Therapeutic Hypothermia After Cardiac Arrest

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ABG	Arterial blood gas
ACS	Acute coronary syndrome
ADH	Antidiuretic hormone
AKI	Acute kidney injury
ATP	Adenosine triphosphate
BNP	Brain natriuretic peptide
CA	Cardiac arrest
CBF	Cerebral blood flow
CI	Confidence interval
$CMRO_2$	Cerebral metabolic rate of oxygen consumption
CNS	Central nervous system
CO	Cardiac output
CPR	Cardiopulmonary resuscitation
CPK	Creatine phosphokinase
CPP	Cerebral perfusion pressure
CYP_{450}	Cytochrome p_{450}
DNR	Do not resuscitate
ECG	Electrocardiography
EEG	Electroencephalography
GCS	Glasgow coma score
HACA	Hypothermia after cardiac arrest
HIE	Hypoxic-ischemic encephalopathy
I/R	Ischemia/reperfusion
ICP	Intracranial pressure
ICU	Intensive care unit
ILCOR	International liaison committee on resuscitation
MAP	Mean arterial pressure
MCA	Median cerebral artery
MI	Myocardial infarction
NCSE	Non-convulsive status epilepticus
NO	Nitric oxide

NMBDS	Neuromuscular blocking drugs
NSE	Neuron-specific enolase
PCI	Percutaneous coronary intervention
PAF	Platelet-activating factor
PT	Prothrombin time
PTT	Partial thromboplastin time
ROSC	Restoration of spontaneous circulation
RT-PA	Recombinant tissue plasminogen activator
S-١٠٠B	S-١٠٠B Protein
SBP	Systolic blood pressure
SCI	Spinal cord injury
SD	Standard deviation
SSEP	Somatosensory-evoked potentials
SVR	Systemic vascular resistance
TBI	Traumatic brain injury
TOF	Train-of-four
VF	Ventricular fibrillation
VT	Ventricular tachycardia

Aim of the study

This review we will examine the potential mechanisms of action and current clinical evidence surrounding the use of therapeutic hypothermia, beside the physiologic changes and potential side effects associated with hypothermia. Currently available methods for inducing hypothermia will also be discussed, and practical recommendations on how to deal with potentially harmful effects, and it will also assess the importance of target temperature, time to achieve target temperature, duration of cooling, and re-warming rate on outcomes following neurological injury to gain insights into important factors which may also influence the success of hypothermia in other organ injuries, such as the heart and the kidney, as well as preventive measures, will be provided to help guide clinicians through this sometimes complex treatment.

Introduction

Although the basic principles of resuscitation were described by Versalius more than ٥٠٠ years ago, the practice of cardiopulmonary resuscitation in its modern form only starts ٥٠ years ago. Despite advances in the understanding and practices of airway management, ventilatory support, external cardiac compression and drug therapy, the outcome of patients undergoing cardiopulmonary resuscitation remained poor **(Hazinski et al, ٢٠٠٥).**

Patients may have spontaneous circulation restored and admitted to the intensive care unit, but then developed complications related to ischaemic insult to the brain as well as to the rest of the body. The term post-resuscitation disease was coined by the Russian resuscitologist Vladimir A. Negovsky in ١٩٧٢ to describe the constellation of pathological processes caused by ischaemia and reperfusion associated with cardiac arrest and the subsequent resuscitation. This is more recently renamed post-cardiac arrest syndrome, because the term resuscitation is now used more broadly to include treatment of various shock states in which circulation has not ceased and the term post resuscitation implies that the act of resuscitation has ended **(Nolan et al, ٢٠٠٨).**

There is evidence to support that proper management in the post-resuscitation phase can improve outcome of these patients, and therapeutic hypothermia is one important component of such management. Therapeutic hypothermia should be part of a standardized treatment strategy for comatose survivors of cardiac arrest **(Sunde et al, ٢٠٠٧).**

Induced (therapeutic) hypothermia, defined as an intentional reduction of a patients' core temperature to ٣٢°C–٣٥°C is being used with increasing frequency as a method to prevent or mitigate various types of neurological injury **(Polderman , ٢٠٠٨).**

The history of using cold to treat patients reveals that it is actually an ancient idea. Hippocrates, a Greek physician living ٤٦٠-٣٧٠ BC, noted men

with severe head injuries survived better in the colder temperatures of winter rather than during the summer. Hippocrates also treated patients through cooling, though the justification used then is understandably different from use in modern medicine **(Soar and Nolan, ٢٠٠٧).**

Induced hypothermia as a therapy for acute brain injury was described in the ١٩٤٠s by Fay. In ١٩٥٠, 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 ١٩٨٠s, 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 **(Hicks et al, ٢٠٠٠).**

The first human clinical study on induced hypothermia for survivors of out-of hospital cardiac arrest was performed by Bernard and colleagues **(Bernard et al, ١٩٩٧)** in ١٩٩٧.

In ٢٠٠٢, results of two clinical trials were published regarding the use of therapeutic hypothermia on unconscious patients resuscitated from out-of hospital cardiac arrest; both demonstrated improved neurologic outcome and one of them improved survival. These findings have been confirmed in other nonrandomized studies, systematic reviews and a meta-analysis (**Holzer et al, ٢٠٠٥).**

According to international guidelines, the use of therapeutic hypothermia is recommended for the treatment of comatose cardiac arrest patients, so in ٢٠٠٣, the International Liaison Committee on Resuscitation advised that unconscious post– out-of-hospital cardiac arrest patients should be cooled when the initial rhythm is ventricular fibrillation. The statement also suggested that cooling may be beneficial after nonventricular fibrillation cardiac arrests **(Nolan et al, ٢٠٠٣)**.

Postcardiac arrest includes several pathophysiologic processes: brain injury, myocardial, hepatic, and renal dysfunction; as well as systemic ischemia/reperfusion response. The severity of these disorders is not uniform and will vary in individual patients based on the duration of the ischemic

insult, the cause of cardiac arrest, and the patient's prearrest state of health **(Nolan et al, ٢٠٠٨).**

Mild hypothermia should be implemented, whenever feasible, in addition to standard supportive and critical care. This supportive care should be adapted to both the specific patient situation and specific peculiarities of the hypothermic situation. Lately, recommendations have been published for the general management of patients treated with hypothermia after cardiac arrest, but none suggest the best sedation-analgesia protocol **(Seder and Kloot, ٢٠٠٩).**

It must be emphasized that hypothermia induces significant pharmacokinetic and pharmacodynamic alterations of most drugs used, including sedatives, analgesics, and neuromuscular blocking drugs (NMBDs) **(Arpino and Greer, ٢٠٠٨).**

Terminology used in relation to manipulation of body temperature:

- Hypothermia is defined as core body temperature of less than ٣٦°C regardless of the cause.
- Induced hypothermia is defined as an intentional reduction of a patient's core temperature below ٣٦°C.
- Therapeutic hypothermia is defined as controlled induced hypothermia; i.e. induced hypothermia with the potentially deleterious effects such a shivering, being controlled or suppressed.
- Controlled or therapeutic normothermia is defined as bringing down core temperature in a patient with fever, and maintaining temperature within a range of ٣٦-٣٧,٥°C, with the potentially deleterious effects such a shivering, being controlled or suppressed.

The degree of therapeutic hypothermia can be mild (٣٤,٠-٣٥,٩°C), moderate (٣٢,٠-٣٣,٩°C), moderately deep (٣٠,٠-٣١,٩°C) or deep (<٣٠,٠°C) according to the target temperature **(Polderman and Herold, ٢٠٠٩).**

*All temperature definitions are summarized in table ١.

Table ١: Terminology used in therapeutic hypothermia

Therapeutic temperature management definitions	
Hypothermia	Core temperature <٣٦,٠°C regardless of the cause
Induced hypothermia	An intentional reduction of a patients' core temperature below ٣٦,٠°C
Therapeutic hypothermia	Controlled induced hypothermia: i.e, induced hypothermia with the potentially deleterious effects, such as shivering, being controlled or suppressed
Controlled normothermia/therapeutic normothermia	Bringing down core temperature in a patient with fever, and maintaining temperature within a range of ٣٦,٠°C–٣٧,٥°C, with the potentially deleterious effects, such as shivering, being controlled or suppressed
Temperature range definitions	
Mild therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to ٣٤,٠°C–٣٥,٩°C
Moderate therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to ٣٢,٠°C–٣٣,٩°C
Moderate/deep therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to ٣٠,٠°C–٣١,٩°C
Deep therapeutic hypothermia	An intentional and controlled reduction of a patients' core temperature to <٣٠,٠°C
Mild hyperthermia	Core temperature ٣٧,٥°C–٣٨,٠°C
Moderate hyperthermia	Core temperature ٣٨,١°C–٣٨,٥°C
Moderate/severe hyperthermia	Core temperature ٣٨,٦°C–٣٨,٩°C
Severe hyperthermia	Core temperature ≥٣٩,٠°C

(Polderman and Herold, ٢٠٠٩).

Pathophysiology of post–cardiac arrest syndrome

The high mortality rate of patients who initially achieve return of spontaneous circulation (ROSC) after cardiac arrest can be attributed to a unique pathophysiological process that involves multiple organs. Although prolonged whole-body ischemia initially causes global tissue and organ injury, additional damage occurs during and after reperfusion. The unique features of post– cardiac arrest pathophysiology are often superimposed on the disease or injury that caused the cardiac arrest, as well as underlying co morbidities. Therapies that focus on individual organs may compromise other injured organ systems **(White et al, ١٩٩٣)**.

The ٤ key components of post– cardiac arrest syndrome are:

(١) post– cardiac arrest brain injury,

(٢) post– cardiac arrest myocardial dysfunction,

(٣) Systemic ischemia/reperfusion response,

(٤) Persistent precipitating pathology **(Neumar et al, ٢٠٠٨).**

The severity of these disorders after ROSC is not uniform and will vary in individual patients based on the severity of the ischemic insult, the cause of cardiac arrest, and the patient's prearrest state of health.

(١) Post–Cardiac Arrest Brain Injury :

Post– cardiac arrest brain injury is a common cause of morbidity and mortality **(Laver et al, ٢٠٠٤).**

Post cardiac-arrest brain injury can be divided into an immediate ischemic phase and a reperfusion phase that occurs after ROSC and may persist for up to ٧٢ h. The immediate ischemic phase, if prolonged, can result in death of neurons related to loss of energy stores, mitochondrial dysfunction, and loss of ion gradients. Cell swelling and lysis ensues and sets the stage for ongoing damage during reperfusion **(Neumar et al, ٢٠٠٨).**

During the reperfusion phase, the return of blood flow to ischemic areas introduces inflammatory mediators and oxygen free radicals. Inflammation and peroxidation of lipids, proteins, and DNA precipitates irreversible neuronal damage. Apoptotic pathways are induced. Influx of calcium resulting in release of glutamate and other neuroexcitatory molecules initiates a cycle of cellular activation that promotes depolarization in adjacent neurons and maintains elevated glutamate levels (excitotoxic cascade). Finally, continued energy consumption (a result of the excitotoxic cascade), mitochondrial dysfunction, loss of ion gradients, and ongoing cellular depolarization contribute to further ischemic injury **(Liu and Yenari, ٢٠٠٧).**

The unique vulnerability of the brain is attributed to its limited tolerance of ischemia and its unique response to reperfusion. The mechanisms of brain injury triggered by cardiac arrest and resuscitation are complex and include 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 **(Bano and Nicotera, ٢٠٠٧).**

Histological, selectively vulnerable neuron subpopulations in the hippocampus, cortex, cerebellum, corpus striatum, and thalamus degenerate over a period of hours to days. Necrosis and apoptosis are complex mechanisms involving biochemical processes such as gene expression and protein migration, as well as biophysical processes such as lipid bilayer breakdown. Apoptosis is ATP dependent, whereas necrosis is not. Both processes play out over hours to days and are associated with poor calcium and sodium management, activation of caspases and proteases, and release of mitochondrial cytochrome c, a potent initiator of apoptosis **(Taraszewska et al, ٢٠٠٢).**

Apoptotic cell death participates in pathogenesis of neuronal cell death after traumatic and ischaemic injury. Both neuronal necrosis and apoptosis have been reported after cardiac arrest. The relative contribution of each cell-death pathway remains controversial, however, and is dependent in part on patient age and the neuronal subpopulation under examination **(Blomgren et al, ٢٠٠٣).**

Prolonged cardiac arrest can also be followed by fixed or dynamic failure of cerebral microcirculatory reperfusion despite adequate cerebral perfusion pressure (CPP). This impaired reflow can cause persistent ischemia and small infarctions in some brain regions. The cerebral microvascular occlusion that causes the no-reflow phenomenon has been attributed to intravascular thrombosis during cardiac arrest and has been shown to be responsive to thrombolytic therapy in preclinical studies. The relative contribution of fixed no-reflow is controversial, however, and appears to be of limited significance in preclinical models when the duration of untreated cardiac arrest is < ١٥ minutes **(Böttiger et al, ١٩٩٧).**

Despite cerebral microcirculatory failure, macroscopic reperfusion is often hyperemic in the first few minutes after cardiac arrest because of elevated CPP and impaired cerebrovascular auto regulation; these high initial perfusion pressures can theoretically minimize impaired reflow. Yet, hyperemic reperfusion can potentially exacerbate brain edema and reperfusion injury **(Sundgreen et al, ٢٠٠١).**

Although resumption of oxygen and metabolic substrate delivery at the microcirculatory level is essential, a growing body of evidence suggests that too much oxygen during the initial stages of reperfusion can exacerbate neuronal injury through production of free radicals and mitochondrial injury. Auto regulation of cerebral blood flow (CBF) is impaired for some time after cardiac arrest. During the sub acute period, cerebral perfusion varies with CPP instead of being linked to neuronal activity **(Richards et al, ٢٠٠٧).**

In humans, in the first ٢٤ to ٤٨ hours after resuscitation from cardiac arrest, increased cerebral vascular resistance, decreased CBF, decreased cerebral metabolic rate of oxygen consumption (CMRO٢), and decreased glucose consumption are present. There is limited evidence that brain edema or elevated intracranial pressure (ICP) directly exacerbates post– cardiac arrest brain injury **(Schaafsma et al, ٢٠٠٣),**

Other factors that can impact brain injury after cardiac arrest are pyrexia, hyperglycemia, and seizures; Fever often follows central nervous system