

Controlled hypothermia in post-resuscitation management: what is so cool about it?

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ABSTRACT

Survivors of successful resuscitated cardiac arrest have a high incidence of severe neurological deficits. The pathophysiology of cerebral injury is thought to be multifactorial, and therapeutic mild hypothermia is one of the strategies that have been shown to minimise this complication. In this article, we outline the theoretical basis for this strategy as well as the clinical evidence to support current practice guidelines advocating its use. We also review the technical aspects of implementing hypothermia after resuscitation as well as the potential side effects. Finally, unresolved issues are discussed as we outline the ongoing prospective clinical trial underway in Singapore in order to evaluate its safety and efficacy in our local population. We advocate further research into this topic, as it has great potential to improve the outcomes of comatose resuscitated patients of cardiac arrest.

Keywords: arrest, cardiac, hypothermia, resuscitation

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INTRODUCTION

Sudden cardiac death is a common and devastating manifestation of ischaemic heart disease. Public health education programmes as well as the increased availability of defibrillator machines in the community have increased public awareness with regard to the importance of early resuscitative efforts, and as such, there is an anticipated rise in the incidence of resuscitated sudden death patients. However, it is recognised that resuscitated sudden death carries with it its own specific complications, the most important being the high incidence of severe neurological deficits in survivors.

The pathophysiology of cerebral injury after successful resuscitated cardiac arrest is the subject of much research, and it is currently thought to be multifactorial. The initial damage occurs during the period of cerebral anoxia and is directly related to the time from onset of cardiac arrest to

the time of return to spontaneous or assisted circulation. Cerebral anoxia not only causes the death of cerebral tissue and neurons, but also primes the brain for further injury during the reperfusion phase. Cerebral inflammation and oedema that disrupt the blood brain barrier potentiate the injury during this phase.

Free radical production during the reperfusion phase is among the most important mechanisms of injury in resuscitated sudden death patients.⁽¹⁾ Neuronal membranes, proteins and DNA are all potentially damaged from the process of peroxidation that is triggered by free radicals in the tissue. Furthermore, the accumulation of intracellular glutamate leads directly to calcium ion shifts from the extracellular to intracellular space, which causes the activation of further degradative enzymes, leading to further tissue damage.⁽²⁻³⁾ The accumulation of glutamate in itself is thought to be directly cytotoxic. These mechanisms persist to cause injury in the acute setting and also for a considerable period thereafter.

EFFECTS OF HYPOTHERMIA ON NEUROLOGICAL FUNCTION

Hippocrates described the beneficial effects of packing bleeding patients in the snow. This was further illustrated by the French surgeon Baron Larrey during the Napoleonic campaign in Russia, who observed the improved survival of soldiers left in the snow as compared to those who were warmed up with blankets and hot drinks.⁽⁴⁾ Moderate hypothermia (28°C–32°C) was used in cardiac surgery in the 1950's in order to minimise cerebral damage⁽⁵⁾ as well as after successful resuscitated cardiac arrest, with promising results.^(6,7) However, it caused significant side effects such as cardiac arrhythmias, and was thus discontinued until interest resurfaced with the introduction of mild hypothermia (32°C–35°C) as a therapeutic strategy to minimise cerebral damage.

Hypothermia is thought to be protective since for each 1°C reduction in body core temperature, the cerebral metabolic rate decreases by 6%.⁽⁸⁾ This causes a reduction in cerebral oxygen and glucose demand and consumption. In addition, hypothermia is thought to reduce the rate of formation of free radicals, the inflammatory cascade

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precipitated by cerebral anoxia as well as the formation of glutamate and subsequent calcium ion shifts. Thus, the beneficial effects of hypothermia probably extend beyond the simple theory of reducing cerebral oxygen demand.

CLINICAL STUDIES OF THERAPEUTIC MILD HYPOTHERMIA AFTER SUCCESSFUL RESUSCITATED CARDIAC ARREST

The first case reports of hypothermia after cardiac arrest were published in 1958 and included four patients with good neurological outcome after in-hospital cardiac arrest.⁽⁷⁾ These patients received open heart massage and were cooled to between 30°C and 34°C for 24–72 hours after the return of spontaneous circulation (ROSC). Since then, small, non-randomised case series with equivocal results using a variety of cooling techniques and end points have been published. Two landmark studies, both published in 2002, have transformed the approach to management of comatose patients after successful cardiac resuscitation. The European multicentre study was performed in nine centres in five countries,⁽⁹⁾ while the Australian study was conducted in four hospitals in Melbourne, Australia.⁽¹⁰⁾

The European group performed a prospective randomised controlled trial, which confirmed that induction of hypothermia in comatose survivors of out-of-hospital cardiac arrest due to ventricular fibrillation (VF) improves the neurological outcome and mortality at six months. 275 patients (76% of whom were men) with a median age of 59 years were included in the study. All patients had ROSC after witnessed cardiac arrest with VF or non-perfusing ventricular tachycardia (VT) as an initial cardiac rhythm. Inclusion criteria were a presumed cardiac cause for the arrest, an estimated interval of 5–15 minutes from collapse to start of cardiopulmonary resuscitation and an interval of less than 60 minutes from collapse to ROSC. Exclusion criteria were a tympanic membrane temperature of < 30°C on admission, cardiogenic shock and a response to verbal commands before randomisation.⁽⁹⁾

All patients received intensive care for 32 hours, according to a detailed protocol with mechanical ventilation. Patients who were allocated to the mild hypothermia group (n = 137) were cooled to a target bladder temperature of 32°C–34°C with an external cooling device, namely a purpose-built cooling mattress with cooling air cover. If cooling did not occur within four hours, ice packs were applied to reach the target core temperature. The temperature was maintained for 24 hours, after which the patients were passively re-warmed. The control group (n = 138) was kept normothermic. The primary outcome measure was a favourable neurological outcome on the Pittsburgh cerebral-performance scale

(able to live independently and work at least part-time) at six months. Secondary outcomes included mortality and potentially harmful side effects. Favourable neurological recovery was seen in 75 of the 136 patients (55%) in the hypothermia group as compared with 54 of the 137 patients (39%) in the normothermia group (p = 0.009, number-needed-to-treat [NNT] = 6). Mortality at six months was 56 of 137 patients (41%) in the hypothermia group as compared with 76 of 138 patients (55%) in the normothermic group (p = 0.02, NNT = 7). The complication rate did not differ significantly between the two groups. The authors concluded that mild therapeutic hypothermia after successfully resuscitated cardiac arrest due to VF increased the rate of a favourable neurological outcome and reduced mortality. The major limiting factors included the inability of the investigators to blind the treating team of the study group, the high proportion of patients screened who were eventually excluded (92%) and relative hyperthermia (core temperatures in excess of 38°C) in the control group. The target temperature could not be achieved in 19 patients in the hypothermic group. There were 22% more complications such as bleeding, sepsis and specifically pneumonia in the hypothermic group, but this was not statistically significant.⁽⁹⁾

The Australian study assigned 77 patients pseudorandomly (depending on odd or even days) to normothermia or cooling with ice packs in order to achieve a body core temperature of 33°C for 12 hours. The primary outcome measure was survival to hospital discharge, with sufficiently good neurological function to be discharged home or to a rehabilitation facility. 21 of the 43 patients (49%) treated with hypothermia survived with a good neurological outcome, compared with nine out of the 34 (26%) treated with normothermia (p = 0.046, odds ratio [OR] 5.25). Mortality at discharge was 22 of 43 (51%) in the hypothermia group and 23 of 34 (68%) in the normothermia group (relative risk [RR] 0.76, 95% confidence level [CI] 0.52–1.10, NNT = 6). There was no difference in adverse effects, although it was noted that patients in the hypothermia group were more frequently associated with a lower cardiac index, higher systemic vascular resistance and hyperglycaemia.⁽¹⁰⁾

Largely on the basis of these two trials, the International Liaison Committee on Resuscitation (ILCOR) Advanced Life Support (ALS) Task Force made the following recommendations in 2003:⁽¹¹⁾

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C–34°C for 12–24 hours when the initial rhythm was VF.
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.

A subsequent meta-analysis with individual patient data analysis confirmed that therapeutic hypothermia improved short-term neurological recovery and survival in patients resuscitated from cardiac arrest.⁽¹²⁾ The authors performed a comprehensive literature search to include only randomised and quasi-randomised controlled trials of adults who were successfully resuscitated, where therapeutic hypothermia was applied within six hours of arrival at the emergency department and where the neurological outcome was compared. Studies without a control group or with historical controls were excluded.

Three trials were identified, two of which were the previously mentioned European and Australian multicentre trials.^(9,10) The third trial was based at a single centre in Europe that had also collaborated in the previous European multicentre trial. However, this single-centre trial had used a different set of inclusion criteria. Hence no patients in the trial were also included in the multicentre trial.⁽¹³⁾ This trial differed from the other two multicentre trials in that the comatose survivors of cardiac arrest had a primary electrocardiographic rhythm of asystole or pulseless electrical activity. Systemic hypothermia was achieved with a helmet device placed around the head and neck containing a solution of aqueous glycerol. The patients were cooled to a target temperature of 34°C for a maximum of four hours.

All authors of the identified trials supplied individual patient data with a predefined set of variables. More patients in the hypothermia group were discharged with favourable neurological recovery (RR 1.68; 95% CI 1.29–2.07). The 95% CI of the NNT to allow one additional patient to leave the hospital with favourable neurological recovery was 4–13. One of the studies followed up the patients for six months or until death, and showed that patients in the hypothermia group was more likely to be alive at six months, with favourable functional neurological recovery (RR 1.44, 95% CI 1.11–1.76).⁽⁹⁾

METHODS OF COOLING

Various cooling techniques have been described, but none of these techniques combine high efficacy with ease of use or availability. External cooling methods such as ice packs to the groin or axillae, cooling blankets, wet towels, fanning and cooling helmets are easy to use, widely available and may be started even in the pre-hospital setting. The main disadvantage of external cooling methods is that they are generally slow at reducing core temperature. Furthermore, it is difficult to maintain the target core temperature when it has been reached. Intravascular cooling methods have also been evaluated. Infusion of 30 ml/kg of crystalloid at 4°C over 30 minutes reduced core temperature from an

average of 35.5°C to 33.8°C and did not cause pulmonary oedema.⁽¹⁴⁾ An intravascular heat exchange coil placed in the inferior vena cava has also been evaluated and reported to be a safe and feasible method of cooling that allows for tight temperature control.⁽¹⁵⁾

TIME OF COOLING

Animal studies have suggested that the earlier hypothermia is induced after restoration of perfusion from cardiac arrest, the better the outcome, although therapeutic benefit was still present in clinical studies when cooling was delayed for several hours.^(16–18) The current ILCOR ALS statement recommends that cooling should be initiated as soon as possible after ROSC; however, it appears to be successful even if delayed for 4–6 hours.⁽¹¹⁾ In the European multicentre study, the time between successful resuscitation and attainment of a target core temperature of 32–34°C had an interquartile range of 4–16 hours.⁽⁹⁾ However, there are still gaps in our knowledge with respect to the optimal duration of therapeutic hypothermia, optimum target temperature, and rates of cooling and rewarming.

COMPLICATIONS OF THERAPEUTIC MILD HYPOTHERMIA

Shivering is a reflex that accompanies hypothermia and is undesirable in the setting of therapeutic hypothermia, as it increases oxygen consumption as well as raises core temperature, thus exposing the resuscitated patient to the risk of neurological injury, as previously discussed. To ameliorate this effect, the use of muscle relaxants and paralytics is typically employed during the period of therapeutic hypothermia.

Mild hypothermia decreases cardiac output by approximately 25% as a result of a reduction in heart rate and direct effects on the myocardium. Increased systemic vascular resistance and central venous pressure in addition to reduction in cardiac output cause mild acidosis and a small rise in serum lactate levels. Arrhythmias become more frequent and significant as core temperature falls below 30°C, although in mild therapeutic hypothermia, the risk is believed to be low.

Acute renal impairment is commonly observed after resuscitated cardiac arrest, and its recovery may be slowed down by the use of therapeutic hypothermia.⁽¹⁹⁾ There is also reflex diuresis from decreased antidiuretic hormone production, and this may lead to further volume as well as electrolyte loss, which in itself can cause direct neurological injury.

Hypothermia causes a mild bleeding tendency through a reversible reduction in platelet count and function, as well as a reduction in the efficacy of clotting enzymes and

plasminogen activator inhibitors. This effect is not detected by standard laboratory coagulation tests, unless they are performed at the patient's core temperature. Fortunately, in a patient who is not actively bleeding and is otherwise haemodynamically stable, this slight increase in bleeding tendency does not appear to have any clinical significance.

As mentioned previously, one of the effects of hypothermia is the reduction of inflammatory and immune responses in the body. This has potentially deleterious effects in so far as it may promote the incidence of opportunistic infections, especially pneumonias in the comatose resuscitated patient. This risk appears to be directly related to the length of time for which cooling is maintained, although currently, there is as yet no role for prophylactic antibiotic therapy. Other effects of hypothermia include a tendency toward hyperglycaemia, mediated by reductions in insulin secretion and sensitivity. Drug pharmacokinetics and pharmacodynamics may also be altered as the core temperature falls.

THERAPEUTIC MILD HYPOTHERMIA IN SINGAPORE

The use of therapeutic mild hypothermia is not a common practice in Singapore. Possible reasons for the slow uptake include the lack of awareness, expertise and infrastructure. To this end, the Department of Emergency Medicine, Singapore General Hospital and the Department of Cardiology, National Heart Centre, Singapore are presently conducting a prospective clinical study in comatose resuscitated sudden cardiac death patients by comparing controlled therapeutic mild hypothermia using external and internal cooling techniques to standard intensive care unit therapy. It is hoped that this study will increase the awareness of therapeutic mild hypothermia in this setting, as well as evaluate its safety and efficacy in the Singapore population.

CONCLUSION

There is good theoretical, laboratory and clinical evidence to support the use of therapeutic mild hypothermia to reduce the incidence of neurological injury as well as mortality in comatose resuscitated patients. It is now recommended for patients with a collapse rhythm of VF or non-perfusing VT, based on evidence from multicentre randomised trial data. The incidence of adverse events and complications appears to be acceptably low, especially if the duration of cooling is not excessively long. It is believed that early cooling carries greater benefit. Issues that remain to be clarified include the optimal cooling technique, target core temperature, duration of cooling and rates of cooling and rewarming. It is hoped

that this therapy will gain greater acceptance and become more widely adopted so as to benefit comatose resuscitated patients whose prognosis is currently extremely poor.

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