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Therapeutic hypothermia after cardiac arrest

[Resuscitation and trauma anaesthesia]

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Outline

Abstract

Purpose of review: Most patients who suffer a cardiac arrest die after the event. Full neurological recovery occurs in only 6–23%. Until recently no specific post-arrest therapy was available to improve outcome. Application of therapeutic hypothermia (32–34°C for 12–24 h) applied after cardiac arrest could help to improve this dreadful situation. This review covers the background of and recent clinical studies into hypothermia after cardiac arrest, and gives some insights into the future of resuscitation, namely suspended animation.

Recent findings: Two randomized clinical trials of mild therapeutic hypothermia applied after successful resuscitation from cardiac arrest showed that hypothermia after cardiac arrest improves neurological outcome as well as overall mortality.

Summary: The introduction of therapeutic hypothermia after cardiac arrest into routine intensive care practice could save thousands of lives worldwide, because only six patients must be treated to yield one additional patient with favourable neurological recovery. New developments in cooling techniques will make early induction of therapeutic hypothermia simple and convenient. The optimal duration and depth of hypothermia will be determined by future trials. Suspended animation is cooling during cardiac arrest to preserve the organism under conditions of prolonged controlled clinical death, followed by delayed resuscitation, resulting in survival without brain damage. This concept was initially introduced for trauma victims who rapidly bleed to death, and proved to be feasible in studies evaluating outcomes following exsanguination cardiac arrest in large animals. Whether the concept of suspended animation is applicable to normovolemic cardiac arrest is under investigation.

Introduction

Cardiovascular disease is the world's leading cause of morbidity and death. About 17 million people worldwide die from cardiovascular disease each year [1]. Many of these deaths are due to sudden cardiac arrest.

Epidemiology of cardiac arrest

In industrial countries, the annual incidence of out-of-hospital sudden cardiac arrest lies between 36 and 128 per 100 000 individuals. Unfortunately, full cerebral recovery after cardiac arrest is still rare. Approximately 80% of patients who are successfully resuscitated present with coma lasting for longer than 1 h. Good neurological recovery of patients admitted to a hospital can be achieved in 11–48% of cases. The rest of the patients die during their hospital stay or remain in a vegetative state [2–4].

Damaging processes during and after cardiac arrest

During cardiac arrest, current therapeutic options include chest compressions, ventilation, defibrillation, and administration of vasoactive and antiarrhythmic drugs [5]. However, after successful restoration of the circulation, further damage occurs. Reoxygenation may lead to deleterious chemical cascades, which lead to further delayed necrosis and apoptosis of neuronal tissue. This secondary damage to the brain after primary successful resuscitation was termed ‘postresuscitation disease’ by Negovsky [6] and consists mainly of four pathomechanisms.

The first pathomechanism is perfusion failure [7], with multifocal no-reflow, transient global hyperaemia due to vasoparalysis, and delayed, prolonged global and multifocal hypoperfusion for up to 12 h after arrest. The second source of damage is reoxygenation injury [8]. Several different cascades lead to delayed calcium loading and consecutively to lipid peroxidation of membranes and primary necrosis [9–11], and/or triggering of programmed cell death (apoptosis) [12,13]. Extracerebral causes, including postanoxic viscera among others, represent the third source of injury [14]. The stasis of the blood during cardiac arrest leads to derangements in its composition and is the last source of injury.

How therapeutic hypothermia can prevent brain damage after ischaemic events

Hypothermia is a state in which the body temperature is below normal in a homeothermic organism. Therapeutic hypothermia, as used for cardiopulmonary bypass in neurosurgery and cardiac surgery, or after cardiac arrest, is instituted in a controlled way, in contrast to accidental hypothermia. With controlled hypothermia, it is possible to avoid possible defence mechanisms such as shivering and catecholamine release. For cardiac arrest, cooling can be started before ischaemia occurs (protection in cardiac surgery), during ischaemia (preservation) and after ischaemia (resuscitation).

The protective effect of therapeutic hypothermia is multifactorial and acts on many different targets of the damaging cascades simultaneously. It is well known that postischaemic hypothermia reduces the number of cells that die in certain brain regions [15–18]. To be beneficial, mild hypothermia must be applied very soon after the ischaemic insult; otherwise, the beneficial effects may be diminished or even eliminated [19–26,27••]. On the other hand, there is evidence that the damaging process after ischaemia can last for several days [24], and so a later start of hypothermia may be beneficial, especially if the duration of hypothermic treatment is extended [21].

The multifactorial protective action of therapeutic hypothermia includes slowing of destructive enzymatic processes, protection of lipid membrane fluidity, and reduction in oxygen requirements without impairing microvasculatory blood flow in low-flow regions during reperfusion after ischaemia [7]. Additionally, therapeutic hypothermia inhibits lipid peroxidation [28], attenuates brain oedema [29]

and reduces intracellular acidosis [30].

Recently, the effects of postischaemic hypothermia on brain injury and apoptotic neuronal cell death were evaluated in rats [31•]. In a model of transient focal cerebral ischaemia, it was shown that therapeutic hypothermia (30°C, 10 h) could reduce cytochrome c release and activation of caspase-3 and -2. This reduction in enzymes involved in apoptosis correlated well with reduced brain infarct volumes and neuronal loss in the CA1 area of the hippocampus at 72 h after the insult.

The effect of regulated therapeutic hypothermia induced with a neurotensin analogue (NT77) on oxidative stress of the brain after a hypoxic cardiac arrest was investigated in another study [32•]. Maximum oxidative stress occurred at 16 h after reperfusion in normothermic animals. Regulated hypothermia (32–34°C, 4 h) reduced oxidative stress to baseline values in the hippocampus during reperfusion from hypoxic ischaemia. This effect could only be reproduced by external cooling if the cooling period was extended to 24 h. This was explained by an increased metabolic rate during external cooling as compared with regulated hypothermia.

Therapeutic hypothermia not only protects neurones but also has beneficial effects on white matter injury [33•] and astroglial cell proliferation [34•].

Clinical trials of therapeutic hypothermia after cardiac arrest

The first case series of hypothermia after cardiac arrest were published in the late 1950s [35,36]. Unsedated patients were maintained hypothermic until they regained consciousness; however, because of haemodynamic and respiratory problems with these early protocols, therapeutic hypothermia after cardiac arrest was not used clinically until the late 1990s.

Several pilot trials of mild therapeutic hypothermia after cardiac arrest [37–41] found improved neurological function compared with historic controls. This led to two randomized trials of therapeutic external hypothermia after cardiac arrest, one conducted in Australia and one in Europe.

The Australian trial [42] included 77 comatose survivors from cardiac arrest of cardiac origin with a primary rhythm of ventricular fibrillation or pulsless ventricular tachycardia. Patients were randomly assigned to hypothermia (33°C, 12 hours; achieved with ice packs) or normothermia. Twenty-one of the 43 patients (49%) treated with hypothermia survived and had favourable neurological recovery, as compared with nine of the 34 patients (26%) treated with normothermia ($P = 0.046$). The odds ratio for favourable neurological recovery with hypothermia therapy was 5.25 (95% confidence interval (CI) 1.47–18.76; $P = 0.011$) after adjustment for baseline differences.

The European multicentre trial [43] included 275 comatose survivors from cardiac arrest of cardiac cause (ventricular fibrillation or pulsless ventricular tachycardia). Patients were randomly assigned to receive therapeutic hypothermia (32–34°C, 24 h; achieved with cold air) or to standard treatment with normothermia. Seventy-five of the 136 patients (55%) in the hypothermia group had favourable neurological recovery after 6 months as compared with 54 out of 137 patients (39%) in the normothermia group (risk ratio 1.40, 95% CI 1.08–1.81). In addition, a significant reduction in mortality at 6 months (risk ratio 0.74, 95% CI 0.58–0.95) was reported. The complication rate in the two trials did not differ significantly between treatment groups. Although there was a trend toward more infections in the hypothermia group, the beneficial effects of the therapy by far outweighed the adverse effects.

Endovascular cooling, a more effective and very convenient method of applying therapeutic hypothermia, was recently used in patients who had suffered a cardiac arrest. With this method, rapid cooling is achieved by inserting a balloon catheter into the inferior vena cava via a femoral vein. The balloons are perfused with cold saline via a ‘closed loop’ internal cooling circuit. The catheter cools the

patient's blood as it circulates past the catheter. The newer devices also have the advantage of allowing automatic feedback control of the patient's temperature and can provide controlled active rewarming [10,17,29,30,44,45].

In a retrospective cohort study [46], 48 consecutive comatose patients who had suffered a witnessed cardiac arrest were cooled with an endovascular cooling device (Icy™ and CoolGard 3000™; Alsius, Irvine, USA) over 24 h to 33°C. They were compared with 847 control patients from a cardiac arrest database. In the endovascular cooling group, 33 out of 48 patients (69%) survived for 30 days or to hospital discharge, as compared with 411 out of 847 (49%) in the control group (95% CI 7–34%). The adjusted risk difference was 15% (95% CI 0–29%). Favourable neurological recovery occurred in 26 out of 48 patients (54%) in the endovascular cooling group, as compared with 281 out of 847 (33%) in the control group (95% CI 7–35%). The adjusted risk difference for favourable neurological recovery with therapeutic hypothermia was 24% (95% CI 10–39%). No major harmful adverse effects have been observed. Although endovascular cooling was associated with laboratory signs of pancreatitis and acute renal failure, these adverse events had no impact on survival to hospital discharge.

In another study [47•], the safety and feasibility of endovascular cooling was assessed in 13 comatose survivors after cardiac arrest. Patients were cooled to 33°C for 24 h using the same device as described above, followed by controlled rewarming. The cooling rate was 0.8 ± 0.3°C/h, and rewarming lasted for 18.3 ± 5.9 h. Five patients (38%) had favourable neurological recovery after 30 days. Both studies of endovascular cooling showed that this modality is able to achieve fast induction and excellent maintenance of resuscitative hypothermia. Furthermore, endovascular cooling appears to be safe and improves neurological outcomes.

The future of therapeutic hypothermia: suspended animation

Cerebral protection before an ischaemic event has taken place since the 1950s to protect the brain against global ischaemia during cardiac surgery, but in sudden cardiac arrest patients it is not feasible logistically. Cerebral resuscitation with mild therapeutic hypothermia after successful restoration of the circulation is described above. The following commentary describes cerebral preservation, which may be feasible during no-flow and low-flow in cardiac arrest using ‘suspended animation for delayed resuscitation’. The concept of suspended animation, which is defined as ‘preservation of the organism during transport and surgical haemostasis, under prolonged controlled clinical death, followed by delayed resuscitation to survival without brain damage’ [48], was introduced for trauma victims who rapidly bleed to death. In these patients, conventional resuscitation attempts are futile and current mortality rates are near 100%.

Suspended animation in exsanguination cardiac arrest

Protective hypothermia for cardiac surgery is slowly induced and reversed with cardiopulmonary bypass. Cardiopulmonary bypass is not yet available for application in the field, and in trauma victims who exsanguinate to the point of cardiac arrest hypothermia must be induced before the brain loses viability (i.e. within the first few minutes of no-flow). Cardiopulmonary bypass cannot induce cerebral hypothermia quickly enough during cardiac arrest. Therefore, the use of an aortic cold flush was introduced to achieve rapid induction of preservative hypothermia first in the most sensitive organs, namely the heart and brain. Cardiopulmonary bypass is used only for resuscitation and rewarming [49,50••]. In a series of experiments, dogs were exsanguinated over 5 min to cardiac arrest no-flow of duration 15–120 min [51–53,54••]. At 2 min of cardiac arrest, the dogs received the aortic flush via a balloon-tipped catheter, advanced via the femoral artery. Cardiac arrest of 15–120 min was reversed with cardiopulmonary bypass for 2 h to restoration of spontaneous circulation. Further treatment consisted of mild hypothermia for 12 h, controlled ventilation for 24 h, and intensive care for 72 h.

The final outcome evaluation at 72 h considered overall performance category, neurological deficit score, and total and regional histologic damage scores in 19 different brain regions. (Overall performance category, neurological deficit score and histologic damage scores are described extensively in the literature [51–53,54••].) The results depended on flush volume and flush temperature. By lowering the temperature of the flushed saline to 2°C, progressively increasing the flush volume and starting the flush at 2 min of normothermic exsanguination cardiac arrest, the brain (tympanic membrane) temperature was decreased to around 34°C, which preserved brain viability during cardiac arrest for 15 min [51] and 20 min [52]. By increasing the flush volume, the tympanic membrane temperature was decreased to around 28°C, which preserved brain viability for 30 min [53], and to around 10°C, which preserved brain viability for up to 120 min [54••]. With hypothermic no-flow durations of 30 min or longer, the flush had to include the spinal cord to avoid paralysis of the hind legs.

Another group explored suspended animation to develop a method to protect the brain during otherwise unfeasible neurosurgical procedures [55]. Dogs underwent asanguinous low-flow perfusion for 3 h with cardiopulmonary bypass with special solutions under ultra-profound hypothermia (<5°C); the animals survived with normal neurological function. Suspended animation was also explored in a clinically relevant pig model [56,57]. Using readily available equipment, profound hypothermia to 10°C was induced via a thoracotomy and direct aortic cannulation. The pigs survived with normal neurological recovery after a total arrest time of up to 40 min, and in another experiment after a low-flow time with cardiopulmonary bypass of up to 60 min.

Suspended animation in normovolaemic cardiac arrest

Sudden normovolaemic cardiac arrest accounts for far more deaths than does exsanguination cardiac arrest. In Europe, the incidence of normovolaemic cardiac arrest is 750 000 patients per year, and good neurological outcome is achieved in only 6–23% of these [58]. Therefore, in the remainder of the review we consider whether the concept of suspended animation can be adapted to normovolaemic cardiac arrest.

One possible approach to suspended animation was demonstrated by Nozari *et al*. [59••] in dogs. In that study, induction of hypothermia was not with aortic flush but with venovenous extracorporeal cooling. After no-flow cardiac arrest of duration 3 min and simulated unsuccessful advanced life support for 17 min, dogs were cooled via venovenous extracorporeal cooling to tympanic temperature of 27°C or 34°C, with ongoing chest compressions for another 20 min. Two control groups were kept normothermic, with and without venovenous blood flow. After 40 min of ventricular fibrillation, the animals were reperfused with cardiopulmonary bypass for 4 h, including defibrillation, to achieve spontaneous circulation. All dogs were maintained at mild hypothermia for another 12 h and kept in intensive care for up to 96 h. All dogs in the normothermic groups achieved spontaneous circulation, but they remained comatose and all except one died within 58 h with multiple organ failure. All dogs in the hypothermic groups survived to 96 h without gross extracerebral organ damage.

In our laboratory, we tested another approach to suspended animation, namely induction of hypothermia with cold aortic saline flush (see below). In exsanguination cardiac arrest the aortic flush balloon catheter could be inserted by paramedics or ambulance physicians in the field, while the patient is bleeding but before arrest occurs. In contrast, in normovolaemic cardiac arrest it is clinically unrealistic to insert the aortic flush catheter before at least 10 min of no-flow, considering the response time of the emergency system and the time it takes to place the aortic balloon catheter.

Studies in cell cultures and rodents support the concept of suspended animation for normovolaemic cardiac arrest. It was shown in myocytes that injury to ischaemic cells takes place only after reperfusion, which initiates several cascades that lead to cell death, but not during ischaemia itself [60,61•,62,63]. When ischaemic myocytes were made hypothermic before reperfusion, injury to the cells was less, even when

the duration of ischaemia was prolonged as compared with cells with normothermic reperfusion [63]. In a mouse model of cardiac arrest, induction of moderate hypothermia to 30°C just before attempted resuscitation resulted in better 72-h survival than in mice in which induction of hypothermia was delayed to 30 min after the start of resuscitation [64••].

The main challenge in bringing suspended animation into clinical practice lies in the rapid induction of cerebral hypothermia. In one study of exsanguination cardiac arrest in dogs, aortic flush with 100 ml/kg saline at 2°C decreased tympanic temperature to approximately 28°C within 4 min [53] with a corresponding brain temperature of 18°C (unpublished data). When we applied the aortic flush as used in the exsanguination cardiac arrest model in dogs [53] in a 30-kg swine after 10 min cardiac arrest no-flow, brain temperature remained above 35°C (unpublished data). One explanation for the difference in brain temperature might be the difference in no-flow time between the two models. In the exsanguination cardiac arrest model, no-flow time before the flush was 2 min, whereas in the normovolaemic cardiac arrest model the no-flow time was prolonged to 10 min. Analyzing the pressure curves during the aortic flush with cold saline in normovolaemic cardiac arrest, we found no pressure difference between arterial pressure in the descending aorta and venous pressure in the right atrium. Adding vasopressin to the aortic saline flush increased the arteriovenous pressure gradient, which resulted in a rapid decrease in brain temperature to 16°C during flush [65].

How could results in cell cultures [60,61•,62,63], small animals [64••], and our study [65] be translated into the routine practice of resuscitating sudden cardiac arrest victims? A futuristic suspended animation scenario might be as follows. When a patient undergoing a cardiac arrest is found, one might opt not to start resuscitation with trickle flow (very poor cerebral and coronorary blood flow) from chest compressions, thus inducing reperfusion injury in a normothermic ischaemic organism. Rather, one could wait for the emergency physician, who will insert a flush catheter in the field and rapidly cool the patient with an aortic flush. Only after hypothermia is achieved are resuscitation efforts begun.

Before suspended animation may be applied in humans, many questions must be answered in large animal outcome studies with long-term intensive care and evaluation of neurological outcome. First, it must be proven that induction of hypothermia after prolonged cardiac arrest no-flow, preceding reperfusion, will improve neurological outcome. Secondly, the limit of duration of normothermic no-flow (i.e. the point of no return) before induction of hypothermia must be determined. Thirdly, once cerebral hypothermia is achieved, it must be evaluated whether chest compressions during hypothermic transport to the hospital yields any benefit. Fourthly, the exact level of hypothermia that allows both mitigation of reperfusion injury and protection during hypothermic no-flow must be determined. Finally, it must be proven that a sudden volume load of 100 ml/kg or more by aortic flush can be tolerated by the organism, and has no adverse effects once restoration of spontaneous circulation is achieved.

Conclusion

In sudden cardiac death, cooling can be started before ischaemia occurs (protection), during ischaemia (preservation) and after ischaemia (resuscitation). Induced mild hypothermia after resuscitation from out-of-hospital cardiac arrest improves neurological outcome. According to a recommendation of the International Liaison Committee on Resuscitation [66••], unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32–34°C for 12–24 h when the initial rhythm is ventricular fibrillation. It was further stated that such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest. The optimal duration of hypothermia and temperature range remain the subject to investigation. There is much evidence that cooling should be started as soon as possible to yield maximum benefit [67], but the importance of cooling rate and rewarming rate is unclear. Whether therapeutic hypothermia would be also beneficial in patients at lesser risk for brain damage or in patients with other causes of cardiac arrest requires further investigation.

Suspended animation (rapid induction of deep cerebral hypothermia during cardiac arrest to mitigate reperfusion injury) proved feasible in studies of outcomes from exsanguination cardiac arrest in large animals. Whether the concept of suspended animation is applicable to normovolaemic cardiac arrest is under investigation. The industry is asked to provide new cooling devices or techniques that can be used for rapid induction of deep cerebral hypothermia early during cardiac arrest, and for maintenance of mild hypothermia once restoration of spontaneous circulation is achieved.

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Keywords: body temperature; brain ischaemia; heart arrest; induced hypothermia; reperfusion injury; resuscitation; ventricular fibrillation; ventricular tachycardia

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