Approximately 150,000 sudden cardiac deaths occur per year in the UK. For those who survive a cardiac arrest, it is estimated that as few as 10% will make a full recovery because of global hypoxic brain injury. Cardiopulmonary resuscitation guidelines and practitioners involved in emergency resuscitation have naturally focused on strategies to restore an effective cardiac rhythm, including early defibrillation, cardiac massage, and drug therapy. However, outcome in patients resuscitated to achieve a spontaneous circulation remains poor. Overall survival to discharge after out-of-hospital cardiac arrest is approximately 5%, and of those admitted to ICU approximately 25–40% will survive to discharge with conventional therapy. Less than 10% of survivors can regain their former lifestyle, largely because of disability caused by hypoxic brain damage. Many require constant care; some remain unable to return to gainful activity because of severe memory problems or cognitive disturbance. The human and economic costs of hypoxic brain damage are not well quantified but are potentially huge. Several factors influence outcome after cardiac arrest: outcome is worse in the elderly (>75 yr), those with chronic ill-health (e.g., malignancy, sepsis, poor exercise tolerance, pneumonia, and renal impairment) or a prolonged resuscitation time.

In recent years, it has become evident that the pathological events occurring at the time of cerebral hypoxia are delayed into the post-arrest period, perpetuating and exacerbating cell damage and neuronal death. Physiological support must therefore be continued to afford any meaningful chance of recovery leading to an independent existence. This approach has been taken by a number of organizations resulting in life support guidelines that not only deal with the cardiac arrest but also the post-arrest period, as well as publications advocating post-arrest care. Attempts have also been made to investigate interventions or therapies aimed at improving outcome after cardiac arrest and recent data have shown that mild induced therapeutic hypothermia (TH) is beneficial in adults and in perinatal asphyxia, but there is no evidence for benefit after severe traumatic brain injury.

Therapeutic hypothermia

In the 1950s, four case reports demonstrated a beneficial outcome when mild TH was utilized in patients who had suffered a cardiac arrest. All four patients were cooled to 32–34°C for 24–72 h and all survived with only one having a moderate residual neurological deficit. The human and economic costs of hypoxic brain damage are not well quantified but are potentially huge. Several factors influence outcome after cardiac arrest: outcome is worse in the elderly (>75 yr), those with chronic ill-health (e.g., malignancy, sepsis, poor exercise tolerance, pneumonia, and renal impairment) or a prolonged resuscitation time.

In 1997, Bernard and colleagues published the first prospective, non-randomized series reporting that both survival and neurological outcome were improved in 22 patients resuscitated from out-of-hospital cardiac arrest and cooled to 33°C for 12 h. Subsequently, two non-blinded, randomized controlled trials were performed in Europe and Australia and published in 2002. Both used similar, highly selective entry criteria [patients with a witnessed, out-of-hospital cardiac arrest secondary to either ventricular fibrillation (VF) or ventricular tachycardia (VT) who remained comatose after return of spontaneous circulation and requiring tracheal intubation and...
ventilation]. All received standardized treatment but were randomized to receive either normothermia or hypothermia (32–34°C) for 12–24 h followed by passive re-warming to normothermia (37°C). The European study reported that 55% of patients receiving TH had a favourable outcome compared with only 39% in the normothermia group. Bernard’s Australian group demonstrated an improvement in outcome from 26% in the normothermia group to 49% in patients treated with TH. Neither study reported a statistically significant increase in complications.

Pathophysiology of neuronal damage

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⁻¹, about 20% of the total cardiac output, allowing an oxygen consumption of 3.5 ml 100 g⁻¹ min⁻¹. There are virtually no stores of oxygen, and thus an uninterrupted circulation is needed, even though some inefficient anaerobic metabolism is possible. Loss of consciousness ensues if the oxygen supply is <2 ml 100 g⁻¹ min⁻¹, and below this level neuronal damage occurs, and is dependent on both the duration and severity of hypoxic ischaemia.

The neuronal damage that occurs during and for up to 72 h after cardiac arrest is initiated by reduced or absent cerebral perfusion and results in early necrosis and also in delayed apoptotic neuronal death, processes which are closely interrelated. Necrosis is a result of widespread cellular membrane breakdown due to severe ischaemia during cerebral hypo-perfusion with a profound loss of ATP production. This causes failure of the Na⁺/K⁺ pump leading to a breakdown of trans-membrane ionic gradients and cellular depolarization. In addition, activation of phospholipases, causes lipolysis which liberates arachidonic acid, and other toxic excitatory neurotransmitters producing an acute increase in intraneuronal Ca²⁺ concentrations.

Reperfusion injury causes delayed neuronal death by apoptosis and auto-phagocytosis. This has been attributed to multiple coexisting mechanisms. One is disruption of the blood–brain barrier, explained by an inflammatory response with leucocyte-derived mediators, reactive oxygen species (ROS) such as nitric oxide (NO) and peroxynitrite, and proteases in reperfused tissue. Inflammatory cytokines (TNF, IL-1, IL-6, IL-8, and IL-10) act as chemo-attractants to leucocytes and activate toxic matrix metalloproteinases, which increase vascular permeability and damage the blood–brain barrier. The interstitial fluid shift increases diffusion distances, impairing microvascular perfusion, and causing inefficient exchange of O₂ and toxic waste substances accumulated during cardiac arrest. Subsequently, generalized mixed vasogenic and cytotoxic brain oedema further reduce cerebral perfusion pressure and contribute to reperfusion injury. Ischaemic upregulation of NO synthetase generates ROS, which cause intracellular acidification and activate neuronal endonucleases and cystein proteases. Anaerobic glycolysis produces excessive lactate, a major source of cellular acidification if not eliminated efficiently. Mitochondrial disruption is central to ATP depletion, which interferes with cellular homeostasis and Na⁺/K⁺ pump function, causing collapse of the electrochemical gradient with intracellular sodium and water influx, and neuronal membrane depolarization. This in turn triggers a massive release of glutamate and other toxic excitatory amino acids (EAAs) such as N-methyl-D-aspartate, which opens ion channels allowing additional intracellular Ca²⁺ influx. Ca²⁺ overload additionally activates intracellular proteases, causing further damage to the cytoskeleton, and fuels ROS synthesis. This is toxic to mitochondria and through them initiates pathways of programmed cell death, that is, neuronal apoptosis. Apoptosis is fuelled by cytochrome c release through mitochondrial permeability transition pores and release of other apoptigenic molecules. This is a delayed process that takes place over many hours after reperfusion, potentially offering a time window for intervention. A generalized inflammatory response also occurs, which has been termed the post-cardiac arrest syndrome.

Effects of hypothermia

Induced mild TH has a number of beneficial effects in the period after initial resuscitation from cardiac arrest. It is accepted that for every 1°C decrease in temperature, there is a 6% decrease in the cerebral metabolic rate for O₂ (CMRO₂). This decrease in oxygen demand is most likely related to the reduction in intracellular metabolic processes and decreased ATP consumption causing a reduction in intracellular acidosis and improved glucose metabolism, attenuating the release of EAAs. Mild hypothermia also improves the ion imbalances associated with ischaemia and reperfusion and reduces brain swelling by preventing intracellular ion and water entry leading to brain swelling via a membrane-stabilizing effect. Glutamate concentrations remain unchanged, caspase release is inhibited, free radical production is reduced, and the degree of apoptosis is diminished. Hypothermia mitigates the calcium-mediated activity of proteases and suppresses the cytokine response, reducing the inflammatory mechanisms involved in delayed injury.

Practical aspects

TH can be induced and maintained in several ways using invasive endovascular or extracorporeal systems or non-invasive surface-cooling devices. Modern devices employ
automatic feedback mechanisms to maintain the desired core temperature. Each device has advantages and disadvantages though there is no evidence that particular systems are superior in terms of outcome. Hypothermia may be induced simply by the rapid infusion of cold i.v. fluids and a study of outcome from cardiac arrest when cold i.v. fluids are infused in the pre-hospital setting is currently underway (http://www.ClinicalTrials.gov/identifier NCT00391469).

It is important to be aware of the widespread pathophysiological consequences of TH. Cardiovascular effects, including bradycardia, arrhythmias, increased systemic vascular resistance, and reduced cardiac output, are common. Fluid requirements increase during rewarming because of vasodilation and inotropes or vasoconstrictors may be required. Renal function is affected by decreased glomerular filtration rate and impaired renal tubular function. Hepatic function is decreased, especially the activity of cytochrome P450 enzymes. Coagulopathy and mild thrombocytopenia can occur and although significant bleeding complications are rare if core temperature is >30°C, caution is necessary in patients after surgery or trauma. Metabolic acidemia, increased plasma lactate, amylase, and hyperglycaemia with insulin resistance occur. Correction of hypokalaemia during TH may lead to hyperkalaemia during the re-warming phase so plasma electrolytes must be monitored frequently. The incidence of wound infections and nosocomial pneumonia may be increased if TH is continued for >48 h. Shivering is frequent even in deeply sedated patients and neuromuscular blocking drugs are usually required. ICU practitioners should be aware that pharmacokinetic values are affected by hypothermia: the volume of distribution, metabolism, and clearance of many drugs are reduced by effects on cardiovascular, renal, and hepatic function so the risks of accumulation and toxicity are increased.

Other target therapies

Despite improvements in understanding the processes involved in post-cardiac arrest, neurological injury, morbidity, and mortality remains high. Nevertheless, advances have increased the potential for specific therapies aimed at moderating these pathophysiological processes. Several groups have investigated the effect of modulating the calcium influx that occurs as part of the reperfusion injury, but results have been disappointing and agents such as lidoflazine and nimodipine have shown no survival benefit. Magnesium sulphate has a potential role as a Ca entry blocker, but there is no compelling evidence that outcome is improved. Attempts to attenuate lipid peroxidation and free radical formation have also been inconclusive. The use of steroids and polyethylene glycol-conjugated superoxide dismutase has been disappointing in post-cardiac arrest models. Attempts at blocking the effects of EAAs at their receptors have also shown no survival benefit.

Increasingly, it is apparent that mitochondria have a pivotal role in the sequence of events that result in neuronal death. Mitochondrial damage occurs early and by preventing a return to normal cellular function results in neuronal death. Attention has therefore turned to strategies aiming to ‘protect’ against mitochondrial dysfunction, and recent data suggest that TH combined with coenzyme Q10 (an essential mitochondrial co-factor) can enhance survival.

Conclusions

There is good evidence to support the use of induced mild TH in patients resuscitated after out-of-hospital VF/VT cardiac arrest. Many centres induce hypothermia for 12–24 h for all patients considered appropriate for admission to an ICU, but uptake in the UK remains inconsistent. The International Liaison Committee on Resuscitation has advised that TH is indicated for patients who fulfil ICU admission criteria, and should also be considered for other patient groups, that is, those with in-hospital arrest and presenting rhythms other than VF/VT. However, there is no direct evidence to support TH in these other groups (i.e. outside the inclusion criteria applied to the original Australian and European trials) and further data are required before firm recommendations can be made. A large randomized trial of TH after in-hospital cardiac arrest is currently underway (http://www.ClinicalTrials.gov identifier NCT00457431).

The optimal method of induction and maintenance of TH and the ideal duration of cooling are unclear. ICU and Emergency physicians should be aware that even with tightly controlled entry criteria (e.g. witnessed arrest and short time to return of spontaneous circulation) morbidity and mortality in the published series remained appreciable. Therefore, and despite our own positive experience using TH, we would emphasize that TH is viewed as one part of overall management. Cerebral oxygen delivery must be maintained and complications minimized in order to realize the benefits. Indeed, recent evidence suggests an improvement in outcome when a systematic treatment protocol is applied after resuscitation.

Until further data are available, TH should perhaps be reserved for those likely to benefit and therefore accurate prognostic tools must be developed to identify these patients early. There is clearly room for further improvements in outcome after cardiac arrest and a need for research into other therapies, for example, aimed at attenuating events at a neuronal level. The current trials of TH are eagerly anticipated.
Therapeutic hypothermia: a new option in the management of cardiac arrest.


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