Cardiac arrest (CA) remains one of the most dramatic, unexpected and life threatening events in life. Survival and neurological recovery differ widely, depending on whether an arrest was witnessed or unwitnessed and the initial cardiac rhythm during resuscitation. Even among patients with successful return of spontaneous circulation (ROSC) who are admitted to an intensive care unit, survival until hospital discharge has historically been <10% ***(Frederickson et al., 2003)***.

Improvements in the survival and neurological outcomes of patients with CA have focused on 2 major points of treatment. The first is increased education to improve immediate post-CA perfusion through national efforts promoting the 4 links in the chain of survival that include early access to emergency department, early cardiopulmonary resuscitation, early defibrillation, and early advanced cardiac life support ***(Nichol et al., 2008)***.

The second point is greater emphasis on post-resuscitation care, which includes optimizing ventilation and oxygenation, avoiding hypotension, treating immediate precipitants of CA such as acute coronary ischemia and initiating therapeutic hypothermia ***(Peberdy et al., 2010)***.

Induction of moderate hypothermia (28°C to 32°C) before cardiac arrest has been used successfully since the 1950s to protect the brain against the global ischemia that occurs during some open-heart surgeries. Successful use of therapeutic hypothermia after cardiac arrest in humans was also described in the late 1950s but was subsequently abandoned because of uncertain benefit and difficulties with its use ***(Marion et al., 1996).***

The application of therapeutic hypothermia after cardiac arrest received encouragement from two independent studies conducted in Europe and Australia**.** These studies aimed to ascertain the efficacy of controlled cooling in cardiac arrest patient demonstrating shockable rhythm following ROSC ***(Bernard et al., 2002).***

In addition, the studies used therapeutic hypothermia several hours after resuscitation and therefore the role for earlier cooling or prolonged cooling was not evaluated. Given that survival rate in these other conditions is very low, it is unlikely that clinical trials will be undertaken to test the efficacy, as a very large sample size would be necessary to show a difference in outcomes. Given that the induction of hypothermia has become more feasible, the side effects are generally easily

managed in the critical care setting, and there may be some benefit for anoxic brain injury. Also, induced hypothermia may have some role in comatose post – cardiac arrest patients ***(Bernard et al., 2002).***

The aim of this work is to conduct a systematic review of currently available evidence on the role of therapeutic hypothermia after cardiac arrest.

Cardiac arrest leads to sudden cessation of blood flow, leading to a rapid exhaustion of cerebral oxygen and adenosine triphosphate stores and decreased cerebral function. Neuronal destruction occurs in the CNS during cardiac arrest (Phase I, "No Flow") and following the return of spontaneous circulation (ROSC) (Phase II, "Low Flow") ***(Xiao, 2002***). The survival of neurons differs, depending on the site, type and period of global anoxia. In general, neurons in the cerebral cortex, basal ganglia and hippocampus are the most vulnerable (***Silbergleit et al., 2002***).

**Physiological changes following ROSC:**

After the recovery of spontaneous circulation, cerebral blood flow initially reaches supernormal levels but falls to below normal over several hours. This reduced cerebral perfusion pressure is a consequence of cerebral vasospasm which occurs due to leukocyte clumping, endothelin release and microvascular coagulation further reduces the cerebral blood flow. Increased cerebral oxygen requirements during the low-flow phase further result in secondary ischemia (***Silbergleit et al., 2002***).

Inflammatory cascade that starts during resuscitation continues following ROSC. The main neurotransmitters that are responsible for inflammatory cascade are matrix metalloproteinase, amino acids (e.g. glutamate) and N-methyl-D-aspartate (NMDA) which causes receptor activation and increased microvascular permeability which further lead to

calcium influx that l results in cerebral edema, raised intracranial pressure and brainstem herniation. Supplementary contributing factors include free radical formation, auto digestion by activated proteases and apoptosis (***Silbergleit et al., 2002***).

The therapies tried for reducing intracellular edema, including NMDA receptor antagonists, albumin, mannitol and hypertonic saline have not proven advantageous (***Xiao, 2002***).

**Benefits of TH on cellular level:**

Following are the benefits of therapeutic hypothermia (TH) which are associated with slowing down of cellular cascade after cardiac arrest by slowing down the cerebral metabolism (approximately 6-8% per 1°C) reducing excitatory amino acids (glutamate) release attenuation and/or reversibility of ischemic depolarization of the CNS leading to membrane stabilization, electrolyte redistribution and normalization of intracellular water concentration and intracellular pH (stabilization of the blood-brain barrier), reduction of oxygen free radical production and lipid peroxidation restoration of normal intracellular signaling mechanisms (including calcium modulation) and inhibition of deleterious signaling mechanisms, such as apoptotic signaling, restoration of protein synthesis and gene expression, inhibition of deleterious inflammatory products (i.e. cytokines, interleukins , arachidonic acid cascade end

products), attenuation of CSF platelet-activating factor (PAF) and inhibition of cytoskeletal destruction (***perberdy et al., 2010).***

**Body response to hypothermia:**

If hypothermia develops (either accidentally or intentionally induced), the body will immediately try to antagonize this disturbance in homeostasis. The initial response will be to decrease heat loss mainly through vasoconstriction in the skin and increasing sympathetic tone. This response complicates trials to induce TH by external cooling. In addition, heat generation will be increased through shivering and in later phases, through the increased metabolism of fats, carbohydrates and proteins. Shivering can result in increases in oxygen consumption of between 40% and 100 % (***Matsukawa et al., 1995***). An undesirable effect particularly in patients with neurological and/or post-hypoxic injury. These responses can be antagonized by the administration of sedatives, anesthetics, opiates and/or paralyzing drugs. Anesthesia and Sedation also increase peripheral blood flow, thereby increasing the transfer of heat from the core to the periphery (***Fischer et al., 1999***).

It should be noted that the effectiveness and capacity of the mechanisms to control body temperature decrease with age. Young patients will react earlier and with greater intensity and effectiveness to changes in body temperature than older patients.

In addition, old patients have a lower rate of metabolism, often a lower body mass index (BMI) and less effective vascular response (i.e., less vasoconstriction). Thus the induction of hypothermia in younger patients will be significantly more difficult than in older patients. Induction of hypothermia in young patients usually requires high doses of sedatives to counteract the above-mentioned counter-regulatory mechanisms. Similarly, achieving hypothermia through surface cooling in obese patients will take more time due to the insulating properties of fat. This implies that the surface cooling of obese patients will be more difficult and require more time to achieve target temperature (***Schaller and Graf, 2003***).

**Metabolic changes during application of TH:**

Hypothermia leads to a lowering of the metabolic rate. Indeed, in the past it was assumed that the protective effects of hypothermia were due solely to the slowing of cerebral metabolism, with associated decreases in consumption of oxygen and glucose. It has since become clear that other mechanisms are involved, which probably play a much greater role than the changes in metabolic rate. Nevertheless, the effects on metabolism are significant and probably play a part in providing neuroprotection. In addition, these changes in metabolism occur in all systems; this means, for example, that there will be a decrease in oxygen consumption and carbon

dioxide production (which implies that ventilator settings should be adjusted), a reduction in feeding requirements, etc. Metabolism is reduced by between 5% and 7% per Celsius degree reduction in body temperature. Cerebral blood flow is decreased but when corrected for the decrease in metabolism, the net result is a relative increase (***Schaller and Graf, 2003***).

Many hypothermia-induced metabolic changes occur relatively quickly, within the first hours. These include changes in energy metabolism and reduction in adenosine tri-phosphate (ATP) requirements. Other changes, such as a rise in lactate level, occur over a longer period of time (>3 h). Induction of hypothermia also leads to an increase in membrane stability, with decreased permeability of cellular membranes, the blood-brain barrier and blood vessel walls (***Chi et al., 2002***).

One of the results of this is a reduction in edema formation that appears to be one of the ways in which hypothermia can protect against neurological injury. In addition, hypothermia can prevent the excessive influx of Ca2+ into the cell, as well as decrease accumulation of the excitatory neurotransmitter glutamate in the extracellular space. Calcium influx and glutamate accumulation are key elements in the destructive pathway that can follow a period of ischemia; calcium influx into the cell can lead to mitochondrial

dysfunction and the activation of various enzymes which can cause additional cell injury and death. Hypothermia also leads to a decrease in intracellular acidosis (although the extracellular pH usually decreases slightly during cooling due to increased levels of lactic acid, glycerol, free fatty acids and ketonic acids) (***Siesjo et al., 1989***).

**Immune response to hypothermia:**

Hypothermia also influences the immune system, with an reduction of neutrophil and macrophage function, suppression of inflammatory reactions and inhibition of the release of pro-inflammatory cytokines (***Kimura et al., 2002***). This effect on immune response may contribute to hypothermia neuroprotective effects but increases the risk of infections. Other anti-inflammatory mechanisms include the prevention or mitigation of reperfusion-related DNA injury, lipid peroxidation and leukotriene production as well as a decrease in the production of nitric oxide. In addition, hypothermia decreases reperfusion injury and free radical production (***Busto et al., 1989***).

**Effects of TH on body systemes:**

Induction of hypothermia induces a large number of physiological changes in the circulatory and respiratory systems, coagulation system, drug metabolism, etc. For the successful use of hypothermia, awareness of these pathophysiological mechanisms is of key importance. The failure to demonstrate positive effects of hypothermia in some clinical trials may be partly due to insufficient regard for side effects causing the negation of protective effects. In addition, unawareness of hypothermia's physiological consequences may lead to over-treatment. For example, even mild hypothermia induces reduction in cardiac output, mild acidosis, a rise in lactate levels and a moderate increase in levels of amylase. These changes are normal, do not signify any deterioration in the patients' condition and do not require treatment (***polderman et al., 2003).***

Naturally, such changes can sometimes be undesired, such as shivering with its associated rise in oxygen consumption and patient discomfort. Many of these physiological effects can be counteracted by suitable medications, such as paralyzers, analgesics or sedatives (***polderman et al., 2003).***

The physiological and pathophysiological effects of cooling depend on the extent of hypothermia. For example, a significant risk for severe Dysrhythmias occur only at

temperatures below 28–30°C. Such low temperatures are now rarely employed in induced hypothermia, although they are used more frequently in specific surgical procedures, such as major vascular interventions (***polderman et al., 2003***).

**Cardiovascular and hemodynamic effects**

Hypothermia is initially associated with sinus tachycardia after which bradycardia occurs. This is due to decreases in metabolism and partly to the direct effects of hypothermia on the heart. Various ECG changes may develop. The risk of dysrhythmias during mild or moderate hypothermia is very low, but increases significantly when the temperature drops below 30°C. The initial dysrhythmia is usually atrial fibrillation, which can be followed (at temperatures ≤28°C) by the risk of ventricular flutter or fibrillation. An additional problem is that dysrhythmias in deeply hypothermic patients are difficult to treat, as the myocardium becomes less responsive to anti-arrhythmic drugs and defibrillation. When TH is applied, therefore, great care should be taken to keep temperatures at 30°C or more, as the risk of clinically significant dysrhythmias increases below this temperature level (***Frank et al., 2003***).

Initially, the induction of mild hypothermia increases myocardial oxygen demand relative to supply; the mechanism is probably a hypothermia-induced increase in plasma levels of

noradrenaline and adrenaline results in an increase in cardiac output and oxygen demand. With further decreases in temperature, slowing in heart rate and metabolism will reduce cardiac afterload and oxygen requirements. Mild hypothermia decreases cardiac output by about 25% and lead to increased vascular resistance and a rise in central venous pressure. During severe hypothermia (≤30°C) left ventricular contractility itself may decrease, leading to systolic and diastolic dysfunction (***Frank et al., 2003***).

In healthy subjects, mild hypothermia (35.5°C) has been shown to increase coronary perfusion. However, coronary vasoconstriction may occur during hypothermia in patients with coronary artery disease. This difference is presumed to be caused by endothelial dysfunction associated with atherosclerosis. This would imply that there is a theoretical risk of myocardial injury during the induction of mild hypothermia in patients with cardiovascular disease, especially in the phase when cooling is initiated and the heart rate temporarily increases ***(Nabel et al., 1988)***.

## Coagulation

Hypothermia induces a mild bleeding tendency with increased bleeding time due to its effect on platelet count and, the kinetics of clotting enzymes, plasminogen activator

inhibitors and other steps in the coagulation pathway ***(Ferrara et al., 1990).***

It should be noted that the laboratory results of standard coagulation tests such as prothrombin time and partial thromboplastin time will remain within normal because these tests are performed at 37°C in laboratories. Tests will be prolonged only if they are performed at the patient's actual core temperature (***Rohrer et al., 1992***).

The risk of significant bleeding is very low in spite of the above-mentioned abnormalities, even in patients with traumatic brain injury (TBI). None of the clinical trials in patients with TBI, stroke, subarachnoid hemorrhage or post-anoxic coma have reported increased intracerebral bleeding associated with cooling (***Resnick et al., 1994***).

## Infection

Evidence from clinical and in vitro studies shows that hypothermia can impair immune function. Indeed, inhibition of inflammatory responses may be one of the mechanisms through which hypothermia exerts neuroprotective effects. Hypothermia inhibits the release of different inflammatory cytokines and suppresses chemotactic migration of leukocytes and phagocytosis (***Salman et al., 2000***).

Hypothermia-induced insulin resistance and hyperglycemia may further increase infection risks. Thus, there are plausible mechanisms for an immunosuppressive effect of hypothermia. Some studies have also stated a higher risk of wound infections associated with hypothermia. This may be associated with both hypothermia-induced vasoconstriction and decreased leukocyte function (***Sessler, 2001***).

## Hypovolemia, fluid balance and electrolytes

The induction of hypothermia can lead to the loss of considerable amounts of fluids due to so-called hypothermia-induced diuresis. This may be especially noted in patients with TBI, in whom diabetes insipidus (induced by cranial trauma) and administration of drugs such as mannitol may exacerbate fluid losses (***Kaufman et al., 1993***).

The impact of this may be significant, especially in patients with TBI or subarachnoid hemorrhage (SAH) where even brief episodes of hypovolemia or hypotension can adversely affect outcome (***The Brain Trauma Foundation, 2000***).

Indeed, any beneficial effects of hypothermia may be lost due to side effects if these are not treated vigorously. Close attention should be paid to the patients' diuresis and fluid