

Prognosis of Hypoxic Brain Injury Post-cardiac Arrest  
Pharmacological and Non-Pharmacological Interventions

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### Abstract

Cardiac arrest is a condition in which the heart abruptly ceases to beat and stops supplying blood to the tissues and vital organs of the body. In order to survive cardiac arrest with good neurological function there must be immediate cardiopulmonary resuscitation, advanced cardiac life support, and quintessential post-cardiac arrest care. However, much emphasis and attention has been given to cardiopulmonary resuscitation and advanced cardiac life support with little consideration to post-cardiac arrest care. Unfortunately, even amidst all the interventions, hypoxic brain injury has been shown by various studies to occur after cardiac arrest.

Hypoxic brain degeneration is part of an umbrella of pathologic condition known as Post-cardiac Arrest Syndrome. This is a complex pathological process that comprises post-cardiac arrest brain injury, myocardial dysfunction, systemic ischemia, and persistent precipitating pathology. Many prominent research studies have revealed the pertinent role that post-cardiac arrest care plays in enhancing patient neurological prognosis. The primary focus of post-cardiac arrest intervention is geared toward improving possible cerebral edema, post-ischemic neurodegeneration and impaired cerebrovascular auto regulation. The thesis therefore strives to analyze the effectiveness of present modalities within the chain of survival and also to unveil novel improvements in this field of study, which comprise both pharmacological and non-pharmacological interventions.

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## Prognosis of Hypoxic Brain Injury Post Cardiac Arrest

### Pharmacological and Non-Pharmacological Interventions

#### **Introduction**

Cardiac arrest is a terminal condition that abruptly takes precious lives with little or no caution. It is the leading cause of death in the U.S. and accounts for about 350,000 deaths annually (Heart Rhythm Foundation, 2010). An otherwise normally functioning person could suddenly be caught in this condition within 24 hours of onset of signs and symptoms. Cardiac arrest may either be recognized or unrecognized. Due to its sudden nature, the annual cases of cardiac arrest in the U.S. occur outside a health care setting in about 400,000 persons (“Cardiac Arrest,” 2005). The duration between the recognition of a sudden cardiac arrest and intervention is usually prolonged and therefore limits the chances of survival. A crucial predicament is the chance of survival with optimal neurological outcome. The chain of survival must be adhered to in a timely fashion. Advanced life support is also highly recommended as an essential component of care in the event of a sudden cardiac arrest. Unfortunately, even amidst all these interventions, various studies have shown hypoxic brain injury to occur after cardiac arrest. In view of this, adequate post-cardiac arrest care must be optimized to preserve some degree of neurological function. This must include preventive measures, treatments, new advancements in the field, as well as other non-pharmacological interventions provided by nurses and aimed at improving the quality of life.

### **Cardiac Arrest**

Cardiac arrest, also referred to as cardiopulmonary arrest, is a condition in which the heart abruptly ceases to beat and stops supplying blood to the tissues and vital organs of the body. This sudden loss of cardiac function eventually results in breathing cessation and loss of consciousness. Several causes contribute to cardiac arrest and, in the event, perfusion to the organs and body ceases, leading to decreased oxygenation to the cells and brain tissue. The hypoxic state of the brain adversely affects the brain stem role in respiration as evidenced by breathing cessation. The general decrease in oxygen supply to the brain also results in degrees of coma (Lewis, Heitkemper, Dirksen, O'Brien, & Bucher, 2007, p. 817-818).

### **Pathophysiology**

Cardiac arrest, unlike a heart attack, is the complete loss of cardiac function in the entire muscle and not just a segment of the heart muscle. The loss of heart function results from an ischemic state of the heart cells and tissue that inadvertently causes severe cellular damage and tissue edema. The primary function of the heart is to act as a muscular pump to supply nutrients and oxygen to the body through the blood. Therefore, a sudden loss of function renders the heart unable to effectively pump oxygenated blood to the body and organs. Consequently, blood and fluid accumulate and pool in the vessels and organs, especially the heart, lungs and brain (Lewis et al., 2007).

The brain happens to be most victimized by the effects of cardiac arrest. Because the brain is a soft tissue encapsulated within the skull, any condition that increases intracranial pressure will enormously affect brain function. The resulting edema in cardiac arrest has a negative impact on the brain because of the limited capacity to expand. This causes an increased

intracranial pressure and subsequent decrease in cerebral perfusion after resuscitation (“Cardiac Arrest,” 2005).

Furthermore, edema formation in the brain leads to compromised membrane integrity, causing Potassium (K) ions to be released in large amounts from the cells and an influx of Calcium (Ca) and Sodium (Na) ions into the cells. Increased Na in the cells aggravates the edema in the cells, while increased Ca levels disrupt “mitochondrial function” and, thereby, a decrease in ATP production and production of harmful free radicals and proteases (“Cardiac Arrest,” 2005). Again, the excessive influx of ions into the cell leads to depolarization and the release of neurotransmitters such as glutamate, which is able to activate a Ca channel that worsens the already existing Ca excess in the cell (“Cardiac Arrest,” 2005). Also, inflammatory mediators are activated, thereby accentuating the compromised vascular integrity. As a result, there is an accumulation of blood clots in the vessels, and this leads to further edema formation. The ensuing outcome is accelerated cell death. Consequently, a number of successfully resuscitated patients have short or long-term cerebral dysfunction (Cardiac Arrest, 2005).

### **Etiology.**

Cardiac arrest primarily results from heart diseases, the most common offender being coronary artery disease (CAD). Dysrhythmias also have the propensity to trigger a cardiac arrest. Other causes may include severe physical stress, genetic disorders or anatomical anomalies (Bucher, 2007). CAD and dysrhythmias, however, are the two major factors that engender cardiac arrest.

### ***Coronary Artery Disease.***

CAD is the group of progressive blood vessel disorders known as atherosclerosis. Atherosclerosis is the major cause of CAD and is characterized by the buildup of lipids and

cholesterol within the arterial walls. Naturally, the endothelial layers of arteries do not react to leukocytes, platelets, and to fibrinolytic and complement factors. Unfortunately, this endothelial barrier is dangerously injured by tobacco use, HTN, hyperlipidemia, diabetes, hyperhomocysteinemia, and certain viral or bacterial infections (Martinez & Bucher, 2007).

CAD develops in stages depending on the rate of lipid and cholesterol deposition from fatty streaks to a fibrous plaque and finally into a complicated lesion. Under normal circumstances, “the endothelium repairs itself immediately, but in the person with CAD the endothelium is not rapidly replaced, allowing LDL’s and growth factors from platelets to stimulate smooth muscle proliferation and thickening of the arterial wall” (Martinez & Bucher, 2007, p. 785). In time, the integrity of the arterial lining is compromised, allowing for platelets and more lipid accumulation and resulting in a complicated lesion. The damage done by CAD is primarily due to continued inflammation and agglutination of platelets and lipids. In time, the vessels become sclerosed and narrowed, causing inadequate amount of perfusion, nutrients, and oxygenation to reach the heart. This can result in either systolic or diastolic heart failure or mixed systolic and diastolic heart failure. The heart becomes a failing pump unable to perfuse the myocardium and the body. Chronic, uncompensated heart failure can result in cardiac arrest.

#### *Dysrhythmias.*

In a normal heart, the electrical impulses are generated by the heart’s natural pacemaker, the sinoatrial node (SA node), which engenders the contraction of the cardiac muscle by transmitting the impulses through the atrium, the atrioventricular node (AV) node, the purkinje system, and throughout the ventricle. This well-organized synchronous impulse activity produces an ideal heart rate of 60-100bpm. However, heart dysrhythmias can occur when the normal electrical impulses that regulate heart beat are dysfunctional, leading to rhythms and rates that

are too slow, faster than the normal rate, or very irregular (Bucher, 2007). Dysrhythmias that are commonly associated with cardiac arrest include ventricular fibrillation, ventricular tachycardia, asystole etc.

Ventricular fibrillation (VF) can be idiopathic in origin or can be cardiac related and is characterized by chaotic rhythm resulting from quivering ventricles. VF negatively affects filling and contraction times, leading to decreased cardiac output. It is also characterized by absent P, Q, R, S, and T waves. Ventricular tachycardia (VT) occurs when the ventricles are rapidly contracting, producing a life threatening dysrhythmia. VT is usually noted with at least a row of three premature ventricular complexes and may or may not have P waves. Asystole, also known as ventricular standstill, represents a complete absence of electrical and as such there are no P, Q, R, S, and T waves (Loyola, 2009).

All forms of symptomatic tachydysrhythmias can be treated with vagal maneuvers such as Carotid massage and Valsalva maneuver. This stimulates the parasympathetic response therefore causing a reduction in the heart rate. Adenosine, the drug of choice for supraventricular dysrhythmias may be administered to reduce the AV conduction rate. VF and VT can be treated with Amiodarone, an antidysrhythmic drug which acts by decreasing membrane excitability and prolonging action potential. Similarly, Lidocaine can be given as an alternative to Amiodarone. It works by suppressing ventricular conduction and automaticity. In the event of refractory VT that is unresponsive to Lidocaine, Procainamide can be used. Other interventions include cardioversion, defibrillation, radio-frequency ablation, etc. (Loyola, 2009).

### **Chain of Survival**

The concept of chain of survival, as related to cardiac arrest, has become a widely acclaimed practice. This is because it has been proven as an effectual means of increasing the

patient's chances of survival in the event of cardiac arrest. It has been empirically tested and tried through extensive research that identifies compliance to this concept as one that increases the number of neurologically whole survivors (Cummins, 1993). This is however mostly accurate when the sequence of events involved in the chain are all performed as rapidly as possible; recognition of early warning signs, activation of the emergency medical system, basic cardiopulmonary resuscitation (CPR), defibrillation, and early advanced care which constitutes possible intubation, and intravenous medications (Cummins). From this, we gather that the chain of survival is made up of separate and unique singular entities that coherently work towards a common destination. It therefore reasons that, "although separate specialized programs are necessary to develop strength in each link, all of the links must be interconnected. Weakness in any link lessens the chances of survival and condemns a community to poor results" (p. 313). The chain of survival is summarized in figure 1, an algorithm developed by the American Heart Association.

Early recognition or accessibility is the beginning of the chain and is one of the most important links in the chain. This is because the success of the subsequent processes is dependent on the success of the first link and therefore has an enormous impact on the final outcome. It is imperative then that the person or persons present during the cardiac event must be sufficiently informed to recognize an emergency and act accordingly. Time is an indispensable factor in this link. Time is required to respond, identify the emergency, and call the attention of emergency services. As soon as the emergency services or appropriate health personnel arrives, the needed appropriate intervention can be initiated with immediate effect.

Immediately after ascertaining a cardiac arrest event, the expected intervention is rapid cardiopulmonary resuscitation (CPR). CPR is a systematized sequence of responses to a cardiac

arrest comprising the recognition of breathlessness, and loss of circulation and the ability to provide basic life support (BLS) and defibrillation (“Cardiac Arrest,” 2005). Once a person is recognized as unresponsive and with absent circulation and breathing, the mnemonic, ABC, which represents airway, breathing, and circulation, must be utilized in implementing the BLS. The main focus of the CPR is to perform rapid chest compressions at such pace, efficiency, and accuracy in order to maximize the neurological prognosis of the patient (“Cardiac Arrest”). In the absence of well trained personnel “endotracheal intubation may be delayed in favor of uninterrupted chest compression, bag-valve-mask ventilation, and timely defibrillation” (“Cardiac Arrest”). Chest compressions are immediately initiated in an attempt to restore circulation. However, in instances where defibrillators are readily present within three minutes, defibrillation is considered prior to chest compressions. Chest compressions must be unremitting as much as possible and should consist of 50% compressions and 50% release. During the course of the compressions, the cardiac output must be evaluated by assessing the reaction of the patient’s pupils to light. If the pupils are normal in size and respond to light, it is a positive indication of satisfactory brain oxygenation and perfusion. Conversely, dilated and light-responsive pupils signify inadequate perfusion and oxygenation to the brain. This however does not imply a brain injury. The onset of spontaneous breathing or eye opening indicates restoration of spontaneous circulation (ROSC) (“Cardiac Arrest”). Although these procedures may have achieved considerable gain, cardiac arrest usually generates dysrhythmias such as ventricular tachycardia or ventricular fibrillation. For the purpose of restoring circulation, these adventitious rhythms must be rapidly converted to sinus rhythms. This requires the mechanism of early defibrillation (Cummins, 1993).

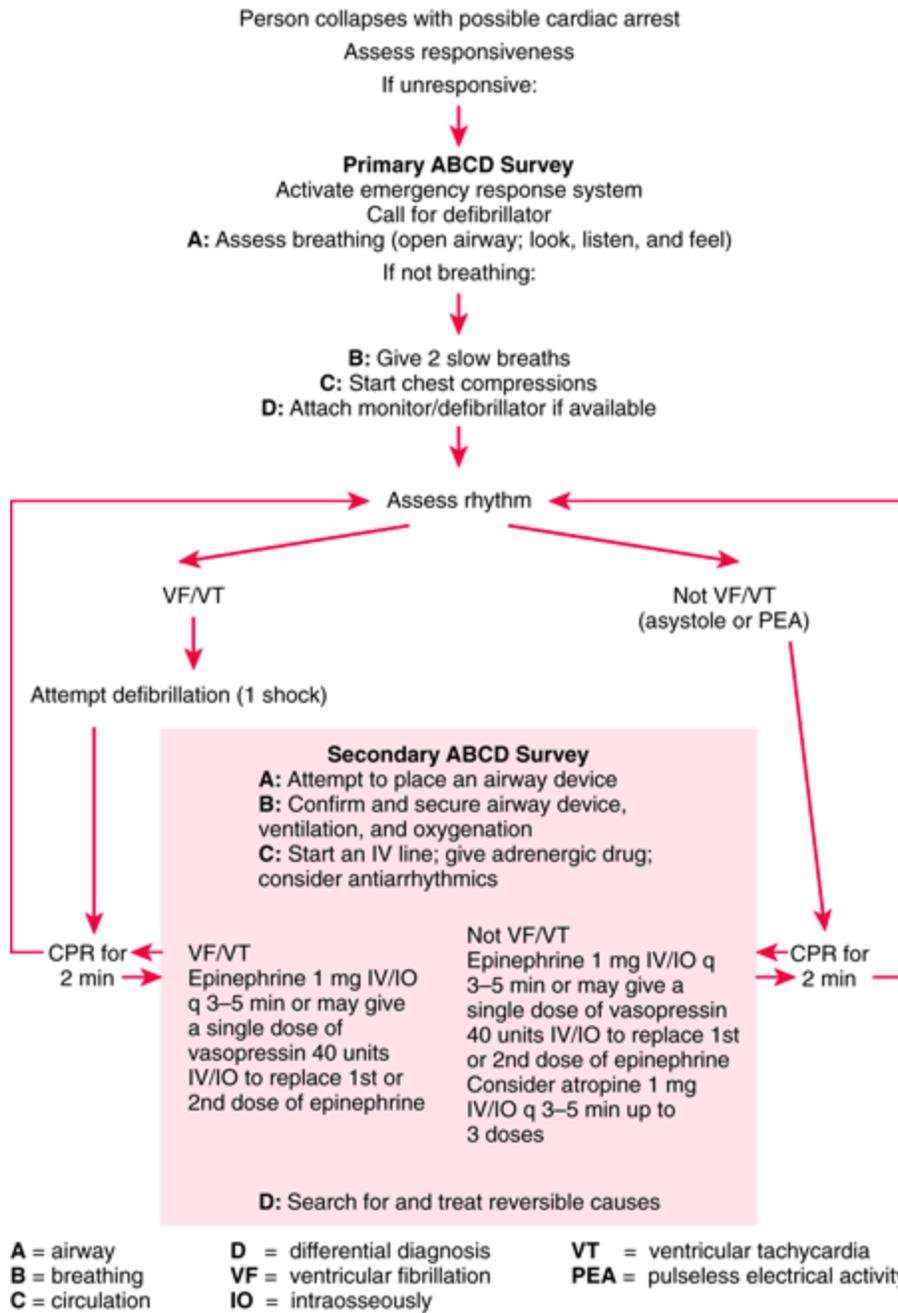


Figure 1. This figure illustrates the standard BLS and CPR algorithm according to the American Heart Association.

Defibrillation is initiated with the primary purpose of restoring normal cardiac rhythm. According to the American Heart Association, in the event of CPR, rescuers must proceed with CPR while the external defibrillator is charged (“Cardiopulmonary Resuscitation,” 2010). The

logic for this intervention is based on the data which shows that “almost 85% of persons with ambulatory, out-of-hospital, primary cardiac arrest experience ventricular tachyarrhythmias during the early minutes after their collapse” (Cummins, 1993, p. 6). The success of early defibrillation cannot be over emphasized. Several studies in England have revealed the success of early defibrillation administered independently of other protocols (Cummins). Even though anti-arrhythmic medications educe similar effects, prompt cardioversion using defibrillators are more effective. Automated external defibrillators (AED) are now utilized due to recent developments not confined to their exclusive use by medical professional but can be managed by minimally trained rescuers including first responders, and other law enforcement agents (“Cardiac Arrest,” 2005).

Defibrillating or AED pads are positioned between the clavicle and the 2<sup>nd</sup> intercostals space and along the border of the right sternum. The other is placed over the 5<sup>th</sup> and 6<sup>th</sup> intercostals space over the apical region of the heart. These devices are charged at high energy levels. Traditional defibrillators were largely monophasic but due to the forward thrust of technology, biphasic models are now widely acclaimed and much preferred over monophasic. Monophasic defibrillators deliver rapid electrical pulses in a single direction while the biphasic type employs reverse and alternative directions with the aim of decreasing electrical threshold (Biphasic, 2008). Biphasic defibrillators are usually fashioned to deliver between 120 and 200 joules while monophasic types are set to deliver 360 joules of electricity. Rhythms are recorded after defibrillation when at least two full minutes of chest compressions have been completed (“Cardiac Arrest,” 2005). An intervention of such magnitude is potentially dangerous due to the electrical current involved. Participants must therefore exercise extreme caution to minimize the risk injury and death.

Unfortunately, these interventions even when executed systematically and appropriately may still be unsuccessful. The patient may remain in a dysrhythmic state, and thus require continuous chest compressions, ventilation and advanced cardiac life support (ACLS) (“Cardiac Arrest,” 2005).

Advanced Cardiac Life Support (ACLS) was established in 1974 by the American Heart Association and is now a generally adapted benchmark for cardiac arrest intervention. It is made up of advanced defibrillation, intubation, intravenous access, and intravenous medication (Cummins, 1993). The ACLS is of significance because CPR and defibrillation, when used individually or in combination are unable to achieve or sustain resuscitation. Hence, the early ACLS link, which consists of endotracheal intubation and intravenous medications are very crucial at increasing the chances of survival. These mechanisms within this link seek not only to restore spontaneous circulation and electrical activity, but to adequately stabilize the patient to prevent further complications. (Cummins, Ornato, Thies & Pepe, 1991, p. 9).

In the course of defibrillation, ACLS protocol is initiated. It follows the same pattern of ABCD (Airway, breathing, circulation, differential diagnosis) as BLS. Airway management is achieved definitely through endotracheal intubation. Ventilation and chest compressions are yet still continued at approximately 8 to 10 breaths per minute and at a rate of 100 per minute respectively (Klein, 2009, p. 239). Intubation provides a patent airway, facilitates effective suctioning, and the administration of highly concentrated oxygen and other drugs (Klein). Breathing assessment must be carried out to validate the effectiveness of ventilation by assessing corresponding chest expansion after ventilation. Placement for the endotracheal tube (ETT) is reviewed by auscultating the epigastric area; gurgling heard in the absence of adequate chest

expansion indicates misplacement and must be immediately corrected. Placement can also be verified by bilateral breath sounds and chest movement with ventilation (Klein).

Circulatory restoration involves a large bore intravenous access (IV access) and the administration of medication or fluids. Although the ETT is available, not all drugs are approved for administration through this route. Approved drugs include epinephrine, lidocaine, vasopressin, and atropine. In instances where an IV access is unavailable, an intraosseous cannulation or central line is created as recommended by the American Heart Association. Normal Saline is the solution of choice because it is a better intravascular volume expander than dextrose (Klein, 2009, p. 240).

Differential diagnosis is the next stage within the chain of survival. At this stage when there has been some progress in resuscitation, investigations are conducted to identify the etiology of the cardiac arrest. As aforementioned, cardiac arrest is usually caused by coronary artery disease and certain kinds of dysrhythmias such ventricular fibrillation, ventricular tachycardia, asystole, pulseless electrical activity, symptomatic bradycardia and tachycardia. An adequate diagnosis of the etiology determines the particular algorithms to be adopted for the requisite intervention. These algorithms have been established by the American Heart Association and are constantly undergoing revision in order to reflect current clinical and evidenced based research (Klein, 2009, p. 240; Heath, Hanson, Long, & Crowell, 2005).

The ACLS standardized protocol for pharmacological intervention of cardiac arrest is dependent on the cause, the nature of rhythm, and the patient's response. The protocol is utilized for the chief purpose of attaining and sustaining cardiac output, resolving hypoxemia, maintaining optimal blood pressure, establishing a balance between the delivery and consumption of oxygen and to stifle ectopic rhythms (Klein, 2009, p. 239-240). It is imperative,

therefore, that consistent ECG and hemodynamic monitoring are present as soon as the ABCD's of BLS and ACLS are completed. For the purpose of this thesis, the drugs discussed will comprise those that are often used in practice to promote spontaneous cardiac resuscitation.

According to the revised ACLS algorithm, research outcomes recommend the use of vasopressin as an alternative to epinephrine in enhancing spontaneous circulation within three minutes of unproductive defibrillation. This is of much significance considering the fact that the ACLS protocol has for the past 3 decades recommended epinephrine as the first drug of choice in the event of unsuccessful defibrillation. Heath et al. (2005) discuss the use of vasopressin as a first line drug therapy for ventricular fibrillation or pulseless tachycardia related cardiac arrest.

Vasopressin, an endothelium-derived peptide is a potent vasoconstrictor that regulates the release of endothelin-1 from endothelial layer of blood vessels. A single dose of 40 units IV/IO is the usual recommended dose. During CPR, vasopressin is administered to optimize vasoconstriction and cardiac output, resulting in increased perfusion pressure and myocardial and cerebral perfusion. A study conducted by Lindner et al. (1992) regarding the 24 hour outcome of patients who received 40 units of vasopressin proved much more effective than patients that were given 1mg of epinephrine.

Epinephrine is yet another potent vasoconstrictor which acts on both alpha and beta receptors, thereby increasing systemic vascular resistance, contractility, arterial blood pressure, heart rate, and the automaticity of cardiac pacemaker cells. Because it causes peripheral vasoconstriction, epinephrine causes a diversion of blood to more vital organs and increases myocardial oxygen requirement, leading to vasodilation. Also by improving automaticity, contraction and electrical activity, the heart is made more sensitive to respond to defibrillation (Klein, 2009, p. 248). Epinephrine can be given IV/IO or via an ETT.

The advantage of vasopressin over epinephrine was challenged by Stiell et al. (2002) after the revision of the ACLS protocol in 2000. Their study evaluated the use of vasopressin or epinephrine for the treatment of pulseless electrical activity, or refractory ventricular fibrillation and asystole. The outcome showed that the “survival to 1 hour ( $P = .66$ ) and survival to discharge from the hospital ( $P = .67$ ) did not differ between patients given vasopressin and patients given epinephrine”. Other studies revealed that vasopressin was more effective at improving cerebral perfusion during resuscitation than epinephrine (Lindner et al., 1992). The Merck Medical Manual also argues that vasopressin has not proven superior to epinephrine (“Cardiac Arrest,” 2005). In a randomized animal study to evaluate the clinical importance of the concurrent usage of vasopressin and epinephrine, improved neurological benefits were recorded (Stadlbauer et al., 2003).

Atropine is a parasympatholytic agonist that causes an increase in heart rate by reducing the vagal tone. It is indicated for asystole, symptomatic bradycardia, bradyarrhythmias, cardiac arrest and high-degree AV nodal block and is administered at a maximum dose of 3mg via IV, IO or ETT. Atropine works by increasing SA node automaticity and AV node conduction activity. Survival benefits for the use of atropine has however not been fully discovered (“Cardiac Arrest,” 2005; Klein, 2009, p. 248, 252).

Calcium chloride (CaCl) is usually administered for cardiac arrest related to hyperkalemia, hypermagnesemia, hypocalcemia, or calcium channel blocker overdose or toxicity. CaCl is not recommended in conditions where the listed electrolyte and drug imbalances are implicated. CaCl must be given slowly via IV to prevent bradycardia. Disadvantages of this drug include ventricular irritability, and coronary or cerebral vasospasm (Klein, 2009, p. 254).

Dopamine is a positive inotropic agent as well as a vasopressor recommended in the treatment of symptomatic hypotension unrelated to hypovolemia. Its impact is dependent on the dosage and the degree of alpha and beta receptor sensitivity. When administered in doses greater than 20mg/kg/min, it causes peripheral vasoconstriction, and increased myocardial contractility. Myocardial workload increases without a corresponding increase in coronary blood supply, a situation that may result in ischemia (Klein, 2009, p. 254; Lehne, 2007).

ACLS is terminated only when the cardiopulmonary status is stabilized, the patient dies, or a lone rescuer is unable to continue CPR. In hypothermic patients, CPR must be persistent until there is restoration of appropriate core body temperature. Before a client is pronounced dead, the duration of arrest, time of treatment, age of client, medical history, etc. are appraised. The basic parameter is usually following the failure to attain spontaneous circulation within 30-45 minutes of CPR and ACLS (“Cardiac Arrest,” 2005). Upon restoration of cardiac status as evidenced by pulses and ROSC and organized rhythm, post cardiac arrest care must be initiated. This is a substantial intervention which must be strictly followed to prevent post resuscitative hypoxic brain injury.

### **Post Resuscitative Hypoxic Brain Injury**

Post resuscitative hypoxic brain injury is considered the major threat to survivors of cardiac arrest:

The devastating neurologic injury that is caused by cardiac arrest has been recognized since the early development of modern resuscitation techniques.

The persistence of unfavorable neurologic outcomes, despite advances in CPR, led the American Heart Association to recognize brain injury after cardiac arrest as an important area for clinical research. In its

2000 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care, the term “cardiopulmonary-cerebral resuscitation” was proposed to emphasize brain injury in relation to cardiac arrest. (Geocadin, Koenig, Jia, Stevens, & Peberdy, 2008, p. 488).

Hypoxic brain injury is part of an umbrella of pathologic condition known as Post-Cardiac Arrest Syndrome. Symptoms of this injury consist of coma, seizures, myoclonus, cognitive dysfunction, possible spinal and cortical stroke, secondary Parkinsonism, and brain death (Field et al., 2008). Hypoxic brain injury is a complex pathological process that comprises post-cardiac arrest brain injury, myocardial dysfunction, systemic ischemia, and persistent precipitating pathology. The extent of damage caused by these disorders after Return of spontaneous Circulation (ROSC) varies with each individual patient based on the severity of the insult, the cause of cardiac arrest, and the patient’s pre-arrest health status. ROSC, if achieved soon after onset of cardiac arrest, will provide a propitious prognosis for neurological outcome and thus prevent the occurrence of the syndrome. However, some patients who initially achieve ROSC after cardiac arrest experience death due to the multi-organ pathology of this syndrome (Neumar et al.).

Post-cardiac arrest injury, if not recognized early enough, usually results in increased rates of mortality and morbidity. Management of post-cardiac arrest syndrome is time-sensitive. Frequent monitoring and early intervention are therefore critical (Neumar et al., 2008). A study of patients who survived cardiac arrest but died afterwards showed brain injury as the cause of death in 68% out-of-hospital and in 23% in-hospital cases. This occurs because the brain is a delicate and vulnerable organ that has limited tolerance to ischemia (Laver, Farrow, Turner, & Nolan, 2004). The complex mechanisms involved in post cardiac arrest brain injury comprise

“excitotoxicity, disrupted calcium homeostasis, free radical formation, pathological protease cascades, and activation of cell-death signaling pathways. Many of these pathways are executed over a period of hours to days after ROSC” (2008, p. 6). Diller & Zhu also propose that certain biological reaction and physiologic processes are initiated gradually and last for several hours or days. These reactions include elevated intracellular potassium, decreased energy levels, and interference in the blood-brain barrier, inflammation and loss of selective neuron which can subsequently cause permanent neurological impairment or death (2008).

It is hypothesized that prolonged cardiac arrest can be associated with failure of microcirculatory reperfusion in the brain even in the presence of optimal cerebral perfusion pressures. Decreased reperfusion causes ischemia and subsequent infarction in certain regions of the brain. They also found out in a study that the “no-flow phenomenon” is attributed to intravascular thrombosis that results during a cardiac arrest (Ames et al., 1968; Wolfson et al., 1992; Fischer et al., 1996).

Again, the damage caused by brain injury, if considerable, can escalate into secondary brain damage consisting of intracranial hypertension, bleeding, hypoxia, and intracranial edema. This progressive sequence is deleterious to the brain parenchyma since the brain’s oxygen reserves are exhausted within 15 seconds with brain energy reserves being depleted within 5 minutes of global ischemia (Wass, Lanier, Hofer, Scheithauer, & Andrews, 1995).

### **Hemodynamic Optimization**

<b><u>General intensive care monitoring</u></b>
Arterial catheter
Oxygen saturation by pulse oximetry
Continuous ECG

<p>CVP</p> <p>ScvO<sub>2</sub></p> <p>Temperature (bladder, esophagus)</p> <p>Urine output</p> <p>Arterial blood gases</p> <p>Serum lactate</p> <p>Blood glucose, electrolytes, CBC, and general blood sampling</p> <p>Chest radiograph</p>
<p><b><u>More advanced hemodynamic monitoring</u></b></p> <p>Echocardiography</p> <p>Cardiac output monitoring (either noninvasive or PA catheter)</p>
<p><b><u>Cerebral monitoring</u></b></p> <p>EEG (on indication/continuously): early seizure detection and treatment</p> <p>CT/MRI</p>

Table 1. Post-cardiac Arrest Syndrome: Monitoring Options

After ROSC is achieved, half the battle is won—it is an intermediate goal. The actual battle becomes to maximize survival rate and neurological outcome. This is important because of the majority of cardiac arrest patients that attain ROSC, only 3-8% survives to hospital discharge. Specific physiologic parameters must be pursued and the cause of cardiac arrest treated. This implies that laboratory studies including ABG, CBC, and blood chemistries, such as electrolytes, glucose, BUN, creatinine, and cardiac markers are of chief significance post-resuscitation. It is imperative then to comprehend the mechanisms involved in hemodynamics:

Early hemodynamic optimization or early goal-directed therapy (EGDT) is an algorithmic approach to restoring and maintaining the balance between systemic oxygen delivery and demand. Monitoring and therapy are initiated as early as possible with the aim of achieving goals within hours of presentation. This involves optimizing preload, arterial oxygen content, afterload, contractility and systemic oxygen utilization. (Field, Breler, Mattu, Silvers, & Kudenchuk, 2008, p. 431).

As noted in Table 1, the hemodynamic entities affecting preload include central venous pressure (CVP) and pulmonary arterial wedge pressures (PAWP). The CVP is the pressure created by volume of blood in the right heart while PAWP is the pressure created by volume of blood in the left side of the heart. The optimization goal is a CVP of 2-6mm Hg and PAWP of 8-12mm Hg (Klein, 2009, p. 155-158). Field et al. (2008) in their analysis of an EGDT study stated that a mean arterial pressure (MAP), central venous oxygen saturation (ScvO<sub>2</sub>), hematocrit, hemoglobin, lactate, urine output and oxygen delivery index of 65-90mm Hg, >70%, >30%, >8g dL, ≤ 2mmol/L, ≥0.5 mL/kg/hr and >600 mL/min/m<sup>2</sup> respectively are necessary to ensure hemodynamic stability (2008). This stability can be arrived through the use of volume expanders or diuretic, venodilators, vasopressors or arteriovasodilators, positive inotropes or negative inotropes, positive chronotropics or negative chronotropics. Inotropes are recommended for the reversal of global myocardial dysfunction. Nonetheless, the duration and severity of myocardial dysfunction impacts the survival rate. An echocardiogram, if utilized early in the resuscitation sequence, will help determine the extent of the damage and consequently guide the course of therapy.

The EGDT algorithm is beneficial in the sense that it helps regulates inflammatory response, reduces the degree of organ dysfunction, and reduces the strain on health care

resources (Field et al., 2008). However if the various treatment discussed above do not prove effectual at restoring adequate perfusion, an alternative will be mechanical circulatory assistance (Laurent, Monchi, Chiche, et al., 2002). In such a situation where pump failure of myocardial dysfunction is refractory to drugs, an intra-aortic balloon counterpulsation can be very helpful. It is inserted percutaneously or via arterotomy into the thoracic aorta and works by complementing coronary artery perfusion, reducing afterload and by optimizing cardiac output (“Cardiac Arrest,” 2005).

It is still common place to have hemodynamic instability post cardiac arrest. This instability presents with dysrhythmias, low cardiac index, and hypotension. Hypotension is managed by correcting CVP values by infusing intravenous crystalloids to expand the volume thereby increasing blood pressure. Dysrhythmias are usually caused by electrolyte imbalances and focal cardiac ischemia and therefore immediate reperfusion with antiarrhythmic drugs is essential in order to arrive at positive outcomes. Post resuscitation, VF or VT may recur. It should be noted that, “prophylactic antiarrhythmic drugs do not improve survival and are no longer indicated. However, patients manifesting such rhythms may be treated with procainamide or amiodarone” (Field et al., 2008; “Cardiac Arrest,” 2005). Normal levels of cardiac index are 2.5-4.2 L/min, and patient’s levels must be kept within these levels. Also, patients that may have developed ST elevation myocardial infarction (STEMI) are candidates for angioplasty or stent placement via coronary angiography. In the absence of a catheterization laboratory or resources, thrombolytic therapy is advised. Thrombolysis after aggressive resuscitation may cause cardiac tamponade (McDonough, 2009; 2005). In spite of promising clinical trials and research, much evidence is still limited.

### **Neurological Pathology and Regulation.**

The brain depends on uninterrupted oxidative metabolism to uphold neuronal function, for cellular detoxification and for the maintenance of membrane integrity. “Normal cerebral perfusion is 750–1000 ml min<sup>-1</sup>, about 20% of the total cardiac output, allowing an oxygen consumption of 3.5 ml 100 g<sup>-1</sup> min<sup>-1</sup>” (Bouch et al., 2008, p. 2). About 8 to 20% of adults have some degree of CNS dysfunction following resuscitation from cardiac arrest. Hypoxic brain injury is a result of direct neuronal ischemic damage and cerebral edema. Damage may evolve over 48 to 72 h after resuscitation. During cardiac arrest, decreased blood circulation in the brain causes global ischemia, necrosis, and injury to the brain. According to Geocadin et al., (2008) during this time, the cerebral cortex, cerebellar Purkinje cells and some regions of the hippocampus are more assailable to injury than the brain stem, thalamus, hypothalamus and subcortical regions. The brainstem surprisingly has much more stability and enduring capacity than most of the other parts of the brain (Geocadin, Koenig, Jia, Stevens, & Peberdy, 2008). Neigh et al. (2004), through their study, suggest a possible correlation between the reduced spinal density of dendrites in the CA1 area of the hippocampus and post-cardiac arrest cognitive impairment (Neigh, Glasper, Kofler, Traystman, Mervis, Bachstetter, & DeVries, 2004). The patient, after cardiac arrest is faced with a dysfunction in the level of conscious and arousal state which is due to ischemic injury to the thalamus and surrounding areas of the cortex. The ischemic injury is as a result of decreased oxygen supply less than 2ml 100g<sup>-1</sup> min<sup>-1</sup>. Oxygen supply below this level automatically causes damage to the neuronal connections in the brain thereby impairing brain function.

This, according to Bouch et al. also causes anaerobic glycolysis, which, if not treated early can lead to lactic acidosis of the brain parenchyma (2008). Anaerobic glycolysis represents

a major neurological setback for most post cardiac arrest patients during the early phase of resuscitation. Anaerobic glycolysis manifests as an attempt to preserve cranial nerve and sensory motor reflexes. However, the concurrent impairment of the cortex and thalamus in association with relative preservation of the brainstem leads to a vegetative and comatose state (Wijdicks et al., 2008, p. 489). Hypoxic brain injury can also have other sensory and functional manifestations. These include psychological and neurological complications such as short-term memory loss, decline in executive function, anomia, visual disturbances, and possible dysfunctional movement such as ataxia, apraxia, spasticity, myoclonus, and quadriparesis (“Cerebral hypoxia,” 2010). Due to the complicated pathophysiology of this complex syndrome, quintessential resolution is required to ensure a positive neurological prognosis.

Prognosis is dependent on certain essential factors. These factors comprise the duration of oxygen deprivation, the extent of brain injury, and the duration of unconscious state (“Cerebral hypoxia,” 2010).

#### ***Controlled Oxygenation.***

The brain tissue thrives on constant oxygen supply in order to perform its biochemical processes. Therefore after ascertaining the crux of the hypoxic brain injury, it is important that oxygen levels are restored to acceptable. The goal then is to ensure 100 percent oxygen supply via mouth to mask, bag- valve-device (BVD) with mask, or ETT (Klein, 2009, p.239 -254).

An evidence report submitted for the case of a hyperbaric oxygen therapy (HBOT) is currently under review. The therapy delivers 100 percent oxygen via inhalation to the client within a pressurized hyperbaric confinement. HBOT causes a state of increased pressure and oxygen levels (McDonagh, Carson, Ash Barry S. Russman, Stavri, Krages & Helfand, 2003).

This therapy has proven very effective:

HBOT is typically administered at 1 to 3 atm. While the duration of an HBOT session is typically 90 to 120 minutes, the duration, frequency, and cumulative number of sessions have not been standardized. Hyperbaric oxygen therapy is the administration of high concentrations of oxygen within a pressurized chamber. HBOT has become the definitive therapy for patients with decompression illness, gas embolism, and severe, acute carbon monoxide poisoning and is a widely accepted treatment for osteoradionecrosis, soft tissue radionecrosis, wound healing, and several other conditions. However, the role of HBOT in the treatment of patients with brain injuries is controversial (McDonagh M, Carson S, Ash J, et al., 2003)

*Antioxidants Therapy (Free Radical Scavengers).*

Free radicals are highly volatile compounds that are normally by-products of cellular respiration and metabolism. Cells are responsible for mounting defense mechanisms to eliminate or reduce the circulating free radicals because these radicals aggravate cerebral injuries by destroying lipids, proteins and nucleic acids. An “imbalance between cellular production of free radicals and the ability of cells to defend against them is referred to as oxidative stress (OS). OS has been implicated as a potential contributor to the pathogenesis of acute central nervous system (CNS) injury” (Gilgun-Sherki, Rosenbaum, Melamed & Offen, 2002, p. 271). Antioxidants are free radical scavengers. They are endogenous or exogenous substances that function to eliminate superoxide radicals (O<sub>2</sub>), and to hinder OS formation thereby preventing further cerebral tissue damage.

**Therapeutic Hypothermia**

Several studies have purported the effectiveness of therapeutic hypothermia and the role it plays in post-arrest intervention:

Induced hypothermia as a therapy for acute brain injury was described in

the 1940s by Fay. In 1950, Bigelow and colleagues reported the usefulness of hypothermia during cardiac surgery. Over the following decade, Rosomoff designed the landmark experimental models of therapeutic hypothermia in brain injury. In the 1980s, researchers in Pittsburgh and Miami approached induced hypothermia for brain injury after cardiac arrest in a more systematic manner. This led to extensive preclinical studies that showed functional and survival benefit in rodent and canine models. The first human clinical study on induced hypothermia for survivors of out-of hospital cardiac arrest was performed by Bernard and colleagues in 1997. In this pilot safety and feasibility study, hypothermia was induced in 22 patients using surface cooling with ice packs and maintained for 12 hours in the ICU. In 1998, Yanagawa and colleagues reported a study of 13 cardiac arrest survivors who were cooled to a target temperature of 33°C for 48 hours using cooling blankets and convective heat loss through alcohol evaporation. Both studies suggested a potential therapeutic benefit to hypothermia after cardiac arrest and paved the way for definitive trial. (Geocadin et al., 2008).

The concept of therapeutic hypothermia was conceived from several studies that reported that brain injury as a result of ischemia causes an elevated body temperature. The fever exacerbates the extent of neurological impairment and lengthens the period of hospitalization. Therefore, fever is associated with a poor neurological outcome post cardiac arrest, and the converse is true (Klein, 2009; Cady, & Andrews, 2009; Cardiac Pathway, 2009; Green & Howes, 2005; Diller & Zhu, 2009; Bouch et al., 2008).

**Sedation and Neuromuscular Blockade**

A primary and apparent disadvantage of therapeutic hypothermia is shivering. Shivering must be prevented or treated because it can nullify the purpose of therapeutic hypothermia as it generates an elevation of the core body temperature thereby increasing oxygen consumption (Nolan, Morley, Hoek, & Hickey, 2003).

Sedation is an essential step performed prior to inducing therapeutic hypothermia. It can be achieved using an infusion of propofol and fentanyl measured using the “bispectral index” of about 40 to 60. Cardiac Pathway (2009), suggests using propofol or lorazepam, and fentanyl while titrating with BIS monitor. Most patients requiring hypothermia may also require mechanical ventilation; therefore sedation supports the efforts of the mechanical ventilation by calming the patient. Cisatracurium is a besylate, a nondepolarizing neuromuscular blocking agent. It is primarily used to relax or paralyze the muscles prior to a procedure such as the one in question. Cisatracurium is also used to prevent shivering, an adverse effect of therapeutic hypothermia. Monitoring is done using electroencephalograms, nerve stimulators, and accurate nursing assessment (Cardiac Pathway, 2009; McDonagh, Allen, Keifer & Warner, 2006; McDonough, 2009). Eventhough ample data supporting this practice are limited, physicians usually sedate and ventilate comatose post-cardiac arrest patients. This ensures the administration of therapeutic hypothermia with considerable ease (Nolan et al., 2003).

**Cooling and Re-warming.**

On therapeutic hypothermia, Nolan et al. purport that the cooling process must begin immediately after the restoration of spontaneous circulation. They also state that the accurate duration, target temperature, and the extent of the process have not been as yet standardized due to the need of further studies (2003).

Various cooling systems and procedures have been invented and tried for the purpose of therapeutic hypothermia. To ensure high efficacy, two approaches of cooling are adopted— external and internal approaches. Each approach has the goal of reducing the core body temperature to a target temperature of range 32°-34 °C. Cardiac Pathway (2009) of the University of Pennsylvania proposes the use of cold normal saline for internal cooling and the Gaymar Medi-therm III 7900 cooling system with Rapr-Round cooling wraps for external cooling. Its usage is shown through the algorithm below;

<b>Gaymar Medi-Therm III Cooling Unit</b>
Keep device plugged in at all times
Connect circumferential torso pad to first cooling hose, fill with water, then apply to patient  Connect (in series) circumferential thigh cooling pads to second cooling hose, fill with water, then apply to patient
Connect temperature monitoring foley to temperature monitoring port on cooling device (if urine output less < 4 cc/hr switch to esophageal temperature probe)
Frequent assessment of wraps to ensure proper cooling.
Set to automatic mode, rapid cooling, with target time of 33°C
Set in automatic mode, gradual, with target temperature of 37°C (this will rewarm patient @ 0.17°C/hr, [1°C/6hrs]).

Table 2. Gaymar Medi-Therm III Cooling Unit protocol according to University of Pennsylvania

McDonagh et al. discuss the infusion of refrigerated normal saline using a specialized femoral catheter and the CoolGuard system. Cooling can also be achieved through the use of intravenous cold crystalloids alongside external cooling with air or liquid blankets (2006). External cooling methods suggested by Nolan et al. include the use of ice packs, wet towels, and cooling head gears, applied to specific points on the upper and lower extremities. Other methods that are available but not considered *prima facie* comprise the peritoneal and pleural lavage, and the extracorporeal cooling. Though considered very efficacious, they are not found in practice because of their extensive invasive nature (Nolan et al., 2003). Cooling takes place within a period of 24 hours accompanied by stable sedation, paralysis, and analgesia.

As noted in the Gaymar algorithm, after 24 hours, when optimal cooling has been maintained, the next step is to slowly re-warm the patient to normal temperature. During the re-warming process, the patient remains paralyzed until a temperature of 36°C is reached. Measures must also be set in place to correct hemodynamic alterations such as decreased cardiac output, central venous pressure, and systemic oxygen concentration (Cardiac Pathway, 2009).

#### ***Seizure Control and Prevention and Glycemic Regulation.***

Seizures that occur over a long period of time may cause cerebral injury. Their occurrence causes an increase in metabolic demands as well as increased intracranial pressures (Geocadin et al., 2008). Seizures should be treated promptly with benzodiazepines, phenytoin, valproate sodium, propofol, or a barbiturate. Each of these medications can potentially cause hypotension, which must be treated (McDonough, 2009). During the process of therapeutic hypothermia, there is decreased insulin sensitivity and secretion resulting in a hyperglycemic state. The resulting hyperglycemia must be corrected per hospital policy or protocol (Cardiac Pathway, 2009; Geocadin et al., 2008; Zeiter, 2005).

### **New Discoveries and Research**

In an attempt to increase efficacy in the implementation of therapeutic hypothermia, BeneChill®, a European privately-managed medical equipment company embarked on a mission to develop novel cooling technologies to this effect. The device is called the RhinoChill™ Intra-Nasal Cooling System. The cooling device promises to overcome the limitation of invasiveness, access, and duration experienced by the use of most traditional methods of cooling. RhinoChill™ technology uses a non-invasive nasal catheter that administers a rapidly evaporating coolant liquid. Its goal is to achieve prompt and safe administration of therapeutic hypothermia through direct conductive heat transfer and indirect convective heat transfer (BeneChill, 2010). Also, due to its portability and simplicity of use, persons that are either less-trained or untrained in the medical field can operate the device during a cardiac arrest before ROSC occurs thereby improving the neurological prognosis. This new technology is however unavailable for sale in the U.S. Studies conducted in Europe reveal that the RhinoChill™ Intra-Nasal Cooling System allows for the brain to be cooled 3 hours faster than by other cooling methods used in the hospital. The timely cooling process of RhinoChill™ during resuscitation attempts promises to increase survival rates, improve neurological outcomes and eventually shorten the length of stay in the intensive care units of the hospital (BeneChill).

Nolan et al. also propose an intravascular heat exchange machine that allows for early cooling and accurate temperature regulation during therapeutic hypothermia (2003).

The reperfusion injury that accompanies post-cardiac arrest resuscitation causes an influx of calcium. A research was executed with this concept in mind to discover the effects of the “calcium influx” on the progress of the syndrome and thus employing the outcome to devise a treatment. Unfortunately, investigative intervention with lidoflazine and nimodipine proved

futile. Likewise, the use of steroids and “polyethylene glycolconjugated Glycolconjugated superoxide” has not yielded promising outcomes. In a similar vein, investigations are on-going regarding strategies that will be effective at shielding the mitochondria from intense damage. This is because the neuronal damage that occur post-cardiac arrest can be attributed in part to early mitochondrial destruction. Protecting the mitochondria will consequently serve as a preventive measure to limit neuronal impairment (Bouch et al., 2008).

Some studies in recent years have also suggested selective cooling involving the brain as a better option to complete body cooling. Complete body cooling runs the risk of systemic complications while selective cooling of the brain, which is only 2% of body mass narrows down to the target organ in question through direct contact with brain tissue or through blood supply to the brain. It is more effective and has minimal complications as compared to whole body cooling (Diller & Zhu, 2009).

### **Prognostication and Nursing Consideration**

Every intervention that takes place from the very onset of cardiac arrest to post-resuscitation is vital to achieving a better neurological prognosis. Prognosis is dependent largely on how soon treatment is administered, the accessibility to optimal facilities and the clients overall health outlook. Time is also very essential in implementing therapeutic hypothermia. Many clinical studies have evidence to this fact. All post-resuscitation interventions have complications. Prevention and immediate treatment of these also contribute to a promising clinical outlook for the patient.

Nurses function as an integral part of the whole to bring about holistic care and also to improve the patient’s chances of survival with good neurological outcome. According to McDonough , “bedside neurological examination remains one of the most reliable predictors of

functional outcome after cardiac arrest” (2009). Neumar et al. also state that the “absence of papillary response, corneal reflex, or motor response to painful stimuli at day 3 is the most reliable predictor of poor outcome” (2008). Nurses also have the responsibility of assisting with BLS, ACLS, and at every stage of treatment.

Nurses must be abreast with the hemodynamic status of the patient in order to report remarkable alterations in status. Also, the patients are at risk for cognitive dysfunction and problems with performing activities of daily living. Nurses must therefore involve the appropriate therapists to help improve patients’ quality of life.

### **Conclusion**

Hypoxic brain injury post-cardiac arrest remains a major concern in the healthcare arena in spite of the improvement in care as well as technological advancement. The American Heart Association and other health care organization have made great impact through the provision of pertinent information about hypoxic brain injury post-cardiac arrest, quintessential post-cardiac arrest care and the conducting of feasibility studies. Amidst all this wealth of knowledge and progress, limitations in regards to hypoxic brain injury post- cardiac arrest are yet inevitable. Research is still on-going to develop a more standardized model of treatment for victims of hypoxic brain injury post-cardiac arrest. Prior to the use of therapeutic hypothermia, many clinical trials with the quest of discovering neuroprotective mechanisms were unproductive. Existing concepts and theories on the efficiency of therapeutic hypothermia have not yielded much result on the actual modus operandi. The mechanism by which therapeutic hypothermia functions remains unsettled though the mechanism is speculated to include a reduction in the release of harmful chemicals, decreased metabolism and cerebral oxygen demand, decreased intracranial pressure, and the preservation of non-ischemic brain tissue. Despite limited

information on the mechanism of action of this therapy, therapeutic hypothermia has provided optimal neurological outcome in post-cardiac arrest survivors.

Therapeutic hypothermia has however not been approved as standard of practice and as such cannot be performed as a routine procedure. Extensive randomized controlled research including varied populations in different locations is required to establish a standardized criteria and mechanism for the use of therapeutic hypothermia in present practice. Research of such caliber will enhance future treatment options for hypoxic brain injury.

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