, therapeutic management for post-cardiac arrest victims has three primary motives: to determine and treat the underlying cause of cardiac arrest, to treat resulting shock and organ failure, and to optimize cerebral protection. Management therapy focuses on treating the underlying pathologies caused by the return of spontaneous circulation, as this is the primary origin of shock, organ failure, and neurological damage.

The cause of cardiac arrest can be determined by the various diagnostic tests previously described. A range of long term treatments such as percutaneous coronary intervention and implantable cardioventricular defibrillators (ICD) are prescribed depending on the cause of cardiac arrest.

Additionally the use of a defibrillator to restore heart rhythm immediately following arrest is has been shown to double the survival of post-cardiac arrest victims.

### Treatment of Shock

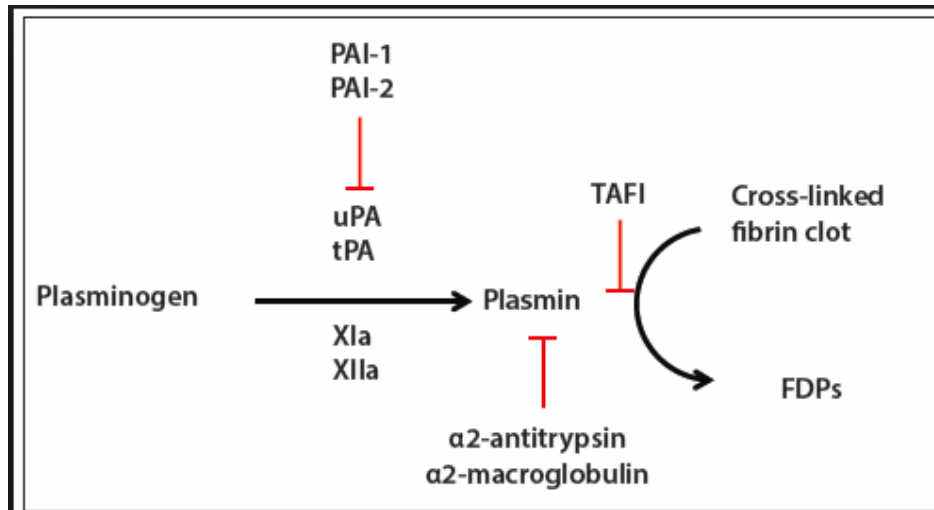
Post-resuscitation shock is typically reversible within 48 - 72 hours, and treatment modalities are similar those of inflammatory shock due to acute heart failure (Nielson, 2010). In order to reverse the effects, ventricular contractility must be restored and measures must be taken to correct hypoxemia, hypotension, and reduced tissue oxygenation. Among patients with cardiac arrest, it has been shown that combined vasopressin-epinephrine and methylprednisolone therapies during cardiopulmonary resuscitation improve survival to hospital discharge, and even have a favorable neurological prognosis. Epinephrine is therapeutic for shock victims because it causes the veins to constrict thereby increasing blood flow, and reduces swelling in airways so that breathing returns to normal.

If the cause of cardiac arrest is coronary artery disease, it is necessary to correct the source of the hemodynamic disturbance. Coronary angioplasty or coronary artery bypass are procedures that involve restoring coronary blood flow. By inserting a catheter through a blood vessel and inflating a small balloon at the site of the atheroma, restoration of blood flow is achieved when the balloon is inflated to compress the atheroma against the blood vessel wall. In coronary

artery bypass surgery, one healthy vessel from the body is grafted to the blocked coronary vessel so that flow bypasses the blocked segment of the coronary artery. Thus, a new path is created for oxygenated blood to flow to heart muscle and the symptoms of shock are reduced.

### Treatment of Organ Failure

Treatment of multiple organ failure, secondary to impaired organ oxygenation and post-cardiac arrest shock, requires the restoration of blood flow. This is achieved by chest compressions during CPR, and therapies that interrupt the underlying pathogenesis of post-cardiac arrest syndrome. Such therapies target the coagulation cascade. Thrombolytic therapy for example, is used as an immediate treatment for thrombosis and upregulation of the coagulation cascade by dissolving blood clots and restoring blood flow. The most commonly used therapeutic drug is tissue plasminogen activator (tPA), which catalyzes the conversion of plasminogen to plasmin - the major enzyme responsible for fibrinolysis (Figure 9). Administration of Factors XIa or XIIa are also used for this enzymatic conversion and clot breakdown, as shown in Figure 9. Administration of Protein C can also serve the same effects as these fibrinolytic enhancers, as it specifically reduces the activation coagulation pathway itself.



**Figure 9 The Fibrinolytic Cascade**

Fibrinolysis is the process that prevents blood clots from growing and interfering with blood flow. Because the activation of the coagulation cascade is upregulated during shock and organ failure phenomenon, it is important to administer therapies to reverse the effects of coagulation. Thus, administration of tPA activates downstream products of the fibrinolytic cascade to dissolve the blood clots formed as a result of reperfusion.

### Treatment of Anoxic Brain Injury

While shock and organ failure dominate the initial clinical picture of post-cardiac arrest syndrome, it is the optimization of the cerebrum that confers greatest long-term protection for post-cardiac arrest victims. Most patients remain unconscious after ROSC because of the severity of the brain injuries sustained during the reperfusion period. The degree of neurological impairments that dictates the prognosis of post-cardiac arrest victims and thus, neuroprotection is necessary to limit neurological consequences so that these patients can survive to hospital discharge.

Because increased levels of calcium and over activation of NMDA receptors triggered by glutamate release is linked to neurological injury caused by the downstream effects of excitotoxicity, it was believed that neuroprotection could be conferred by administration of calcium channel blockers or glutamate antagonists. However, there has been no argument for routine use of these as neuroprotective drugs. Rather, medications are given for management, rather than reversal of anoxic brain injury (Xiang, 2016). Steroids are given to reduce cerebral swelling secondary to brain anoxia – however, at the expense of further damage of the brain. Barbiturates may also be given to allow brain tissue time to recover during the anoxic insult, as well as anti-seizure medication. Cannabinoids have also been found to exert some antioxidant effects.

Neurological impairment worsens during the inflammation caused by reperfusion and CPR – thus, promising reversal therapeutic interventions are those that exert anti-inflammatory effects and treat neurological deficits during this phase. Induction of hypothermia for example, has been found to be an effective treatment because it targets the pathophysiological events and slows down the ischemic cellular cascades during ROSC.

Long term management of anoxic brain injury can be achieved with targeted temperature management (TTM) techniques - specifically, induction of therapeutic hypothermia (TH) has been consistently found to confer protective neurological effects. Hypothermia is protective when it is induced before or during an anoxic insult because the brain tends to reach a higher temperature

during periods of oxygen deprivation. For example, hypothermia is used for cerebral protection during operations involving cardiopulmonary bypass, in order to preserve neurological function.

Though the mechanism remains unclear, therapeutic hypothermia is effective in delaying neurological damage when it is induced shortly after trauma, as it reverses the effects of the early inflammatory response during the reperfusion phase (Mongardon, 2011). It decreases cerebral metabolism, reduces apoptosis and mitochondrial dysfunction, slows the cerebral excitatory cascade, decreases the local inflammatory response, and reduces ROS production. There is also evidence that it decreases the resulting cerebral edema during cardiac arrest, further delaying neurological impairment (Zhang, 2016).

Because the mechanism of action of therapeutic hypothermia with regards to inflammatory and the immune responses remains unclear, it is important to supplement this treatment method with other neuroprotective therapies to ensure the efficacy of TH. Minocycline, a tetracycline derivative, has been shown to be neuroprotective for victims of stroke. In the same respect, it inhibits activation and proliferation of microglia, migration of neutrophils, and release of other proinflammatory cytokines in for post-cardiac arrest victims (Plane, 2010). Statins, a 3-hydroxy-3 methylglutaryl reductase inhibitor, has also been shown to provide neuroprotective effects following cerebral ischemia. The use of this coenzyme in conjunction with therapeutic hypothermia may ameliorate oxidative stress and improve endothelial function by attenuating the inflammatory response

(Vaughan et al., 1999) Similarly, molecular hydrogen has been shown to have therapeutic effects for cerebral ischemic injury through its antioxidant and anti-inflammatory mechanisms of action. (Hayashida, 2012).

## Specific Aims

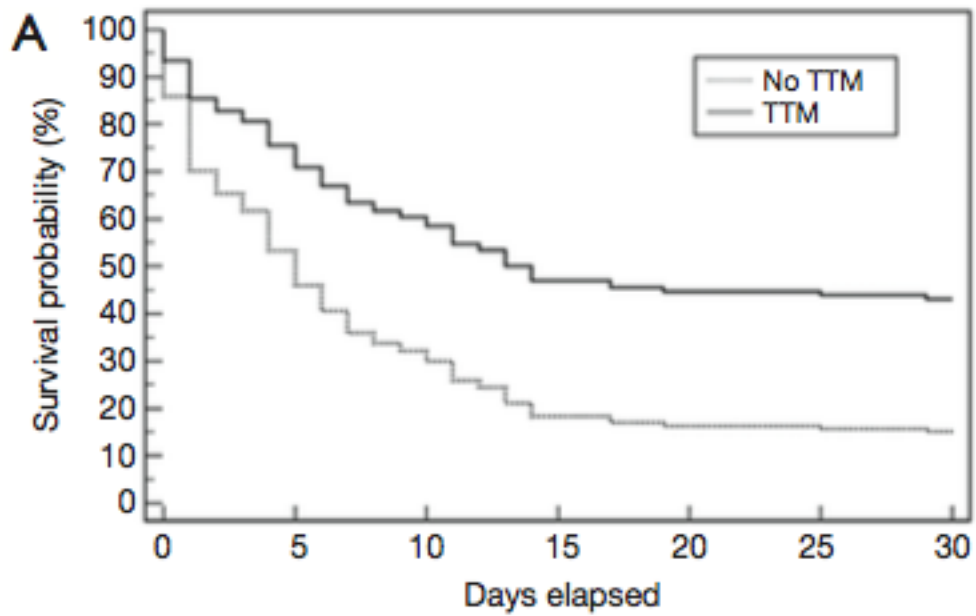
### **Specific Aims of the following thesis include:**

1. Comprehensive review of literature to characterize the nature of post-cardiac arrest syndrome.
2. Investigation into the current evidence for TTM use.
3. Conclusion of the efficacy of TTM in predicting positive outcomes for post-cardiac arrest victims.

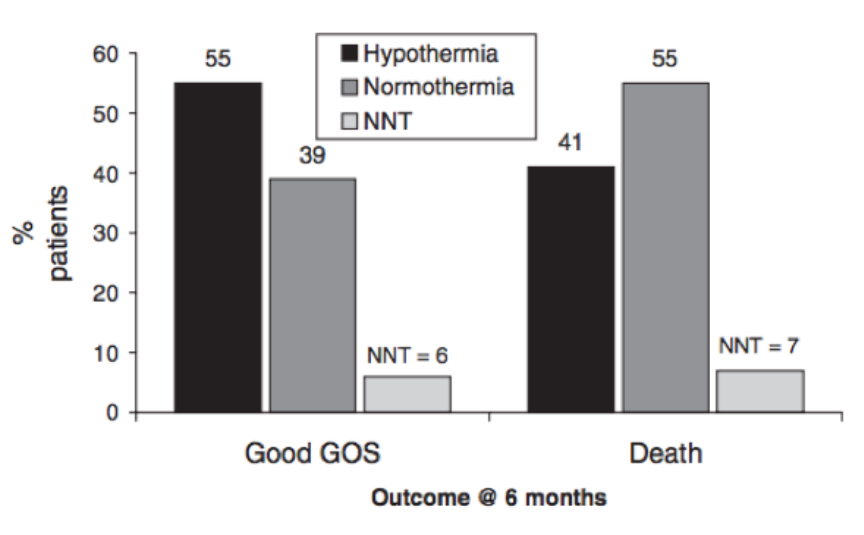
## **PUBLISHED STUDIES**

### **Uses of Targeted Temperature Management**

Normal body temperature is maintained at a core temperature of 36.5–37.5 °C through thermoregulation, but it can deviate depending on external or internal conditions. Hypothermia is defined as having a core temperature <35°C, and most persons do not survive core temperatures < 28°C. While hypothermia is a known cause of death in cold climates, mild to moderate hypothermia has been used for centuries to preserve life in warranted situations. In Ancient Greece, physicians induced hypothermia in trauma patients to control hemorrhage. In one early instance of hypothermia induction intended for neurological protection, the patient was cooled to < 30°C. Although neurological function was restored, numerous systemic complications arose. It has been shown however, that inducing milder hypothermia 32°C - 34°C is beneficial, as it minimizes extraneous complications meanwhile restoring cerebral function. Today, induced hypothermia is also used in comatose cardiac arrest survivors, head injury, neonatal encephalopathy, and to preserve neurological function during cardiopulmonary bypass operations (Polderman, 2015).



**Figure 10 Therapeutic hypothermia improves survival after cardiac arrest**



**Figure 11 Long term Outcomes of Targeted Temperature Management**

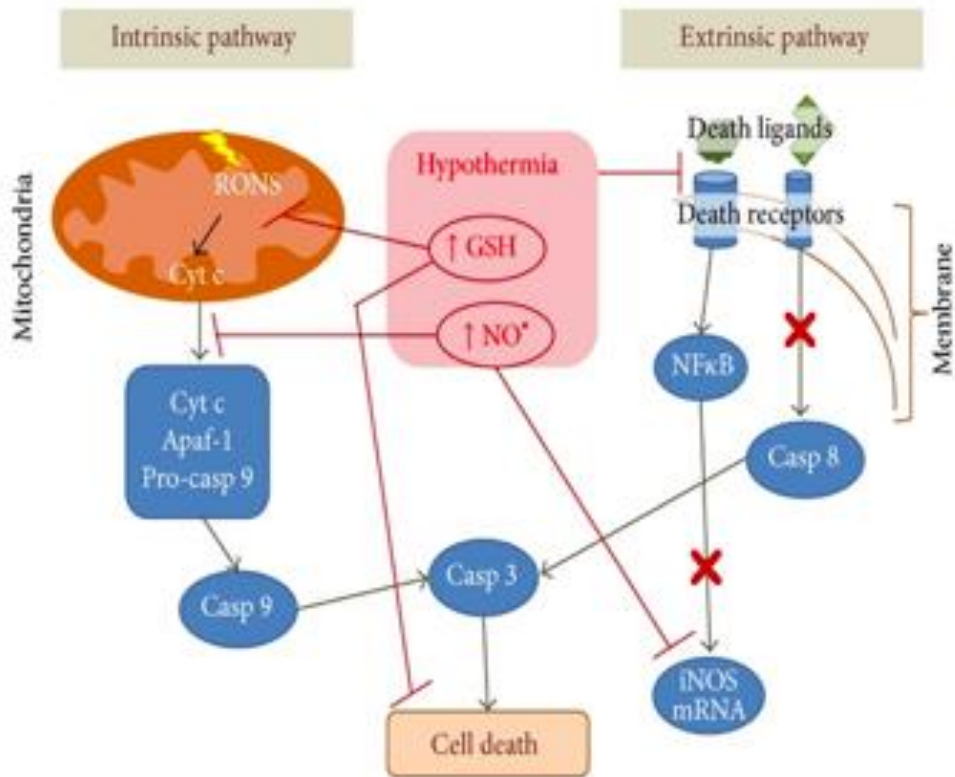
GOS – Glasgow Outcome Scale – Degree of Recovery Scale

Although the exact mechanism of action of therapeutic hypothermia remains unclear, there are several established effects that exert protection by reversing the pathologies associated with neurological ischemia. Of the greatest significance is the reduction of cerebral metabolism, which causes the brain to consume less O<sub>2</sub> and glucose. It is known that cooling the core temperature by one degree Celsius decreases cerebral metabolism by 6-8%, and reduces the amount of oxygen required by the brain. Hypothermia decreases heart rate and slows the metabolism, which decreases the cardiac afterload and oxygen demand (Luscombe, 2006). Because a lesser concentration of O<sub>2</sub> and glucose are available under conditions of neurological ischemia, hypothermia is therapeutic because it balances O<sub>2</sub> consumption and availability, thereby minimizing the deleterious neurological effects.

Of great clinical significance is the effect of hypothermia on the reduction of calcium overload and free radical formation. Because free radicals directly cause endothelial injury, it is important to reduce their formation to better the prognosis of post-cardiac arrest survivors. ROS are responsible for the rupture of the outer mitochondrial membrane and subsequently, the release of pro-apoptotic proteins such as cytochrome c (Alva, 2013). Hypothermia reverses the calcium overload caused by ischemia and thus, reduces cellular necrosis and apoptosis. The mechanism involves the blockage of the cell signaling pathway of necrosis and apoptosis, and upregulation of protective genes following ischemia (Zhao et al., 2007). Experimental assays have shown that when hypothermia is

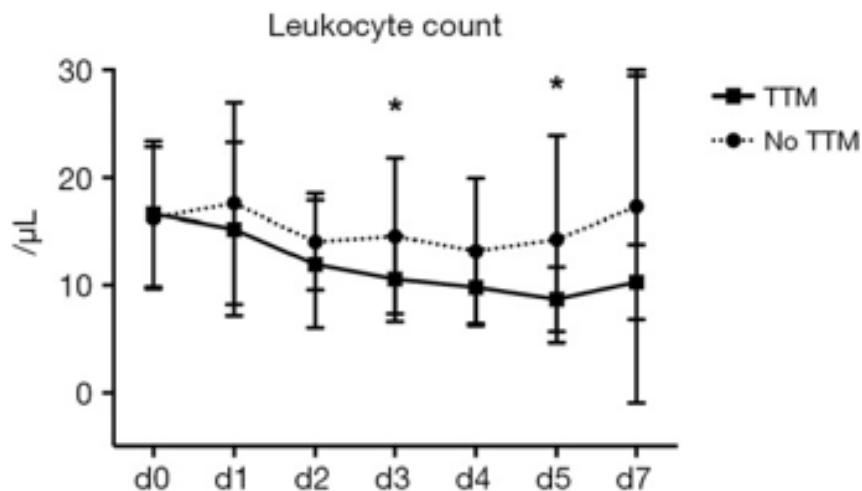
applied during an ischemic episode, it inhibits pro-apoptotic molecules and induces an increase in anti-apoptotic molecules in ischemic—affected tissues (Figure 12) (Eberspaicher, 2003).

Caspases are a family of protease enzymes that initiate programmed cell death and inflammation. While neurological ischemia increases caspase activity, directly hypothermia inhibits it and thus, minimizes neurological tissue necrosis. Reduction of neurocyte apoptosis in the hippocampus for example, has been shown to prevent memory deficits associated with hypoxemia (Alva, 2013)

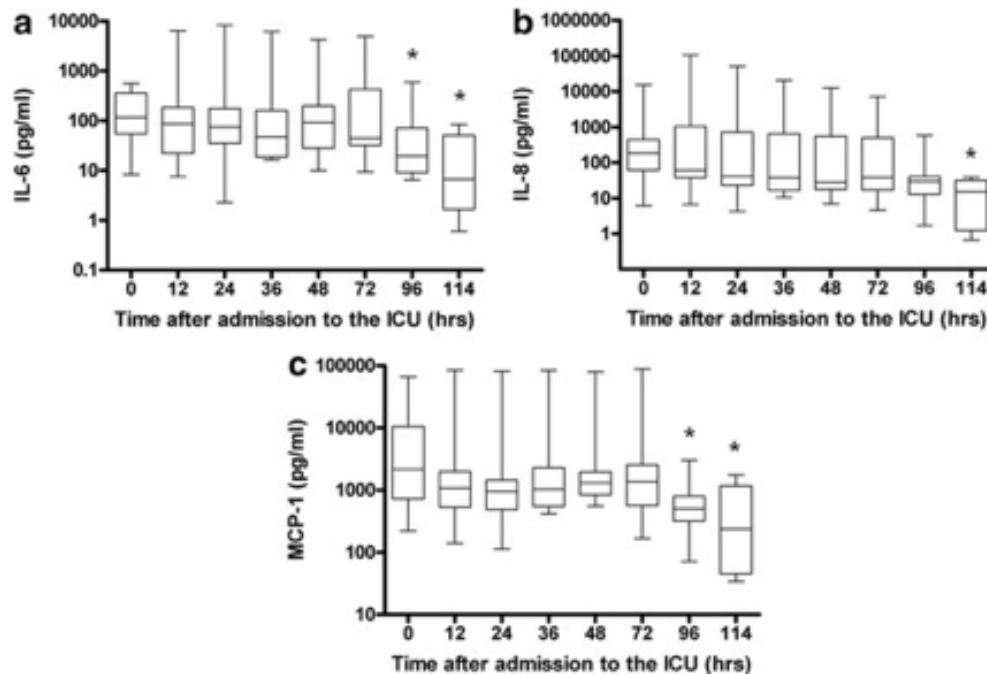


**Figure 12 Modulation of Apoptosis by Hypothermia**

Hypothermia also suppresses the inflammatory cascade by decreasing cytokine production, meanwhile reducing leukocyte migration within neurocytes to restrain the upregulation of the inflammatory response initiated by hypoxia (Figure 13) (Dufner et al, 2016). This not only protects the victim from neurological damage, but also from remote organ injury (Gunderson et al., 2001). This was learned from an experiment in which hypothermia was applied to rats induced into hemorrhagic shock via the withdrawal of blood. Relative to the control group, the hypothermic rats' organ injury was ameliorated, as reflected by the decreased levels of plasma markers of organ function: alphaGST, and creatinine. Overall, the survival rate of the hypothermic rats was greater than the normothermic control group by over 16%.



**FIGURE 13 Leukocyte count: TTM v. No TTM (141)**



**FIGURE 14 Cytokine and Chemokine profiles of patients during cooling (0-72 hours) and rewarming phases (72-114 hours)**

Neuronal injury following ischemic episodes is also associated with activation of N-methyl-D-aspartate (NMDA) receptor due to enhanced glutamate efflux and reduction of glutamate uptake. Increased levels of glutamate results in neuronal excitotoxicity by binding NMDA receptors, which is mediated by ischemic activation of voltage-gated calcium channels. It is hypothesized that hypothermia improves ionic homeostasis and reduces neurotoxicity by providing a means of NMDA receptor blockage (Nishizawa, 2001). Although the exact mechanism is unknown, induction of hypothermia is correlated with reduced

calcium concentrations and accordingly, reduced extracellular glutamate concentrations.

### **Techniques for Inducing Hypothermia**

Obtaining the accurate core temperature in post-cardiac arrest victims is crucial because body temperatures above the target may not provide sufficient neuroprotection, while overcooling beyond the target temperature typically produces systemic complications. Invasive and non-invasive techniques exist to cool the core body temperature, and each technique has its own advantages and disadvantages. In general, endovascular cooling techniques have the benefit of obtaining a more accurate target temperature, at the expense of being more invasive. The standard procedure for endovascular cooling is to insert a catheter with a 30 ml kg<sup>-1</sup> crystalloid solution chilled to 4°C, and infuse it into the patient's veins for 30 mins. This technique is known to drop the core temperature by approximately 1.7 degrees. It is a fast, efficacious, and safe method – but it does not maintain the patient at cool temperatures (32-34°C) for longer than 3-4 hours without rewarming (Kliegel, et al., 2007).

In general, the goal is to allow the body to cool for 12-24 hours. In order to maintain the cooled temperature for several hours, it is necessary to utilize additional cooling techniques. Repeated administration of cold infusions would result in fluid overload and cardiac decompensation. However, less invasive techniques such as applying icepacks to major blood vessels and cooling

blankets has been shown to adequately supplement endovascular cooling techniques to maintain the targeted temperature (Kliegel, et al., 2007). On their own however, these non-specific techniques tend to cause unintentional overcooling, resulting in other systemic complications (Caulfield, 2011).

### **Benefits and Consequences of TTM**

Although TTM has been shown to significantly improve the prognosis of cardiac arrest survivors and reduce the extent of neurological ischemic damage, there are several side effects that must be considered when employing this technique. Studies have found that the extent of these complications depends on the duration of cooling and the deviation from a core target temperature of 32-34°C. Prolonged hypothermia and cooling beyond 32°C tends to increase the degree of metabolic rate and inflammatory response suppression, and electrolyte imbalance. Following TTM, rewarming occurs and unavoidably reverses the therapeutic effects of hypothermia. This phase resembles hypoxia, as there is an increased production of oxygen free radicals, and metabolism is increased.

The goal of TH is for neurological preservation to balance out against systemic side effects. Endovascular cooling achieves an accurate and controlled temperature for TTM, so it is the preferable method of TH induction. However, it results in whole-body hypothermia - which influences all organ systems. Hypothermia has specific therapeutic effects on neurological injury, but it can have negative effects on various systems including the cardiovascular,

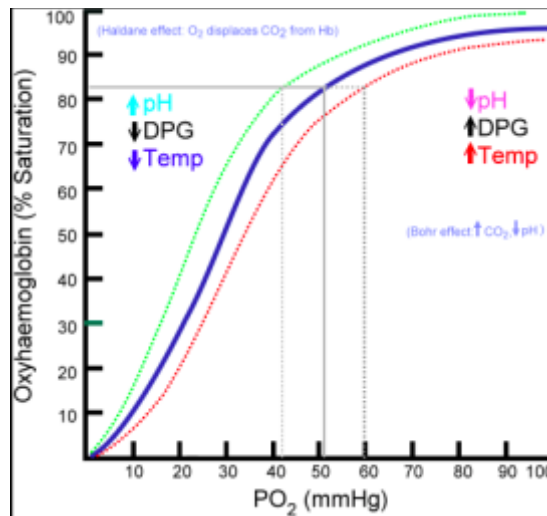
respiratory, renal, hemodynamic, and bone marrow systems if overcooling occurs (Luscombe, 2006).

Mild hypothermia can cause ECG changes such as an increased PR interval, the appearance of an Osborn wave, and a widening of the QRS complex. These arrhythmias typically occur when the temperature is dropped below 30 degrees, and the therapeutic effect of hypothermia is counteracted as these arrhythmias result in ventricular fibrillation and ultimately, cause cardiac arrest (Luscombe, 2006).

It is also known that temperatures below 32 degrees increases the incidence of pulmonary complications (O'Phelan, 2015). Cool core temperatures suppress the immune system by downregulating complement activation and inhibiting the release of cytokines. If hypothermia is prolonged (>24 hours), the patient's risk for infection increases because the immune system's response to foreign invaders is weakened, and the risk for pneumonia for example, is greatly increased.

Cold diuresis is also observed during the induction phase of therapeutic hypothermia. Cool temperatures cause the ascending Loop of Henle to absorb less solute, and diuresis results. Peripheral vasoconstriction caused by cool temperatures also increases the core fluid volume. This increases the mean arterial pressure, and induces a diuretic response. As the circulatory temperature decreases, the solubility of gases in blood also increases. Thus, the affinity of hemoglobin for oxygen increases, and respiratory alkalosis can result (Figure

15).



**Figure 15 Hemoglobin-oxygen affinity increases under hypothermic conditions**

Left shift of the curve causes respiratory alkalosis, reduced offloading of O<sub>2</sub>, which further impairs O<sub>2</sub> delivery

Hypothermia reverses the hemodynamic disturbances initiated by cardiac arrest by inhibiting the coagulation cascade and improving blood flow. This inhibits the formation of micro thrombi in the brain but at the same time, this can increase patients' bleeding risk. Depending on whether or not the patient has a traumatic injury or is bleeding, this can have detrimental effects due to increased blood loss. In vivo experimental results indicate that temperatures below 35°C can induce platelet dysfunction. Below 33°C, the activation of clotting enzymes in the coagulation cascade can also be inhibited. However, the clinical effects tend to be minor, and typically only present an issue when the patient has

experienced a traumatic injury or is actively bleeding (Polderman, 2012).

Hypothermia also affects the bone marrow's production of blood cells. Under hypothermic temperatures, platelets leave the circulation and bleeding time is lengthened due to the reduced number and function of platelets. White cell count also decreases, further aggravating a state of immunosuppression under hypothermic conditions (Luscombe, 2006).

Most studies assessing the reversal effects of hypothermia have been conducted on animal models. In one study, the long term effects of induced hypothermia on the inflammatory response in pigs was assessed. Levels of inflammatory cytokines such as IL-6 and IL-10 were measured during early and late posttraumatic phases. Although there are significant anti-inflammatory effects of induced hypothermia during early and late phases, rewarming occurs during the late posttraumatic phase and is associated with an increased inflammatory response. It was found that increases in the inflammatory response occurred as the concentrations of pro-inflammatory mediators increased and anti-inflammatory mediators decreased. Therefore, it can be reasoned that therapeutic effects of hypothermia cannot be sustained for long periods of time. (Alva, 2013). Relative to normothermic controls, the imbalance of pro and anti-inflammation associated with hypothermic conditions and inevitable rewarming contributes to systemic complications, which appears to have a negative effect on the mortality of multiple trauma patients treated with TTM. However, when multiple trauma patients were compared against cardiac arrest victims, TH

resulted in an overall improved outcome following ischemia and reperfusion secondary to cardiac arrest (Horst, 2016).

If TTM techniques are unavailable up to 24 hours following trauma, it may not present any therapeutic effects. In previous studies, inducing hypothermia 48 hours following trauma conferred no benefits as leukocyte count decreased, but neurological function was not preserved. Therefore, the incidence of infection increased due to a suppression of the inflammatory response, with no added benefit.

It has been reasoned that the benefits of TTM on neurological injury due to cardiac arrest should be the same, regardless of the underlying cause of cardiac arrest. However, in one study (Leão, 2015), the survival rate of cardiac arrest victims with various etiologies were compared following TTM. It was found that among the causes of cardiac arrest, myocardial infarction is associated with the highest probability of survival and the best neurological outcomes. Thus, the potential risks and benefits of TTM is generally not the same across all causes of cardiac arrest (Nielson et al., 2014)

### **The TTM Trial and Target Temperature**

One issue regarding use of TTM, is the deliberation over the most optimal target temperature. Although international guidelines recommend a temperature of 32° to 34°C, this data has been deduced from experiments performed on

animals (Colbourne, 1994). In the international TTM trial (Nielsen, et al.) published in the New England Journal of Medicine, 950 unconscious adults after out-of-hospital cardiac arrest were randomly assigned to targeted temperature management groups at either 33°C or 36°C (Figure 13, Table 1). The outcomes of interest in this study included an all-cause mortality by the end of the trial, and composite of poor neurological function or death at 180 days, evaluated with the Cerebral Performance Category (CPC) scale and the modified Rankin scale (mRS).

The Cerebral Performance Category Scale (graded 1-5) classifies the neurological status and interprets outcome among survivors of cardiac arrest. The modified Rankin scale (graded 1-6) is used to measure the degree of disability of individuals who have suffered neurological damage (see appendix I for scale parameters). At the three-month follow-up, 54% of the patients in the 33°C group did not make it to hospital discharge following TTM and scored poorly on the CPC scale. In the group assigned to 36°C TTM, 52% of patients in the group died or had poor neurological function. Because similar mortality rates were observed between moderate and mildly cooled groups in humans, the degree of cooling according to international guidelines has been challenged.

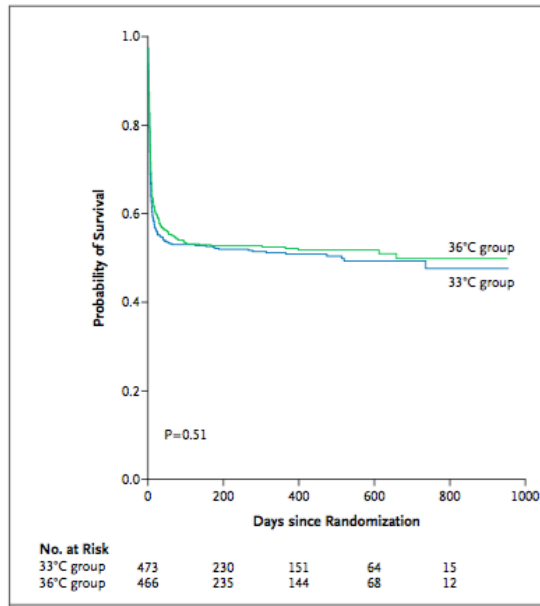


Figure 16 Probability of Survival for TTM 33°C v. 36°C

Variable	33°C Group	36°C Group
<b>CPC at follow-up†</b>		
Total no. of patients	469	464
Category — no. (%)		
1	195 (42)	183 (39)
2	23 (5)	39 (8)
3	17 (4)	20 (4)
4	6 (1)	2 (0.5)
5	228 (49)	220 (47)
P value for trend	0.85	
<b>Best, or lowest numerical, CPC during trial</b>		
Total no. of patients	472	466
Category — no. (%)		
1	209 (44)	205 (44)
2	25 (5)	41 (9)
3	37 (8)	37 (8)
4	201 (43)	183 (39)
5	NA	NA
P value for trend	0.89	
<b>Modified Rankin scale score at follow-up†</b>		
Total no. of patients	469	464
Score — no. (%)		
0	88 (19)	89 (19)
1	69 (15)	83 (18)
2	50 (11)	34 (7)
3	17 (4)	19 (4)
4	8 (2)	11 (2)
5	9 (2)	8 (2)
6	228 (49)	220 (47)
P value for trend	0.67	

Table 1 CPC and mRS comparison of TTM 33°C v. 36°C

## **Best Outcomes of Targeted Temperature Management**

Relative to other causes of cardiac arrest, TTM has the best outcome on victims of myocardial infarction. Therapeutic hypothermia appears to be beneficial in this case because it reduces infarct size, microvascular resistance and reperfusion injury (Kang, 2016). In a prospective study investigating the prognostic factors associated with survival to discharge in OHCA victims, it was found that a shockable rhythm, and a shorter time to return of spontaneous circulation were also associated with better outcomes (Sathianathan, 2016).

## DISCUSSION AND CONCLUSION

The International Liaison Committee on Resuscitation guidelines on hypothermia after cardiac arrest, recommends that patients with OHCA and a shockable rhythm be cooled to 32°C - 34°C, for 12 to 24 hours. Cooling between 32°C - 34°C has been shown to preserve neurological function, meanwhile limiting other systemic complications. However, these guidelines are based on in animal in vivo and in vitro studies. The novel 2013 TTM trial based on human subjects showed that there is no difference between mild (36°C) and moderate (33°C) cooling. Thus, further studies should aim to investigate TTM at different degrees in human subjects.

The effectiveness of TTM therapy appears depend on source of the injury – as victims of cardiac arrest have a higher survival rate after TTM induction than other subgroups. Within cardiac arrest victims, cardiac arrest secondary to myocardial infarction shows the highest rate of recovery compared to other causes. Because myocardial infarction is the most common cause of cardiac arrest, TTM induction has been linked to good outcomes.

TTM use is strongly supported by pathophysiological evidence. Hypothermia reduces metabolic demand and ischemic-reperfusion injury – thereby reducing the effects of excitotoxicity, ROS formation, BBB disruption, necrosis, and apoptosis. Analysis of cytokine and chemokine profiles in animals shows a reduction of inflammatory mediators – thus indicating the mechanism by

which therapeutic hypothermia likely attributes its success. Additionally, TH has been shown to downregulate the activation of the coagulation cascade. Again, future studies should aim to analyze these profiles in humans, in order to make a conclusion regarding its effectiveness in increasing the survival of cardiac arrest victims.

In order to confer the greatest benefit, TH must be carefully administered. Care must be taken for precision cooling so that the patient's core temperature does not drop below 32°C. Additionally, possible non-cardiac arrest factors must be taken into consideration. If the cardiac arrest victim is also a multiple trauma patient or is actively bleeding for example, cooling below 35°C can proliferate systemic side effects and induce platelet dysfunction. These effects counteract preservation of neurological function, and reduce the likelihood of a positive outcome.

Furthermore, the best outcomes for cardiac arrest victims occur when TH techniques are employed shortly after the cardiac arrest episode. The effectiveness of TH is also related to whether or not the victim has a shockable initial rhythm and a shorter ROSC time. Despite the many factors that must be considered, TTM is a widely used therapy that proves to be therapeutic for a condition with a <10% survival rate. Future studies should aim to investigate human subjects and induce therapeutic hypothermia on cardiac arrest victims at different durations and degrees. If it were possible to cool only the brain, this

could provide information as to whether or not this would produce a better or a worse prognosis, than cooling the whole body.

## APPENDIX

### Cerebral Performance Scale (CPS)

CPC Score	Definition
1	Conscious and alert with normal function or only slight disability
2	Conscious and alert with moderate disability
3	Conscious with severe disability
4	Comatose or persistent vegetative state
5	Brain dead or death from other causes

### Modified Rankin Scale (mRS)

mRS Score	Definition
0	No symptoms
1	No significant disability. Able to carry out usual activities, despite some symptoms
2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
3	Moderate disability., Requires some help, but unable to walk unassisted.
4	Moderate severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
6	Dead

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## CURRICULUM VITAE

### MIRIAM FAHIM

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### Education

**Martin Luther King High School** 2009 - 2011

**University of California, Los Angeles-** 2011-2015

*-Bachelors of Science*

**Boston University** 2015- 2016

*-Masters of Science in Medical Science Candidate*

**Eastern Virginia Medical School-** 2016- 2020

*-Doctor of Medicine (M.D.) Candidate*

### Experiences

#### **San Juan Pediatrics**

Medical Scribe

*April 2015 - August 2015, December 2015 - January 2016*

I performed documentation in the Electronic Health Record and gathered information from the patients' visits - ultimately working with the pediatrician to deliver efficient patient care.

#### **Venice Family Clinic**

Clinician Assistant

*February 2013 - February 2015*

I performed the workup of scheduled patients, took patient vitals, and briefed physicians on the patient's medical history and the reason for their visit.

### **Swartwood Test Prep Co.**

MCAT Instructor

*April - August 2015, May – August 2016*

## **Projects**

### **Bladder Diameter Ratio in Spina Bifida Patients**

RESEARCH INTERN – Children's Hospital of Orange County  
*May – August 2016*

I am currently working on a retrospective study in which I am evaluating objective measures of what constitutes normal bladder shape, as defined by a bladder diameter ratio. Ultimately, I am working to understand the link between changes in bladder shape in children with spina bifida based on a known marker of disease progression, trabeculation. I hope my findings will help clinicians treat patients with neurogenic bladder with a tailored and less invasive approach. My role entails evaluating spina bifida patient X-rays – including voiding cystourethrograms and ultrasounds, and documenting relevant lab results, surgical history, and instances of infections.

### **Spontaneous Spinal Cerebrospinal Fluid Leaks and Intracranial Hypotension**

RESEARCH INTERN – Cedars-Sinai Medical Center  
*September 2013 - August 2015*

I worked on an independent study at the Pituitary Center at Cedars-Sinai Medical Center. My study analyzed the effects of cerebral spinal fluid leakage on the distortion of the pituitary stalk, and my aim was to determine whether hyperprolactinemia may be used as a diagnostic marker for spontaneous intracranial hypotension (SIH). I helped evaluate pituitary function in patients with SIH prior to an after treatment via blood patch placement, surgery, or saline infusion. Specifically, I documented the incidence of and investigated the pathogenesis of hyperprolactinemia and pituitary adenoma by correlating brain MRI findings, hormone levels, (brain sagging & pituitary enlargement), serial

prolactin levels, and pituitary size, pre and post treatment. I worked closely with my principal investigator to develop the protocol, submitted to the IRB, recruited study participants, coordinated study procedures, and worked with neurosurgeons, endocrinologists, and staticians to evaluate the data.