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Hypothermia as Treatment in Cardiac Arrest: Pathophysiology

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Sudden cardiac arrest (CA) remains an unresolved public health problem. It is the major cause of death in western countries and some of the few survivors remain neurologically disabled. In this article, we explore the effects of sudden cardiac arrest on the brain, how pharmacology has failed to produce a reliable solution, and how hypothermia can offer an effective treatment in certain cases.

The Brain During Cardiac Arrest

During the initial no-flow period, loss of brain oxygen stores and unconsciousness occur within ten to twenty seconds. The 'four minutes limit' concept is supported by evidence that brain glucose and adenosine triphosphate (ATP) stores are depleted and the membrane pump is arrested within three to five minutes of complete ischaemic anoxia, at least in normothermic conditions. This ATP loss leads to membrane depolarisation with shift of the Ca²⁺ into neurons, as well as an increase in the brain of the concentration of free fatty acids and extracellular concentration of excitatory amino acids (EAAs), particularly glutamate (Glu). These mechanisms seem partially responsible for the selective vulnerability of some neurons in certain regions, such as the hippocampus, neocortex, and cerebellum.

Neurotoxic cascades that are deleterious to the brain are provoked during the reoxygenation and reperfusion period, which are essential in restoring energy charge. EAAs play a major role in neurotoxic cascades. In underperfused tissue, the presynaptic terminals' release of Glu, and the extracellular concentration of this EAA substantially increases. Upon binding with Glu, a conformational change occurs in membrane-bound proteins, allowing the opening of the Glu-activated ion channels. This leads to an influx of Ca²⁺ and Na⁺ into the threatened cell, which initiates an elaborate cascade of events, culminating in DNA damage and thereby triggering an enhanced programmed death of individual cells through "apoptosis".

Pharmacology Fails to Offer Solution

Because ischaemia and reperfusion are overwhelming processes and neurotoxic cascades are complex and involve many steps, pharmacological agents affecting a single portion of these biochemical events will probably have only minimal beneficial effects. So far, an abundant number of neuroprotective agents have been developed and evaluated with promising results in animals, but in humans the results have proven frustrating. Moreover, interventions that are effective for protection and preservation before and during the insult were not typically effective after the ischaemic insult, during the resuscitative stage. Data obtained from "healthy animals" are not necessarily applicable to "sick patients". Interventions that seem effective after brain trauma or focal ischaemia in rats are not consistently effective after CA in monkeys, dogs or humans. Although the different pharmacological strategies have been disappointing, hypothermia appears to offer a promising solution.

Hypothermia Steps in to Fill the Breach

Hypothermia is a state of body temperature, which is below normal in a homeothermic organism. When considering therapeutic hypothermia, we should distinguish between mild (32°–34°C), moderate (28°–32°C), deep (15°–25°C), and profound (<15°C) therapeutic hypothermia.

We should also differentiate between core temperature, such as oesophageal, central venous, pulmonary artery, urinary bladder, rectal temperature, and brain temperature, such as deep brain, cortical, epidural, tympanic membrane, nasopharyngeal, and intra-ventricular temperature.

Finally, we should differentiate between accidental, spontaneous and uncontrolled hypothermia, which is physiologically deleterious because of homeothermic defences and induced, controlled hypothermia, which under a poikilothermic condition can be therapeutic. Poikilothermia in humans, such as avoidance of shivering, thermogenesis, sympathetic discharge and vasoconstriction, can be caused by the ischaemia- or trauma-induced coma or by sedation or anaesthesia, with or without neuromuscular blockade. Therapeutic hypothermia is different from hibernation, which is poikilothermic down regulation of metabolism and blood flow without tissue hypoxia.

Therapeutic hypothermia offers the possibility to be induced prior, during and after the insult, though resuscitative hypothermia is less studied than protective and preservative hypothermia. There is, however, growing evidence that resuscitative hypothermia will have some clinical applications. The limiting ability of CPR techniques to resume heart function and the longer interval time needed to reach the scene, might partially explain these disappointing results. Moreover, return of spontaneous circulation, which is important to restore cellular function, may at normothermia provoke deleterious chemical cascades resulting in secondary brain damage.

Either multifaceted treatment strategies or a combination of a single-molecule targeted drug are required to achieve survival without brain damage, because of the multi-factorial pathogenesis of the post-arrest neuronal death. Until recently, there was no therapy available with a documented efficacy in preventing brain damage after CA. Mild hypothermia (33°C) was discovered to mitigate brain damage significantly when induced before, during, or after CA. Therapeutic mild hypothermia (33°C) seems to attenuate the EAA overflow, the overproduction of nitric oxide, and cell apoptosis and thereby mitigates the neurotoxic cascades that occur during the ischaemic insult and during reperfusion.

Studies on Therapeutic Mild Hypothermia

The 2002 European Hypothermia After Cardiac Arrest (HACA) study included only patients who had witnessed CA and initial rhythm of ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT). In this study, the cooling was started at the emergency department and maintained for 24 hours. Survival rates and positive neurological outcomes were significantly higher in the hypothermic group compared to normothermic group (55% vs. 39%).

In a second study, (Bernard et al. 2002), which included 77 patients with the same inclusion criteria as in the HACA study, the cooling was started earlier in the ambulance. The target temperature was 33°C for a period of twelve hours. The authors report a significant improvement of the neurological outcome and survival (49% in the hypothermic group vs. 26% in the normothermic group).

In a later study (Hachimi-Idrissi et al.), only comatose patients after CA of presumed cardiac origin and displaying asystole or pulseless electrical activity (PEA) were included. In this study, a helmet was used as a cooling device for a four-hour period and then the rewarming phase occurred spontaneously over the next eight hours. Favourable neurological recovery occurred in two out of sixteen patients in the hypothermic group and none in the normothermic group.

Advisory Statement Offers Guidance

In June 2003 the International Liaison Committee on Resuscitation formulated an advisory statement for resuscitative mild hypothermia in selected categories of comatose patients resuscitated from CA of cardiac origin. Specifically, it deals with those patients displaying a VF or VT and with no refractory shock or persistent hypoxemia. The extension of resuscitative mild hypothermia to other CA categories of cardiac origin and displaying other rhythms than VF or VT is speculative at the present moment.

Conclusion

Therapeutic mild hypothermia undoubtedly improves the outcome of patients suffering from CA. However, several questions remain unanswered, such the ideal duration of cooling itself, the time frames for inducing hypothermia as well as in the re-warming phase, the level of cooling, and the suitable types of CA. Additional tools in the treatment of this condition with hypothermia would be the design of new techniques or cooling devices that would be both easy and inexpensive to use in the ambulance or pre-hospital setting.



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