

Therapeutic Temperature Management

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INTRODUCTION

Therapeutic or Induced hypothermia is a deliberate event done in a controlled manner to try and protect tissues from ischaemic injury.

The successful use of hypothermia to protect against neurological damage has been described as early as the 1940's, but further studies were abandoned due to the side effects and technical aspects involved in cooling patients in a controlled manner.

Interest has since been rekindled, and over the last 15 years hypothermia has been studied and tested for a vast number of cardiac and neurological emergencies.

Available evidence suggests that fever (regardless of cause) adversely affects neurological outcome, hence targeting temperature control is vital to comprehensive management of any patient.

Fever is an independent predictor of poor outcome especially if it is present early following brain injury.¹

Furthermore, evidence also suggests that hypothermia can prevent or limit myocardial injury.²

This presentation aims at discussing some core definitions, the underlying mechanisms, physiology, side effects and the practical aspects of induced hypothermia.

THERMOREGULATION

Core body temperature is normally tightly regulated within 0.2 -0.3 °C of 37°C in an unanaesthetized patient. This is done by balancing heat production and heat loss.

Heat production is governed by the basal metabolic rate (BMR), which may be increased by muscular activity (shivering); hormones (adrenaline, noradrenaline, thyroxine); and dietary intake.

Heat loss occurs through radiation (vasodilatation); conduction; convection (lack of piloerection); evaporation (sweating).

Other factors governing the above processes include:

Body surface area, the temperature difference between the body and its environment, and behavioural processes (eg. posture; exercise; clothing; oral intake ; finding shade/shelter).

The hypothalamus is thought to be the thermostat in human beings with the brainstem and spinal cord also being involved by integrating signals at multiple levels in the neuroaxis.

The anterior hypothalamus is responsible for heat conservation (direct reflex vasoconstriction and reduction in sweating), while the posterior hypothalamus is responsible for heat generation and maintenance (shivering and BMR is increased). During anaesthesia, the above mechanisms are abolished.

DEFINITIONS

Hypothermia:

Core body temperature is less than 36°C

Mild Hypothermia:

Core body temperature 34°C - 35.9°C

The typical bodily response at this temperature is to maintain heat. The sympathetic nervous system is thus stimulated, resulting in increased heart rate, blood pressure and cardiac output. This ensures that the core organs are protected.

Moderate Hypothermia:

Core body temperature 32°C - 33.9°C

The body becomes *adynamic* to reduce heat loss. Metabolism shuts down. HR, BP, Oxygen demand decreases.

Moderate Deep Hypothermia:

Core body temperature 30°C - 31.9°C

Shivering ceases and level of consciousness becomes progressively depressed.

Deep Hypothermia:

Core body temperature less than 30°C

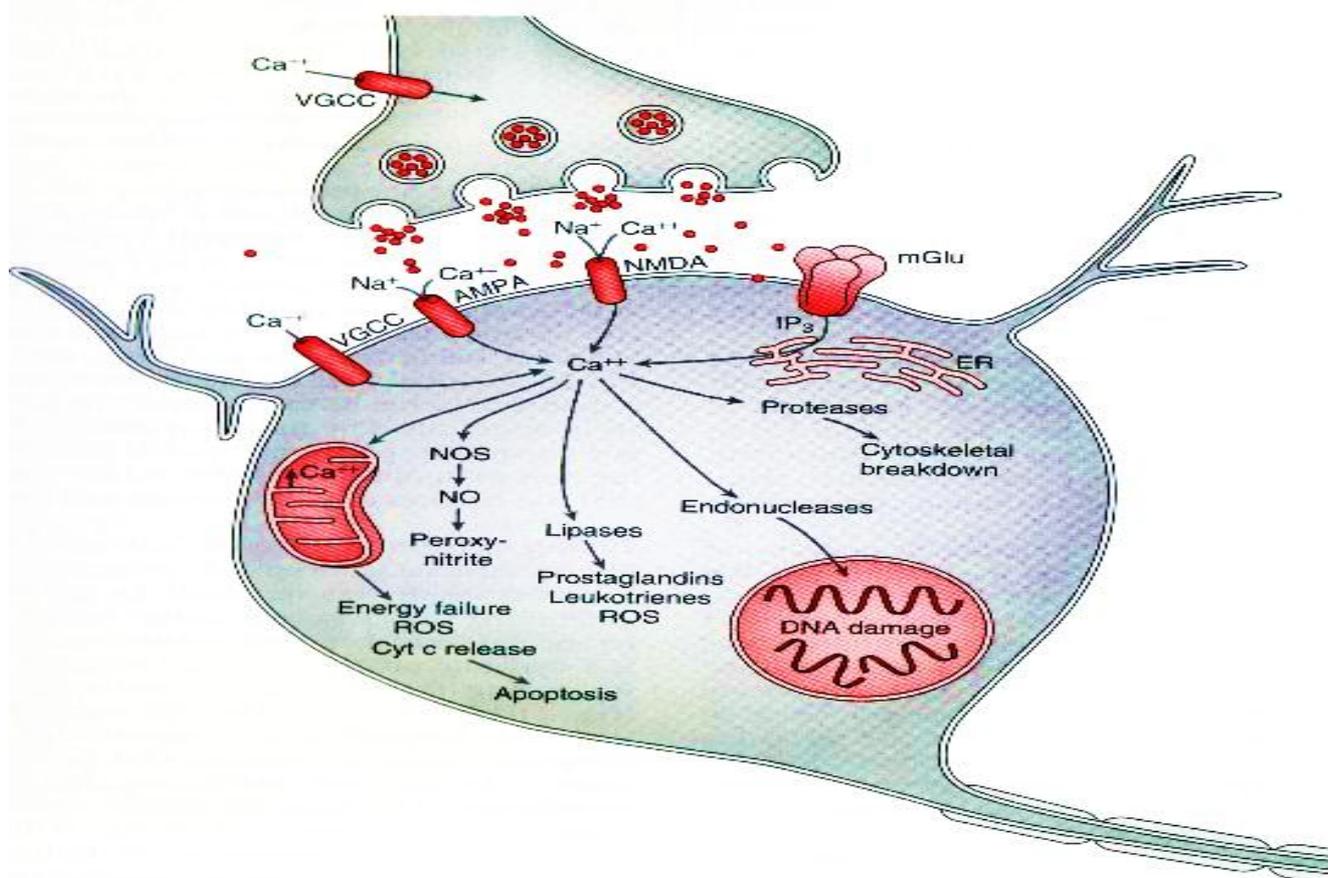
UNDERLYING MECHANISMS and PHYSIOLOGY OF THERAPEUTIC HYPOTHERMIA

Brain injury, regardless of the cause (whether ischaemia/reperfusion or traumatic brain injury), triggers a cascade of chemo-biologic events at the cellular level. These processes are further destructive to the brain, and cannot be abrogated. However, all of these processes are temperature sensitive; being stimulated by fever, and mitigated by hypothermia.

In addition, the tolerance of injured neurones to heat is much lower.

1. Pathophysiology of Cerebral Ischemia

The brain has a high energy requirement but very limited energy storage capacity. It is therefore very vulnerable to injury in the face of substrate supply interruption. The figures below provide a graphical overview of the changes the cellular level during ischemia.



Miller's Anaesthesia 6th ed

During ischemia, ATP depletion leads to neuronal depolarization and the subsequent release of supranormal levels of neurotransmitters, especially glutamate. Excessive stimulation of ligand-gated channels and the simultaneous opening of voltage-dependent Ca^{2+} channels permit rapid entry of Ca^{2+} into the neurons, as well as excessive entry of Na^+ . The energy requiring calcium extrusion/re-sequestration process is inhibited by the lack of ATP, and high intracellular levels of Na^+ may result in the reversal of the Na^+ - Ca^{2+} exchanger.

Excessive free calcium results in activation of numerous enzymes: *protease activation* causes breakdown of the cytoskeleton of the neurons. *Lipases* damage plasma membrane lipids and release arachidonic acid, which is metabolized by the cyclooxygenase and lipooxygenases to yield free radicals and other mediators of cell injury. *Activation of NOS* leads to NO and subsequent peroxynitrite, and *activated endonucleases* cause damage to DNA which subsequently renders the cell susceptible to apoptosis (“programmed cell death”).

Reperfusion of ischaemic tissue, with the products of oxidative metabolism (from mitochondria and activated phagocytes) results in a release of reactive oxygen species (also free radicals) which further exacerbate the injury. An acute phase response is also generated, with an increase in pro-inflammatory mediators (IL-6 and TNF).

The consequence of these processes is intra and extra cellular acidosis as well as neuronal death, either by necrosis or apoptosis.

Apoptotic processes occur relatively late in the post perfusion phase and tends to continue for 48-72 hours.³

Apoptosis is determined by mitochondrial dysfunction, disorders in cellular energy metabolism and release of the caspase enzyme system.

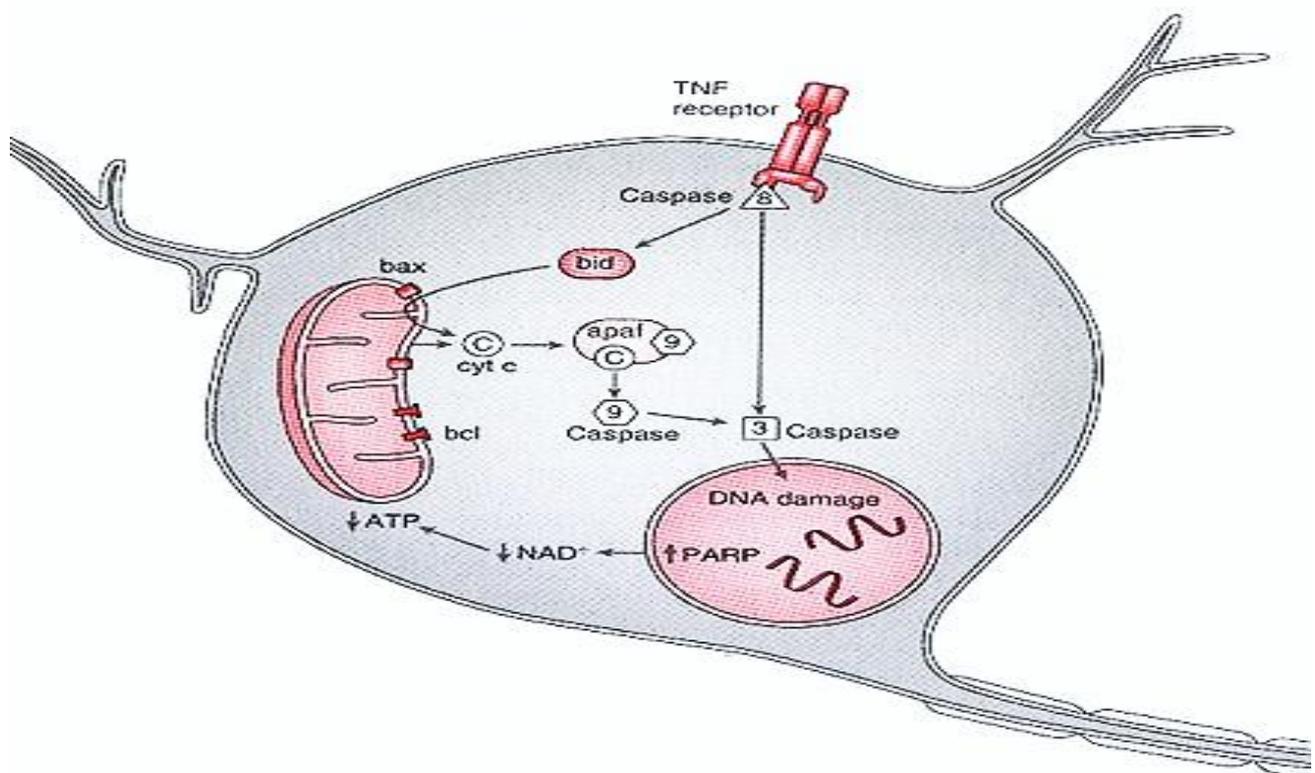
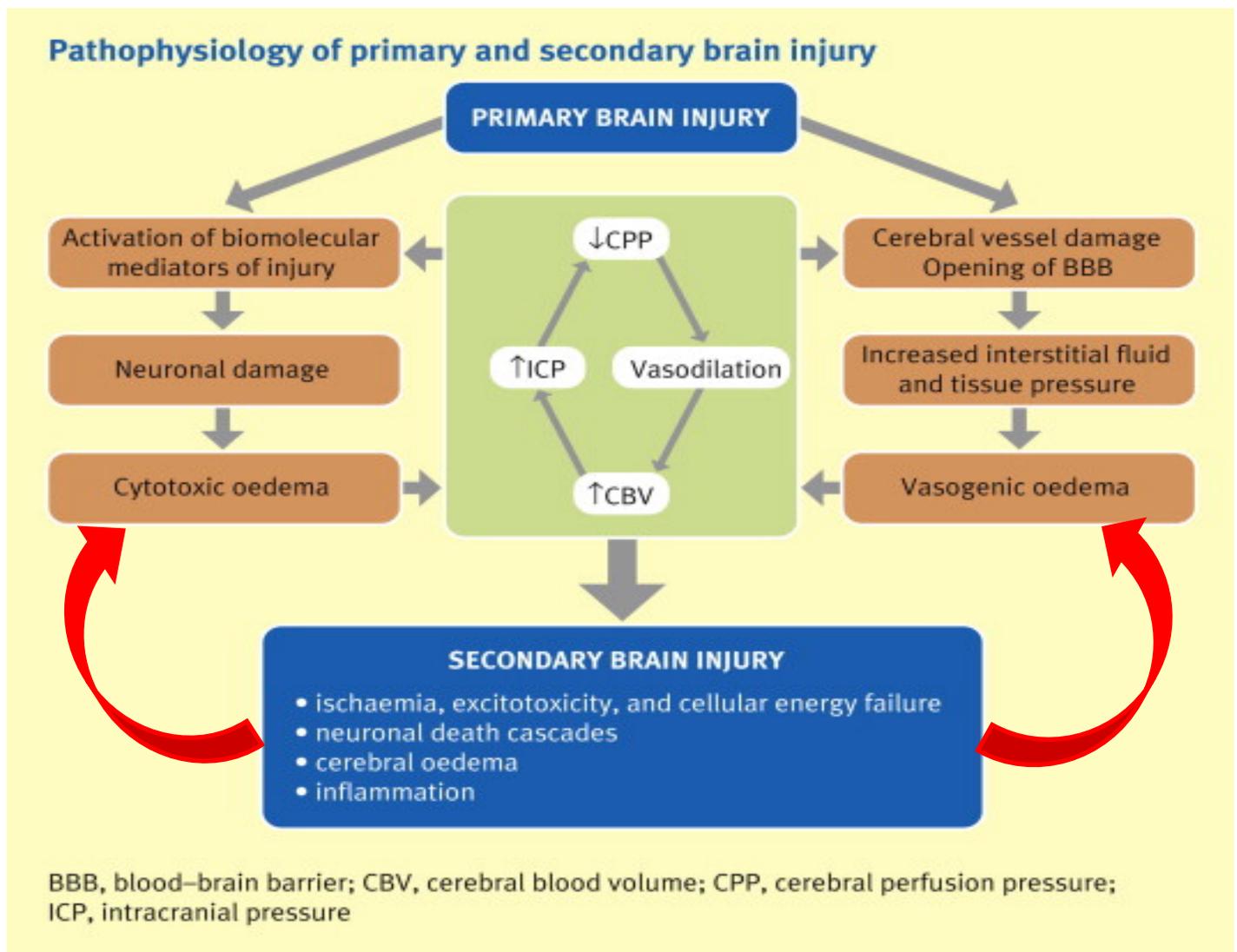


Diagram Showing the Cellular Processes Leading to Neuronal Apoptosis

2. Vascular permeability, BBB disruption, and Oedema formation:



Pathophysiology of intracranial hypertension

The above diagram depicts the vicious cycle of how primary and secondary brain injury cause disruption of the BBB, increased vascular permeability and oedema formation, which ultimately increases ICP and impairs cerebral perfusion pressure.

Injury of any type stimulates an inflammatory response and causes direct damage to cells and blood vessels.

With brain injury massive amounts of pro-inflammatory mediators like TNF- α and IL-1 are released together with activation of the complement system about 1 hour post injury and remain elevated for up to 5 days.^{4,5} These processes lead to chemotaxis of activated leukocytes across the BBB into the injured brain cells which cause further injury, and thus propagate another vicious cycle.⁶ This manifests clinically as intracranial hypertension.

Although brain oedema (with resultant raised ICP) can occur within a few hours of injury, it typically peaks after 24-72 hours after injury⁷, and has been well documented to be the cause and perpetuator of neurological damage in traumatic brain injury⁸, stroke, encephalitis and meningitis. Evidence also suggests that cerebral oedema following hypoxia from cardiac arrest can also cause severe brain damage.⁹

Other pathophysiological processes that occur during hypoperfusion include:

- 3. Coagulopathy:** Cardiopulmonary arrest and resuscitation results in activation of the coagulation cascade and formation of microthrombi, within the coronary and cerebral microcirculation.
- 4. Vasoactive mediator imbalance:** Following ischaemia or trauma, there is a relative imbalance of thromboxane-PGI₂ as well as increased endothelin-1 production. This imbalance accentuates vasoconstriction, thrombogenesis with further hypoperfusion in the injured brain.
- 5. Impaired Brain Glucose Utilization:** Following severe injury to the brain there is an initial increase in glucose metabolism in the first few hours, followed by a persistently decreased metabolic rate with ineffective glucose utilization.
- 6. Brain temperature and fever:** Fever = Body temperature > 38.3°C.
Brain temperature in normal individuals may be slightly higher than core body temperature. When patients become febrile this gap may increase to as much as 2°C.^{10,11}

As previously mentioned, fever is an independent prognosticator for outcome and morbidity following brain injury, especially if seen within 72hrs after cardiac arrest, immediately following spinal cord injury, in the first 24 hours following ischaemic stroke; in the first 72 hours following haemorrhagic stroke and in the first 10 days of subarachnoid haemorrhage (which is seen in up to 70% of patients).¹²⁻²⁰

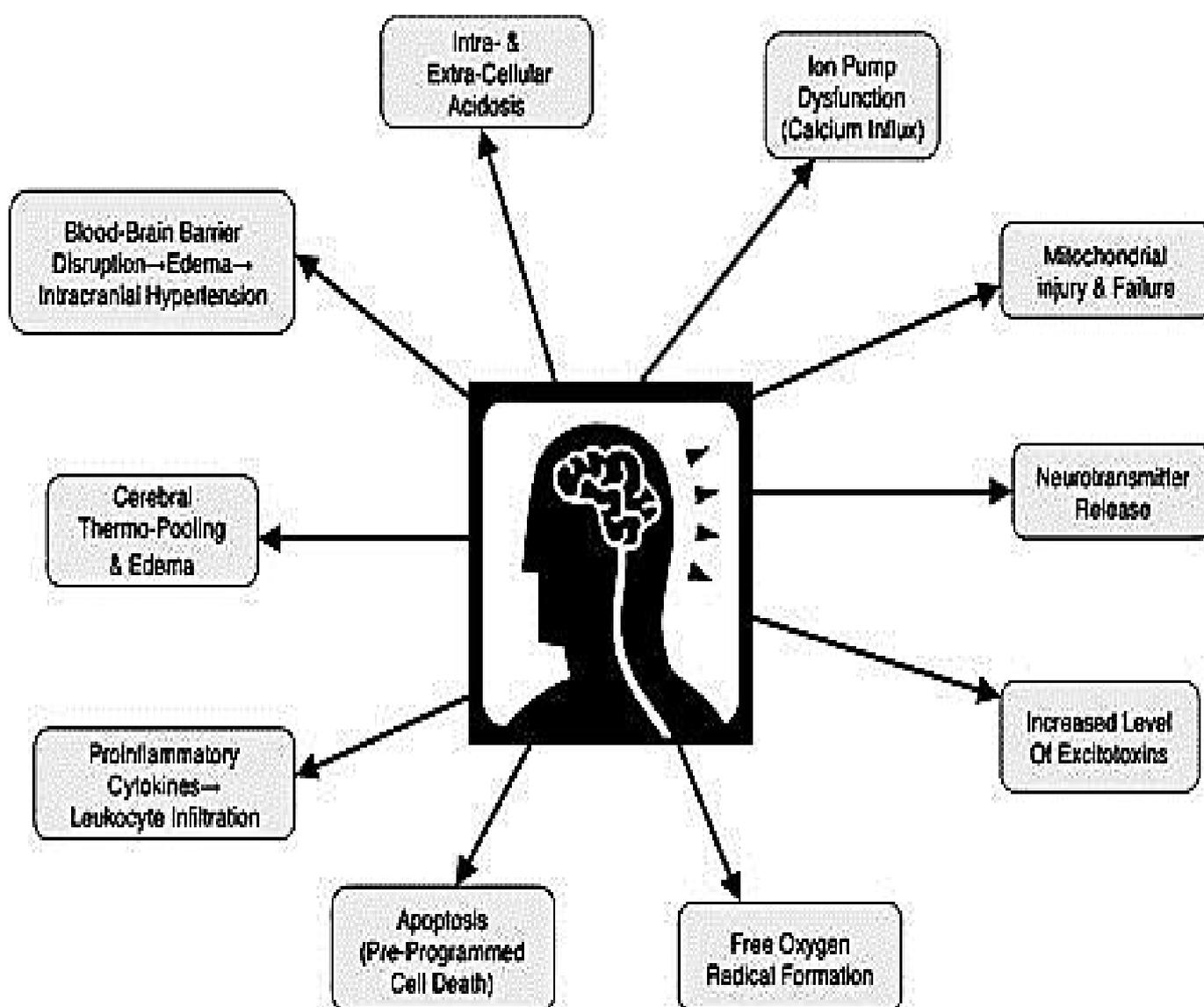
The mechanisms implicated that cause fever include acute phase proteins in the first 24 hours, damage to the hypothalamus, blood in the CSF and activation of inflammatory cascades. Fever can also cause further damage by disrupting the BBB and further potentiates heat sensitive excitotoxicity causing increased neurotransmitter, free radical and glutamate increase - all of which generates further heat in the damaged area of the brain.

The above-mentioned destructive mechanisms result in excessive heat generation within the injured brain. This entity is termed *cerebral thermopooling*. This refers to the process whereby excess heat generated in injured areas of the brain becomes more difficult to remove via the normal heat dissipation mechanisms (lymph and venous drainage) due to development of local brain

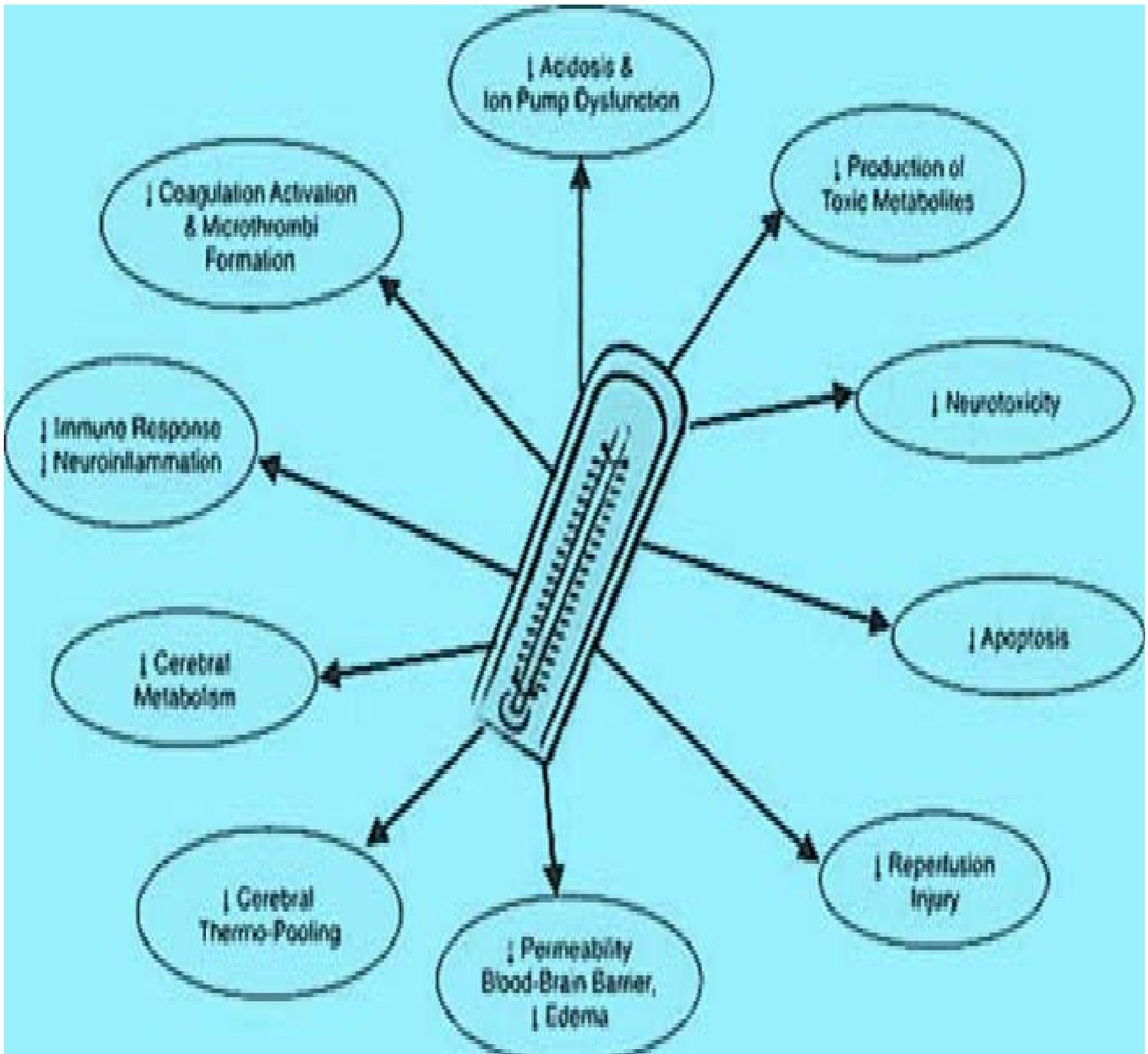
oedema. The heat thus becomes trapped in injured areas, further adding to hyperthermia-related injury.²¹

The brain – body temperature relationship is unpredictable. Dissociation of this relationship is frequent, with brain temperature exceeding core body temperature, after severe neurological injury. With pyrexia, this dissociation may be even greater.

This can give rise to another vicious cycle: Brain injury leads to general over heating of the brain; more overheating occurs especially in injured areas; this leads to local and sometimes general brain oedema, which then makes it more difficult to remove the excess heat.



EFFECTS OF THERAPEUTIC HYPOTHERMIA



1. Reduced metabolic demand

Cerebral metabolism decreases by 6-10% for every 1°C drop in body temperature. When core temperature drops to 32°C, the BMR decreases to 50-65% of normal; hence O₂ consumption and CO₂ production decrease by the same percentage.

2. Reduced disruption of blood brain barrier and oedema formation

While hypothermia has been used to decrease ICP in many studies, the overall mortality seems to have remained unchanged. This could be due to improper implementation and management of the side effects of hypothermia.

3. Preserves cerebral autoregulation

4. Improved brain glucose utilization:

Following severe injury to the brain there is an initial increase in glucose metabolism in the first few hours, followed by a persistently decreased metabolic rate with ineffective glucose utilization.

5. Improved metabolic recovery:

Hypothermia increases the speed of metabolic recovery with better preservation of the high energy phosphates and decreased accumulation of toxins.

6. Reduced free radical and reactive oxygen species formation:

(linear relationship => the lower the temperature, the fewer ROS) and increases expression of immediate early genes which stimulate the production of cold shock proteins – which are protective

7. Alters apoptotic signals by inhibition of the caspase system

8. Reduced proteolysis

9. Cell membrane stabilization

10. Decreased excitotoxic damage

13. Reduces lactate and tissue acidosis

14. Reduction in neuronal calcium influx and toxicity

15. Reduces ischemia-associated gene expression

16. Inhibits inflammation and cytokine production

17. Inhibits spreading depolarizations

CONSIDERATIONS DURING CONDUCT OF HYPOTHERMIA

1. Changes in metabolic requirements:

Due to the decreased the metabolic rate and the consequent parallel decrease in O₂ consumption and CO₂ production, ventilator settings need to be adjusted. If ventilator settings are left unchanged this will lead to hyperventilation, with potentially adverse consequences such as cerebral vasoconstriction^{45,46}. The decrease in O₂ consumption will increase oxygen levels in the blood. This high O₂ concentration poses a theoretical risk of reperfusion injury when tissue reperfusion occurs.

Therefore, ventilator settings should be adjusted as temperature decreases, and tailored according to frequent blood gas analyses, especially in the induction phase. Blood gas values are temperature dependent, and if blood samples are warmed to 37°C before analysis (as is common in most laboratories), PO₂ and PCO₂ will be over estimated and pH underestimated in hypothermic patients.

There are 2 options for blood gas management of the hypothermic patient:

Alpha-Stat Management:

Blood gas management when CO₂ values measured at 37°C are kept constant (for example, at 40 mm Hg) regardless of the patient's actual core temperature.

pH-Stat Management.

PCO₂ is corrected for temperature and is maintained at a prespecified value. This implies that the temperature-corrected pH will remain constant during pH-stat management and will increase during alpha-stat management. The jury is still out on which method is superior, but choice of pH management depends in part on whether or not cerebral autoregulation is preserved, the precise nature of the neurological injury and the presence or absence of brain oedema.

Strictly applied alpha-stat management could lead to hyperventilation and cerebral vasoconstriction, which may increase ischaemia in an injured brain. Strict pH-stat management could lead to hypercapnia, cerebral vasodilation, and increased ICP, which increases brain oedema.

For accurate temperature correction, blood samples should be analyzed at the patient's real temperature; this can be most easily accomplished by performing on-site analysis in the ICU. If this is not possible, the blood gas values can be estimated in the following way.

In a sample assayed at 37°C:

- Subtract 5 mm Hg PO₂ per 1°C that the patient's temperature is <37°C;
- Subtract 2 mm Hg PCO₂ per 1°C that the patient's temperature is <37°C;
- Add 0.012 pH units per 1°C that the patient's temperature is <37°C.

Thus, a sample from a patient with a core temperature of 33°C analyzed in the lab at 37°C with the results pH 7.45, PCO₂ 35 mm Hg, and PO₂ 80 mm Hg would have the following temperature-corrected values: pH 7.50, PCO₂ 27 mm Hg, and PO₂ 60 mm Hg. Decreased metabolic demands require that feeding should be adjusted to reflect this.

2. *Electrolyte shifts/disturbances:*

Hypothermia causes a metabolic acidosis due to a relative increase in fat metabolism and an increase in lactic acid. At the onset, hypothermia causes urinary diuresis, renal tubular dysfunction, increased excretion of electrolytes, and decreased creatinine clearance.

Shiozaki et al ²² found a much higher incidence of hypernatremia and hypokalemia in the TH group in one of their trials.

Induced hypothermia typically causes a decrease in magnesium and potassium as well as in phosphate, and calcium.²³ Magnesium may help prevent vasospasm after injury and ischemia and attenuate reperfusion injuries and hypomagnesemia is associated with increased mortality in the intensive care setting. Hypomagnesemia has also been linked with poor outcomes in cases of neurological injury.²⁴

3. **Changes in drug metabolism:**

Decreased core temperature can alter the pharmacokinetics and pharmacodynamics of many medications such as anti-arrhythmics, neuromuscular blockers, sedatives, anaesthetics, analgesics, and anti-epileptics. Cytochrome P-450 dependent reactions are impaired and, for the most part, plasma levels of drugs will be higher and their effects prolonged.

4. **Coagulopathy:**

Hypothermia causes a decrease in platelet count and function, which is typically reversed with rewarming. The clotting cascade is also affected, especially below 34°C as evidenced by prolonged prothrombin and partial thromboplastin times. Significant bleeding, however, is rarely seen.

5. **Haemodynamic effects and Dysrhythmias:**

During the induction of hypothermia, there is an initial increase in heart rate, cardiac output, systemic vascular resistance, and blood pressure. In the range of 32°C to 35°C, decreases in heart rate, blood pressure, and cardiac output are seen with an increase in central venous pressure (CVP). Consistent with this is a decrease in the cardiac index. Below 32°C to 33°C, there is an increased risk of cardiac dysrhythmias, and J waves, first-degree heart block, and prolonged QT may be seen on the ECG. Between approximately 30°C and 33°C, increased tachyarrhythmias have been observed, usually beginning with atrial fibrillation. Below 28°C, ventricular dysrhythmias may first appear but can be seen at lesser degrees of hypothermia.

6. **Ileus:**

Intestinal dysmotility/ileus is common. There may also be an increased risk of stress ulcers due to increased gastric acid production and decreased HCO₃⁻ secretion, micro-infarcts lead to areas of tissue necrosis and ulcer formation and increased bleeding tendency due to platelet dysfunction.

7. **Insulin resistance:**

Hypothermia causes insulin resistance and a decrease in insulin production by the pancreas²⁵ and hyperglycemia can be seen with temperatures in the mildly hypothermic range. This often requires the use of high doses of insulin to maintain normothermia during the hypothermic phase, but it needs to be titrated downwards meticulously during the rewarming phase, when insulin sensitivity is restored. This is especially problematic when the patient is rewarmed too rapidly.

8. **Pneumonia and wound infection**

An increased incidence of neutropenia and susceptibility to infections, particularly pneumonia, has been reported. The incidence ranges between 30-50%²⁶. A recent study by Mongardon et al showed that despite increase in care costs, long-term and clinically relevant outcomes were not impaired, and therefore therapeutic hypothermia should not be discouraged.²⁷

9. ***Lactic acidosis***
10. ***Pancreatitis***
11. ***Rebound fever in the rewarming phase of TH***
12. ***Postcooling diuresis***
13. ***Increased creatinine***
14. ***Increased liver enzymes***

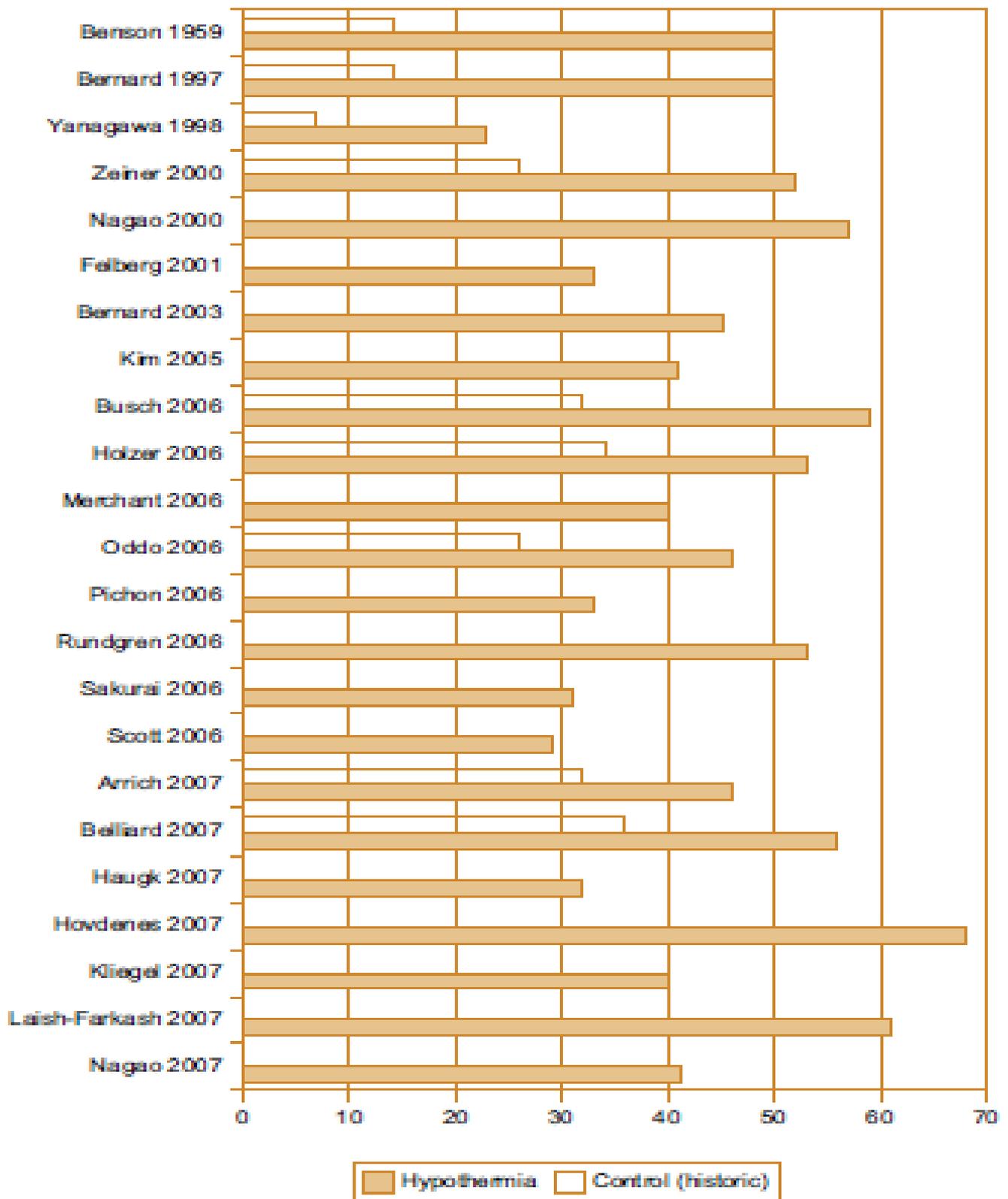
EVIDENCE FOR USE OF HYPOTHERMIA

Cardiac Arrest

After successful restoration of circulation post cardiac arrest, further destruction occurs. Reoxygenation (as previously described) may lead to deleterious chemical cascades, which cause further delayed necrosis and apoptosis of neuronal tissue. “**Postresuscitation Disease**”, as it was termed by Negovsky²⁸, is the secondary damage of the brain after successful primary resuscitation. TH should be initiated as early as possible after return of spontaneous circulation (ROSC) because the extent of brain damage is related primarily to the length of ischaemia.

The Advanced Life Support Task Force of the International Liaison Committee on Resuscitation (ILCOR) recommends that “adult patients who are comatose (not responding in a meaningful way to verbal commands) with spontaneous circulation after out-of-hospital VF cardiac arrest should be cooled to 32–34 °C for 12–24 h. Induced hypothermia might also benefit comatose adult patients with spontaneous circulation after out-of-hospital CA from a non-shockable rhythm or in-hospital cardiac arrest.”²⁹

The evidence in support of the above consensus guideline is incontrovertible. There have been over 20 non-randomised and up to 5 randomised trials that consistently show that neurological outcome is improved with controlled hypothermia; ranging between 23-68%, depending on other patient confounders (see table and graphs below).^{30,31}



The Hypothermia After Cardiac Arrest trial (HACA)¹² and the Australian study (Bernard et al)³², published in 2002, have been landmark publications in convincing the medical fraternity that hypothermia confers benefit, especially when the presenting rhythm is VF. The HACA trial enrolled 273 patients and found that 75/136 patients (=55%) had good outcomes versus 54/137 (=39%) in the control.

The Australian study included 77 patients, and showed that 21/43 (49%) patients in the hypothermic group had good outcome compared with 9/34 (26%) in the normothermic group.

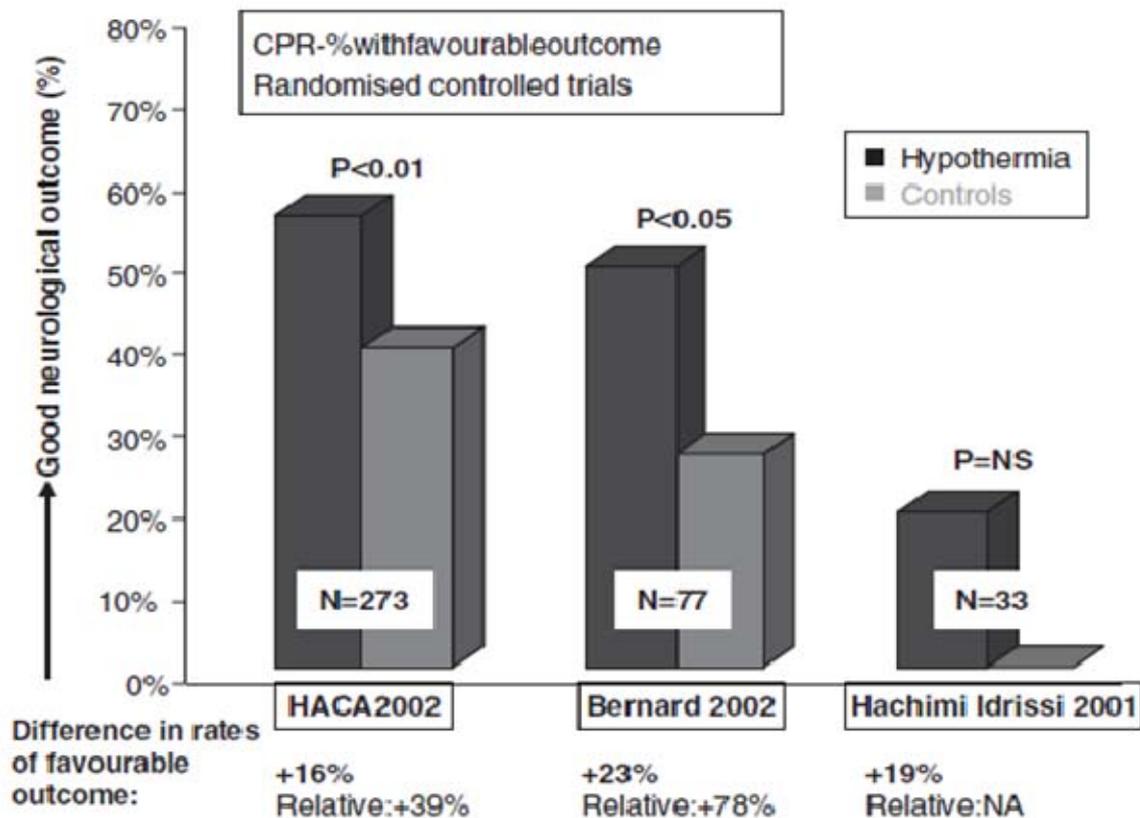


Figure 2.

Results of the three randomized-controlled trials assessing the effects of hypothermia in patients with witnessed cardiac arrest and an initial rhythm of VT/VF. The black bars show the rates of favourable neurological outcome in patients treated with hypothermia, the grey bars the rate of favourable outcome in controls.

Kim³³ et al, in their meta-analysis of 2 randomised and 12 non-randomised studies found that TH is associated with reduced in-hospital mortality for adults patients resuscitated from non-shockable CA. Although the quality of these trials was poor and there is need for further non-randomised studies to prove these findings, the trend toward using hypothermia early is definitely being established.

The above findings are significant to the anaesthetist and surgeon, who are in a unique position to be able to initiate hypothermia post arrest immediately after ROSC, especially when transfer to ICU is a protracted process. Many hospitals in USA and Europe have now included hypothermia into their Post Cardiac Arrest Care Bundle in order to make it standard practice. It stands to reason that South

Africa needs to follow suit and incorporate it into our current practice, not just to save a life, but to improve quality of life in survivors.

STROKE

Greer et al³⁴, in the pooled analyses covering 14431 patients with stroke and other brain injuries, showed that fever is consistently associated with worse outcomes across multiple outcome measures.

Therapeutic hypothermia is currently the most promising neuroprotective candidate for stroke. It acts on tissue at risk in the penumbra and has been shown to reduce the cerebral infarct size, oedema formation and ICP³⁵.

Although there is an increasing body of data supporting the utility of hypothermia in acute stroke, there have been no large-scale randomized studies proving efficacy, hence further trials are needed to define the optimal time window and temperature regimen necessary for maximal treatment.

TRAUMATIC BRAIN INJURY

The use of hypothermia in traumatic brain injury can be divided into:

- *The use of hypothermia as a neuroprotectant* – in an attempt to inhibit the post-injury biochemical cascade.
- *Hypothermia for the treatment of raised intracranial pressure.*

The publications on this topic remain inconclusive. The more recent review of these publications on TBI to date, propose that the best available evidence support the use of early prophylactic mild-to-moderate hypothermia in patients with severe TBI (Glasgow Coma Scale score ≤ 8).

When short-term cooling studies were analysed separately, mortality and neurologic outcome remained unaffected. However, long-term or goal-directed cooling studies demonstrated considerably reduced mortality and a higher likelihood of good neurologic outcome. The maximum benefit occurred when cooling was continued for at least 72 hours and/or until stable normalization of intracranial pressure for at least 24 hours was achieved.³⁶⁻³⁸

The collective interpretation of these studies is impossible; as they include a heterogenous group of patients, with markedly varying extent of brain injuries, and even more varying patterns of associated injuries, all of which impact on outcome. Even more confounding, are the vastly diverging management protocols.

However, it is clear, that hypothermia does reduce intracranial pressure. Whether this is significant in the muddle of factors that impact on patient outcome remains to be determined.

HYPOXIC ISCHAEMIC ENCEPHALOPATHY IN NEONATES

The last ILCOR guidelines published in support of TH included 1 large trial (CoolCap, n = 235), 1 small randomized control trial (n = 67), and several feasibility trials. Since then, several large cooling trials have reported significant overall improvement in death.

The cumulative data from these trials indicate “a consistent, robust beneficial effect of TH for moderate to severe neonatal encephalopathy.”³⁹

PERIOPERATIVE HYPOTHERMIA

Hypothermia is often used to protect the heart, brain, spinal cord or kidneys perioperatively, and thus increase the available operative time.

The IHAST2 study (Intraoperative Hypothermia for Aneurysm Surgery Trial) failed to show any benefit of this technique in the case of cerebral aneurysmal surgery.⁴⁰

It is also being widely used to protect the spinal cord and prevent paraplegia during high aortic-cross-clamp surgery, despite there being very little clinical data to demonstrate its efficacy.

Hypothermia is routinely used in cardiac surgery to reduce metabolism and increase operating time. It has also been observed that patients who underwent deep hypothermia, and did not develop postoperative hyperthermia, had fewer cognitive deficits than their counterparts.

Three case series (n=36 patients) have shown that hypothermia can control intracranial pressure during orthotopic liver transplants in patients with liver failure with hepatic encephalopathy and can also serve as a bridge to transplant. Other areas of interest include ARDS, grand-mal seizures, acute disseminated encephalomyelitis, and even radiocontrast-induced nephropathy.

METHODS OF INDUCING HYPOTHERMIA

THE IDEAL DEVICE:

- Induces rapid temperature reductions
- Maintains target temperature within a steady range
- Preferentially cools the target organ (i.e. the brain)
- Is environmentally versatile (lightweight, small, transportable, and sturdy)
- Is implementable in any setting even during the resuscitation itself

Unfortunately this device does not exist.

A combination of techniques is used to induce and maintain TH. It can be divided into non-invasive/surface cooling and invasive cooling (summarized in the table below).

Noninvasive techniques	Invasive techniques
Caps or helmets	Intraventricular cerebral hypothermia
Cooling blankets	Extracorporeal circulating cooled blood
Hydrogel-coated cooling pads	Infusion of cold IV fluids
Ice packs	Peritoneal lavage with cold exchanges
Immersion in cold water	Retrograde jugular vein flush
	Nasal, nasogastric, and rectal lavage
	Nasopharyngeal balloon catheters

IV indicates intravenous.

SURFACE COOLING:

Surface cooling is most widespread because it is relatively simple to implement. Several methods can be used:

- Low-cost techniques include ice packing and alcohol bath.
- Cold air–forced blankets and rubber mats
- Total body cold-water immersion has been described, but this method may compromise the quality of monitoring and therapy.
- Higher-cost devices that control temperature through an internal feedback mechanism:
Arctic Sun device (self-adhesive, hydrogel-coated pads that circulate temperature-controlled water under negative pressure), Coolblue, Koolkit, ThermoWrap and the thermosuit system (recirculating cold-water through the pads)

Achieving the target body temperature with surface cooling techniques alone usually takes 2 to 8 hours, a relatively long time.

Except for the commercial cooling devices, the conventional ones lack the feedback loop to modulate temperature precisely. There is a high incidence of overcooling, intensive nursing care is required, clinicians need to be experienced in maintaining goal temperature, and the rate of decooling is erratic⁴³.

The exaggerated shivering response triggered by surface cooling is another major disadvantage with this technique.



Head wrap, vest, lower body blanket - e.g. **Blanketrol® III** total body Hyper-Hypothermia water therapy system



Arctic Sun System

INVASIVE COOLING TECHNIQUES

Endovascular cooling provides better time within the target temperature range, less temperature fluctuation, and better control during rewarming.

Invasive cooling methods include:

- cold carotid infusions,
- single-carotid artery perfusion with extracorporeal cooled blood circulation,
- ice water nasal lavage
- cardiopulmonary bypass
- cold peritoneal lavage
- nasogastric and rectal lavage
- infusion of cold intravenous fluids (4°C)

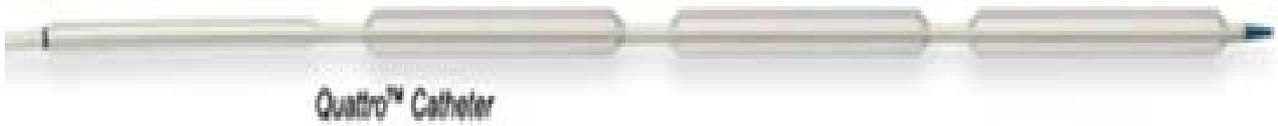
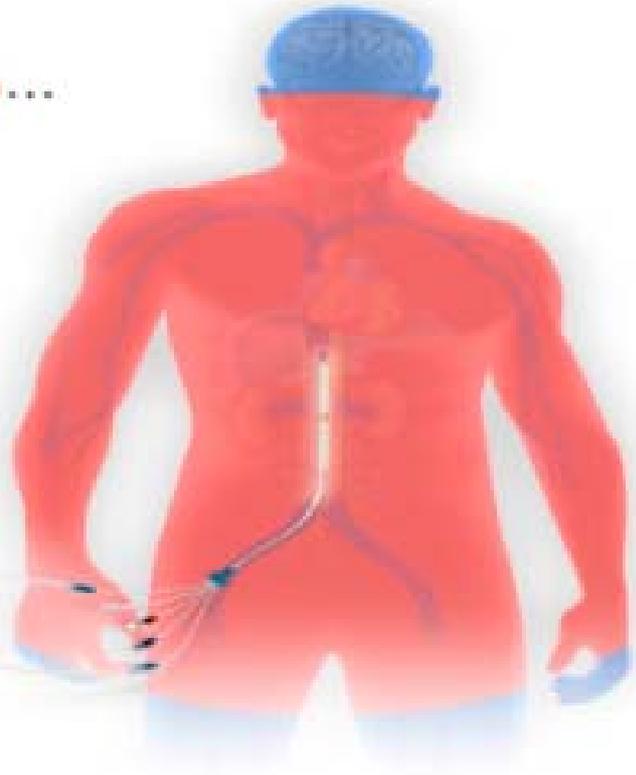
With the exception of cold IV fluid infusion, all invasive cooling techniques are currently limited to the in-hospital environment.

Endovascular heat-exchange devices circulate cold saline through an indwelling venous catheter placed percutaneously. These multilumen catheters have 2 to 3 cooling balloons and therefore require insertion into a major vein. The femoral site tends to be the more preferable one because of the lower likelihood of dysrhythmias.

They are subject to the same complications as CVC's including injury during insertion, catheter-related blood stream infection and venous thrombosis. Some catheters, like the Alsius system ([Thermogard XP™](#)) can also be used as a CVC. Different catheters that can be used with the Alsius system, according to length, insertion site and heat exchange power.



or to warm...



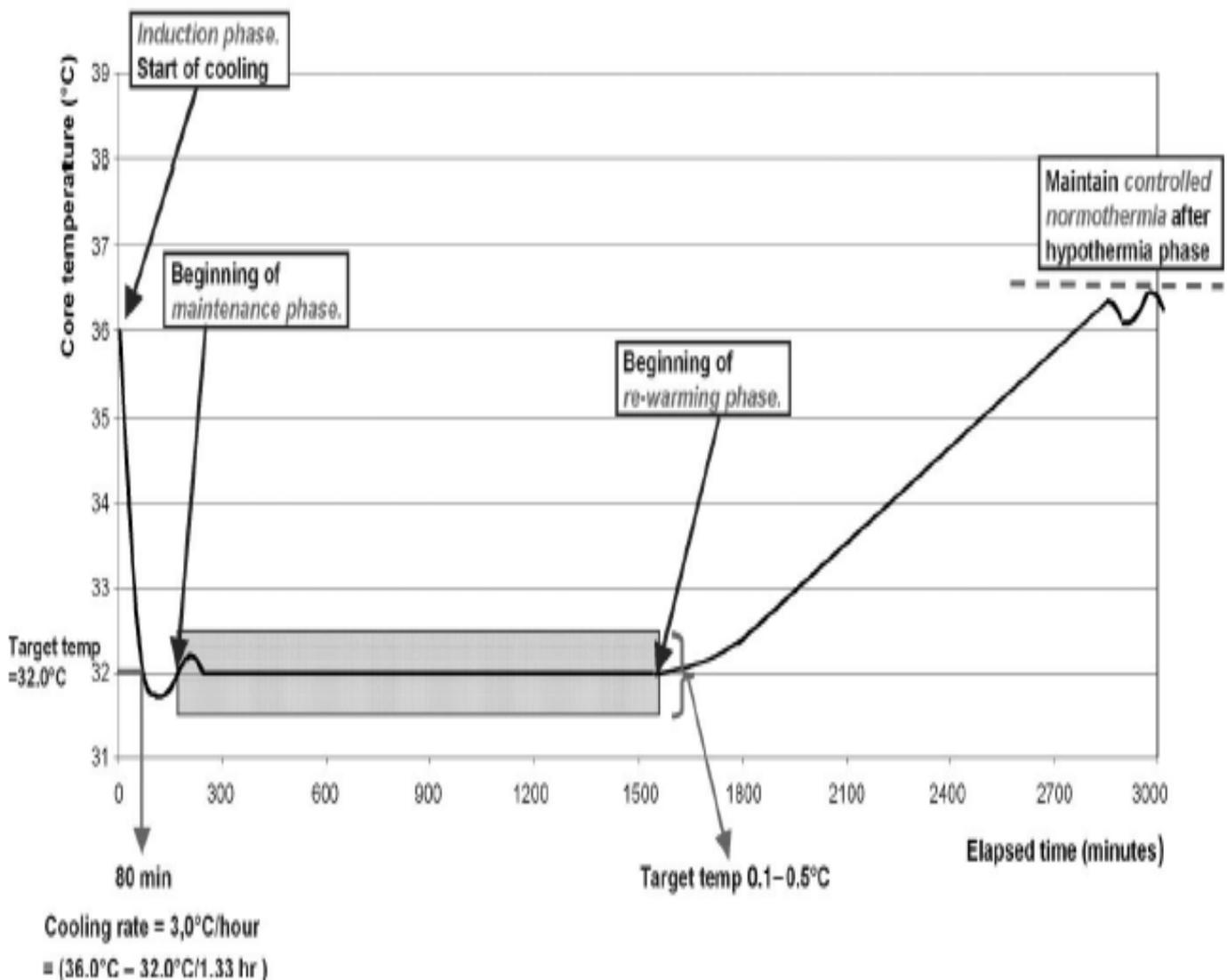
Different catheters that can be used with the Alsius system, according to length, insertion site and heat exchange power

CLINICAL ASPECTS OF THERAPEUTIC HYPOTHERMIA

Four key factors determine the success or failure of cooling treatment. These are:

- **Speed of induction** of hypothermia: rapid cooling yields better outcomes
- **Duration** of cooling
- **Speed of rewarming** (this should be slow lest the destructive processes be reinitiated; this happens frequently if rewarming speeds are high)
- Proper management and **prevention of side effects**

Temperature modulation during therapeutic hypothermia may be divided into 4 phases: induction, maintenance, decooling/rewarming, and normothermia.



The phases of hypothermia treatment-Polderman.CritCareMed.2009

The induction phase should last between 30 and 120 mins; rapid cooling may lead to a small overshoot, which should be accepted provided it is no greater than 1°C. The maintenance phase usually lasts 24 hrs in cardiac arrest patients (may be longer for other indications) and should be characterized by no or minimal fluctuations in temperature. The rewarming phase should be slow and controlled, with rewarming rates of 0.2°C to 0.5°C in cardiac arrest patients and lower rewarming rates for other indications. Fever should be prevented after rewarming.

The algorithms below by Seder et al suggest the following protocols: ⁴⁴

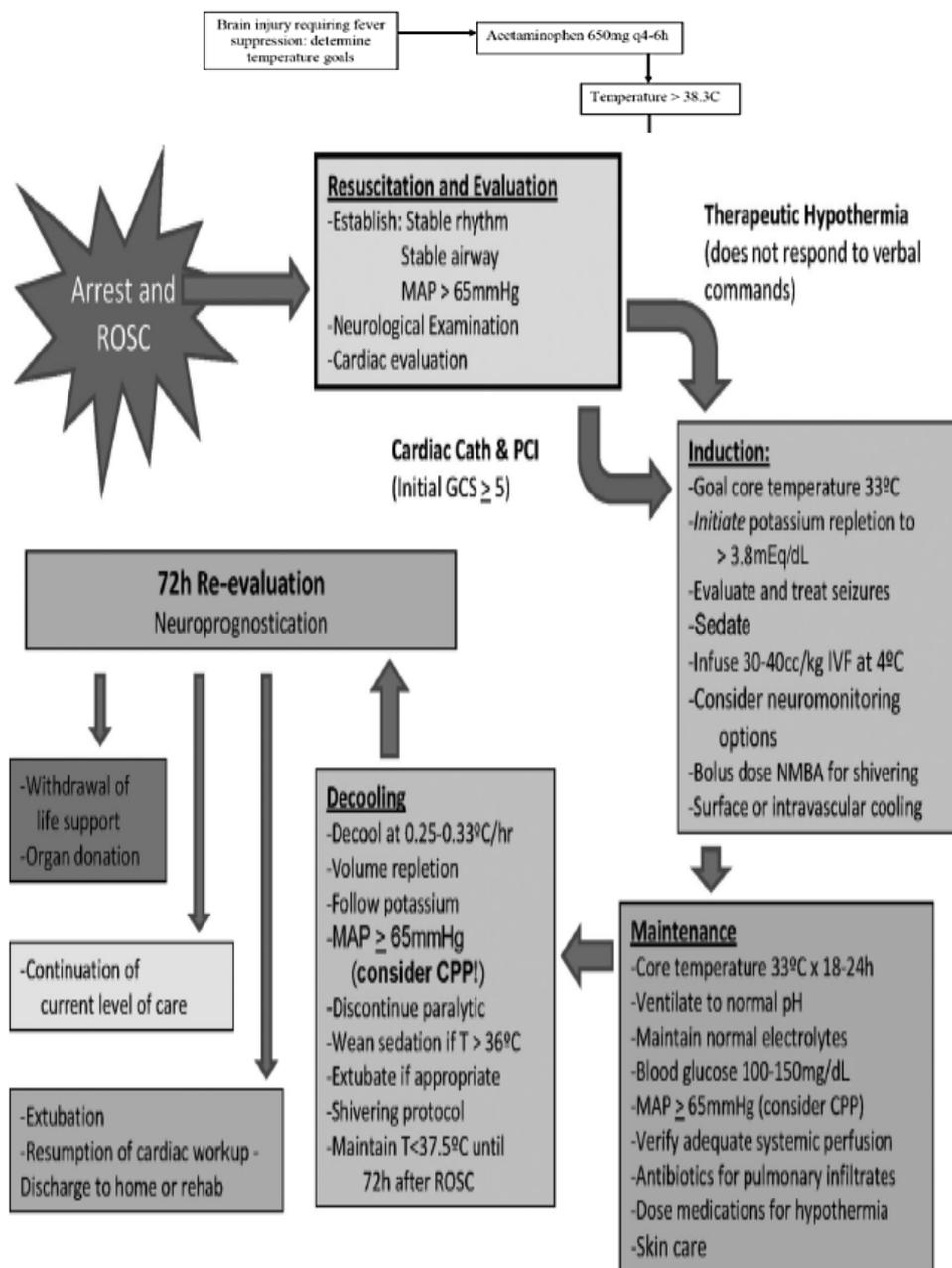


Figure 1. Treatment of the cardiac arrest survivor. ROSC, return of spontaneous circulation; MAP, mean arterial pressure; Cath, catheter; PCI, percutaneous coronary intervention; GCS, Glasgow Coma Scale; IVF, intravenous fluid: normal saline or lactated Ringer's solution; NMBA, neuromuscular blockade agents; CPP, cerebral perfusion pressure; T, temperature.

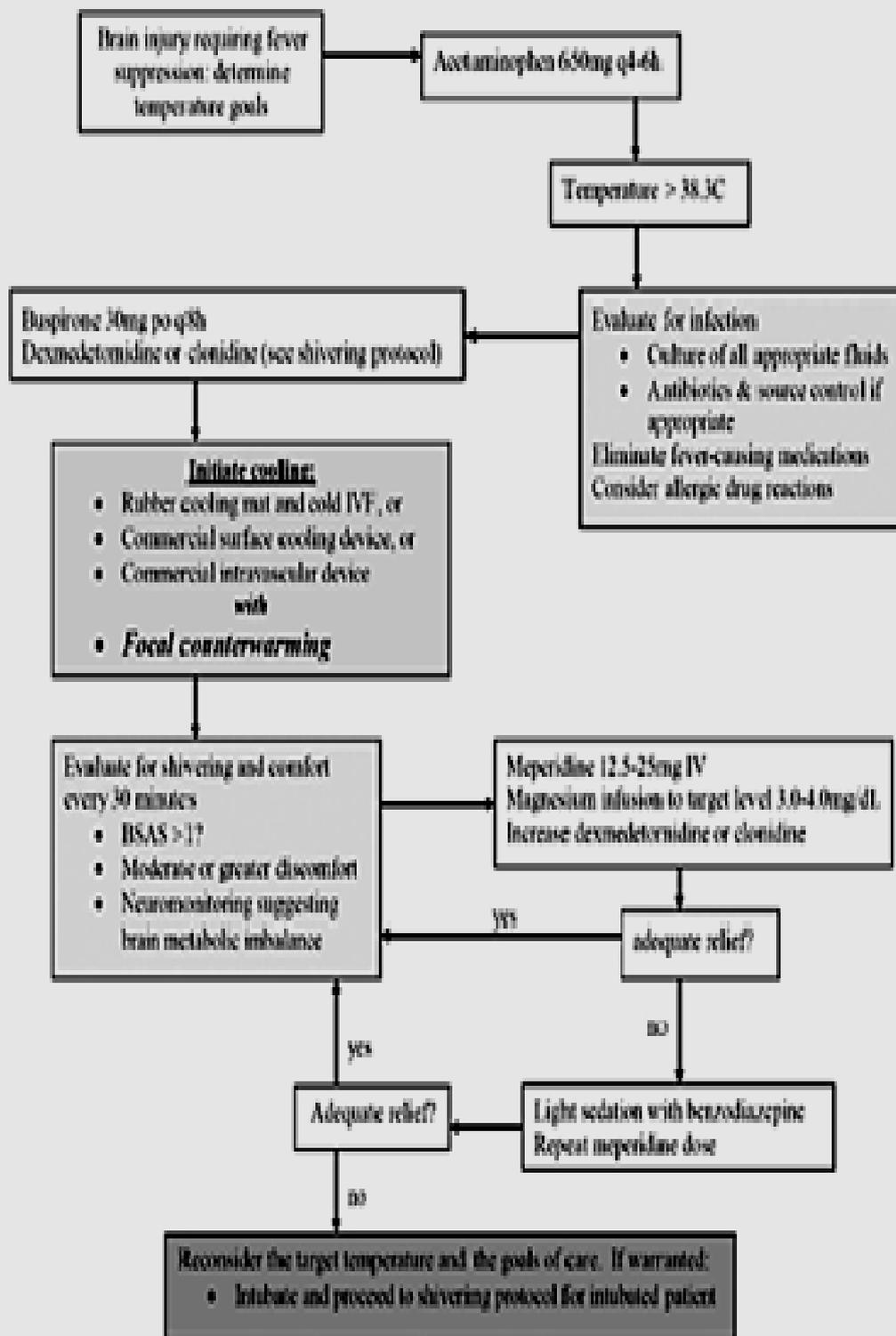


Figure 2. Suggested algorithm for therapeutic normothermia in the nonintubated patient. *IV*, intravenous fluid; *BSAS*, Bedside Shivering Assessment Scale (Appendix 1).

INDUCTION

- Neurological assessment should be done before induction (GCS, cranial nerves, reflexes, general motor tone, convulsive or non-convulsive seizure activity and myoclonus), especially if neuromuscular blockade is to be used.
- The patient should be adequately sedated. Depth of sedation needs to be ascertained before starting neuromuscular blockade. Either empirical heavy sedation or EEG/BIS monitoring can be used to titrate sedation.
- Continuous core temperature monitoring is required. Options include bladder (if patient is not oliguric), rectal, central venous, or oesophageal measurement.
- Induction of TH should be instituted as soon as possible after return of spontaneous circulation following cardiac arrest.
It can be performed with cold fluid infusion, or with a commercial surface device or intravascular cooling device, or a combination of these.
Most commonly, a rapid bolus administration of 30 to 40 mL/kg cold (4°C) isotonic resuscitation fluid, targeting a core temperature of 32°C to 34°C has been most widely used. It decreases temperature by 2-4°C without compromising left ventricular function or causing pulmonary oedema.
- One important factor that needs one needs to cognisant of is the *hypokalaemia* caused by rapid induction. Replace K⁺ if levels are <3.8mEq/dL, and monitor electrolytes 3-4 hourly.
- It has been advocated that TH should be started on scene by emergency personnel. The new Chillcore™ system is a mobile unit that allows for 3-4 litres of IV fluid to be stored as low as -6°C even in extreme temperatures. The advent of this system implies that there should be no reason (except for lack of resources) why TH cannot be started in the emergency department or on-table in the theatre setting.



MAINTENANCE

This is usually done in an ICU setting. Cooling can be maintained with ice packs applied to the neck, groin and axillae, or any of the surface or invasive devices described above.

- The goal is to maintain haemodynamic and metabolic homeostasis.
- Haemodynamic monitoring, such as invasive or non-invasive CO monitors, can be used to guide interventions. If renal function is normal, then urine output measurement is also an option. SvO₂ measurements or direct invasive monitoring of brain metabolism may also be considered
- MAP should be adequate to maintain cerebral perfusion (>65mmHg)
- Mechanical ventilation should target normal pH and CO₂ (avoid hypercarbia) and lung protective strategies should be used
- Antibiotics should be started if there is any suspicion of a pneumonia
- Maintenance of blood glucose levels to target values between 6.5-8.5mmol/l
- Normal electrolyte levels (potassium, magnesium and phosphate)
- Decrease drug dosages and administer it cautiously, due to decreased drug metabolism.
- Aggressive management of shivering
- Neuromonitoring devices should be considered to monitor ICP, seizure activity, inadequate cerebral blood flow and cerebral metabolic demand.

DECOOLING/ REWARMING PHASE

The most haemodynamic instability occurs here. The “Postresuscitation syndrome worsens the vasodilatation that occurs during rewarming, thus exacerbating hypotension. Increased ICP and low CPP’s may also occur during this time.

- Slow cooling in a controlled manner is therefore preferred with a goal rate of 0.2°C to 0.5°C per hour until the patient is at 36.5°C or 37°C.
- Fluid boluses, inotropes, and vasopressors may be necessary to maintain CPP.
- If significant hemodynamic instability or signs of elevated ICP occur slow down or stop the rewarming process.
- Discontinue neuromuscular blockade when the patient temperature reaches 35°C and wean sedation when the body temperature reaches 36°C.

THERAPEUTIC NORMOTHERMIA AFTER REWARMING

Rebound fever is a common phenomenon which exacerbates brain injury. Therefore normothermia should be maintained after rewarming. The duration of therapeutic normothermia is usually 72 hours from ROSC.

Target temperature should be between 36.5-37.5°C, and shivering should, again, be aggressively controlled.

THERAPEUTIC TEMPERATURE MANAGEMENT SHIVERING PROTOCOL (Bernard et al, Crit Care Med 2009)

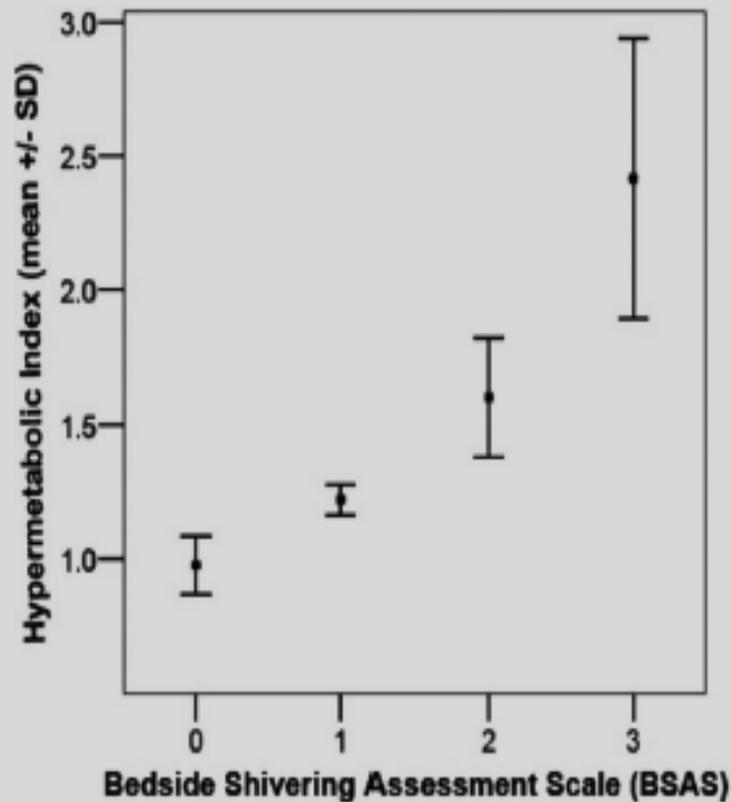
Nonintubated patient

1. Acetaminophen 650 mg every 6 hrs when temperature <35°C and 650mg every 4 hrs when temperature >35°C.
2. Focal counterwarming: warm air blanket or warm packs to face, neck, and extremities.
3. Buspirone 30 mg (enteral) q8h plus: a. meperidine (pethidine) 12.5 to 25 mg intravenously every 4hrs.
4. Dexmedetomidine 0.3 to 1.5 ng/kg/min or clonidine 0.1 to 0.3 mg (enteral) every 8hrs.
5. Magnesium infusion to target serum level of 2.5 to 3.5 mg/dL.
6. Cautious intermittent administration of a low dose benzodiazepine for comfort.
7. Reconsider therapy: If Bedside Shivering Assessment Scale is 2 or 3, neuroprotective gains of therapy are likely overbalanced by the metabolic cost. If therapy is determined to be necessary, intubate and proceed as below.

Intubated patient

1. Acetaminophen 650 mg (enteral) every 6 hrs when temperature <35°C and 650 mg every 4 hrs when temperature >35°C.
2. Focal counterwarming: warm air blanket or warm packs to face, neck, and extremities.
3. Sedate: intravenous propofol, midazolam, or bolus-dose lorazepam. Place bispectral index monitor and follow sedation and neuromuscular blockade algorithm (see below). Sedation *must* be maintained throughout the period of neuro muscular blockade.
4. Administer 25 to 50 µg/hr intravenous fentanyl or equivalent narcotic.
5. Monitor the Bedside Shivering Assessment Scale and bispectral index every 30 to 60 mins.
6. Administer vecuronium 0.1 mg/kg by intravenous bolus whenever Bedside Shivering Assessment Scale >1, or cisatracurium 0.15 mg/kg by intravenous bolus and 3µg/kg/min infusion.

7. If bispectral index >50, evaluate for and treat shivering; if index remains >50 after shivering is eliminated, obtain immediate EEG and increase sedation until bispectral index <50.
8. Discontinue neuromuscular blockade daily for neurological examination and several hours before weaning sedation.
9. Neuromuscular blockade is associated with long-term neuromuscular weakness, and should be avoided when the synergistic factors of corticosteroids and sepsis are present.



Score	Definition
0	None: no shivering noted on palpation of the masseter, neck, or chest wall
1	Mild: shivering localized to the neck and/or thorax only
2	Moderate: shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	Severe: shivering involves gross movements of the trunk and upper and lower extremities

The bedside shivering assessment scale and associated energy expenditures

CONCLUSION

Mild to moderate controlled hypothermia has become one of the most significant breakthroughs in the treatment of, and protection against neurological damage. Although there is lack of consensus currently on patient selection, precise duration of cooling and speed of rewarming, we need to develop protocols to allow for hypothermia to become a routine part of resuscitation in appropriate conditions. Although we are often hampered, in our setting, by availability of equipment and its cost, the high workload demand for limited nursing resources and the misperception that inducing hypothermia is exclusively an ICU intervention, it is impossible for us to ignore this modality as part of our treatment protocols. With studies showing that even paramedics can successfully initiate TH in the field, and with the advent of equipment like the Chillcore™, we, as critical care providers, cannot afford to *not* pursue this intervention aggressively. It is apparent that further research in the South African perspective is warranted to streamline this process, but I believe, to ignore its use would be a failure in comprehensive patient management.

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