

Therapeutic hypothermia after cardiac arrest

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Purpose of review

Patients who are successfully resuscitated following cardiac arrest often have a significant medical condition termed postresuscitation disease. This includes myocardial stunning, metabolic abnormalities and neurologic injury from global ischemia. There are no clinical signs or diagnostic tests for 24–72 h to distinguish patients who will and will not recover neurologic function.

Recent findings

Therapeutic hypothermia had been advocated for decades as a treatment to improve neurologic outcome after cardiac arrest. The early studies focused on moderate hypothermia, which was associated with complications and was not clearly beneficial. Over the past decade, studies have focused on mild hypothermia with target temperatures of 32–34°C. Two recent multicentered, randomized, controlled trials have demonstrated improved neurologic outcome with mild therapeutic hypothermia applied to comatose survivors after cardiac arrest compared with a normothermic control group.

Summary

As a result of these studies the International Liaison Committee on Resuscitation recommends that 'Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation'. Mild therapeutic hypothermia should also be considered for patients with in-hospital arrest and asystole and pulseless electrical activity who are comatose after return of spontaneous circulation.

Keywords

cardiac arrest, heart arrest, hypothermia, postresuscitation, ventricular fibrillation,

Introduction

The survival of patients who suffer cardiac arrest depends upon a chain of survival that is only as successful as the weakest link in the chain. This chain includes citizen awareness, early access to emergency medical services, early cardiopulmonary resuscitation (CPR), early defibrillation, optimal emergency care and optimal postresuscitation care. Too often, the emergency care is effective in restoring a pulse for the patient suffering cardiac arrest; however, the patient later dies in the hospital. More than half the time that there is restoration of spontaneous circulation (ROSC), the patient does not survive to hospital discharge.

Clinicians are always concerned that patients who do not wake up immediately following a cardiac arrest have suffered severe neurologic impairment from global ischemia during the arrest. Data from the second Brain Resuscitation Clinical Trial gives us some insight into the extent of the problem. Patients who were comatose after ROSC were entered into the study comparing lidoflazine with placebo. No benefit was found for the use of lidoflazine. More than 80% of both the control and experimental groups died within 6 months, most within a few days of the arrest. Of those who survived, only 23% recovered with good neurologic function [1].

Prognosis following resuscitation

It would be very useful to have clinical signs or diagnostic tests that gave us prognostic indicators of neurologic dysfunction after a cardiac arrest. Cerebral dysfunction can occur because of damage from the period of no flow during the arrest, poor cerebral blood flow during cardiopulmonary resuscitation (CPR) and decreased blood flow even after ROSC. The best prognostic sign is a patient who has regained consciousness following ROSC. This return to consciousness, however, may be a gradual process and take days to evolve. Unfortunately there are, at present, no clinically relevant predictive tools that can be used immediately after ROSC to distinguish patients who will wake up from those who will not. In a meta-analysis of 11 studies involving almost 2000 patients in cardiac arrest, there were no immediate clinical signs to predict neurologic outcome. The best clinical signs were the following: absent corneal reflexes at 24 h; absent pupillary response at 24 h; no motor response at 24 h; and no motor response at 72 h. The estimate of poor outcome for comatose patients following arrest was 77% which increased to 97% with negative clinical indicators at 24–72 h [2]. An electroencephalogram after

Curr Opin Crit Care 12:213–217. © 2006 Lippincott Williams & Wilkins.

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Current Opinion in Critical Care 2006, 12:213–217

Abbreviations

CPR cardiopulmonary resuscitation
PEA pulseless electrical activity
ROSC restoration of spontaneous circulation

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1070-5295

24–48 h of care may also be a useful prognostic guide [3**].

Postresuscitation disease

Negovsky [4] described postresuscitation disease as a specific multiorgan pathophysiologic state of patients who resuscitate following cardiac arrest. Patients who have ROSC following a cardiac arrest have a clinical syndrome affecting cardiovascular, neurologic, pulmonary, renal and metabolic systems.

Myocardial dysfunction after resuscitation from cardiac arrest has been described in both animal models as well as clinical studies [5,6]. In a study of 165 patients who had ROSC after out-of-hospital cardiac arrest, 55% had hemodynamic instability requiring vasoactive drugs during the first 72 h following resuscitation. The myocardial stunning or dysfunction was related to the overall time required for resuscitation. Left ventricular ejection fraction was depressed in all patients. Hemodynamic instability was not predictive of neurologic outcome and myocardial dysfunction was reversed in 72 h [6].

The quality of in-hospital care following resuscitation from cardiac arrest is vital in optimizing the chances for survival and good neurologic outcome. Temperature control is important; fever, which may be a manifestation of brain injury, worsens neurologic outcome. Thus, fever should be aggressively treated. Blood glucose control in critically ill patients has been shown to impact outcome. Thus, close monitoring of blood glucose and treating hyperglycemia is recommended as part of the critical care treatment of patients following cardiac arrest. Most of the patients will be intubated and mechanically ventilated following resuscitation. It is uncertain how long mechanical ventilation is necessary and this must be individualized based on maintaining acceptable oxygenation status. Cardiovascular status will be affected by myocardial dysfunction in most postarrest patients; the patient may need pressor support for maintaining adequate systemic perfusion until the myocardial dysfunction reverses in 24–72 h [3**]. Skrifvars *et al.* [7] demonstrated that multiple factors play a role in 6-month outcome following resuscitation from a cardiac arrest. Significant factors in the database included glucose control, electrolytes especially potassium, and the use of β -blocking agents.

Hypothermia: historical perspective

Case reports dating back to the 1950s document the use of therapeutic hypothermia following cardiac arrest. Feldman *et al.* [8] reported a case of a 2-year old girl who was cooled to 33°C for 48 h and had complete neurologic recovery. Benson *et al.* [9] reported a series of cases in which only one of seven patients survived

when no cooling was used compared with six of 12 survivors when hypothermia was induced. The target temperature was 31–32°C. In addition, there have been many case reports of patients surviving prolonged periods of cardiac arrest and resuscitation when they were found in a hypothermic state [10].

The mechanism by which hypothermia exerts its effects is unknown. During cardiac arrest, the brain suffers from global ischemia when blood flow is stopped. Reperfusion injury can occur when blood flow resumes, first with minimal perfusion provided during CPR and then with ROSC. Reperfusion injury could occur with the generation of oxygen free radicals, inflammatory mechanisms and excitatory amino acids. Extracerebral effects of the cardiac arrest can worsen central nervous system damage with poor perfusion from a stunned myocardium and blood disorders that can also worsen cerebral injury [11•]. Postulated mechanisms for the beneficial effects of hypothermia following global ischemia include a reduction of cerebral oxygen consumption, suppression of free radical reactions, protection of lipoprotein membranes, reduction of demand in low-flow regions, reduction of intracellular acidosis, and inhibition of excitatory neurotransmitters [12,13].

Moderate therapeutic hypothermia

Therapeutic hypothermia can be divided into three categories depending on the depth of the hypothermia. Mild hypothermia is 32–34°C, moderate hypothermia 28–32°C, and severe hypothermia less than 28°C. The initial studies on hypothermia were done in the late 1950s with a moderate target temperature. Choosing the target temperature for therapeutic hypothermia is a balance between the risk of complications from the treatment and potential benefits. The studies and conclusions for the use of moderate hypothermia were discrepant; consequently, it was never widely adopted because of concerns about its potential detrimental effects. For example, Steen *et al.* [14] reported that animals cooled to 29°C had worse survival compared with normothermic animals with regional cerebral ischemia.

About 15 years ago, researchers again focused on therapeutic hypothermia but the target temperature was in the mild hypothermia range. Sterz *et al.* [15] studied the effects of mild hypothermia with a target temperature of 34°C after prolonged cardiac arrest in animals. Neurologic outcome was best in the groups that received mild hypothermia. Brain histopathologic damage scores were lower in the hypothermic animals. The key to the successful implementation of therapeutic hypothermia in clinical practice was the realization that mild hypothermia (32–34°C) was efficacious with few complications.

Mild therapeutic hypothermia

Major clinical trials have been done using mild therapeutic hypothermia following cardiac arrest. The Hypothermia after Cardiac Arrest Study Group performed the largest randomized clinical trial of hypothermia [12]. In this multicentered trial with blinded assessment of outcome, adult patients who remained comatose after suffering cardiac arrest from ventricular fibrillation were randomized to therapeutic mild hypothermia and normothermic groups after ROSC. The arrest was of presumed cardiac etiology, estimated down time no longer than 15 min and time to ROSC no more than 60 min from the time of collapse. Patients in the hypothermic group had an external cooling device applied and set to a target temperature of 32–34°C. The temperature was maintained for 24 h followed by passive rewarming over 8 h. All patients were intubated, sedated and paralyzed. Standard critical care was delivered to both groups and the temperature was continuously monitored by bladder catheter. Only 8% of all patients in cardiac arrest were eligible for the study with 275 patients entered [12].

For patients in the hypothermic group, it took 105 min to initiate cooling measures. The median time to achieve the target temperature of 32–34°C was 8 h. Outcome was assessed at 6 months and 55% (75/136) of patients had a favorable neurologic outcome in the hypothermic group compared with 39% (54/137) in the normothermic group ($P = 0.009$). After adjustment for all the baseline variables, the risk ratio was 1.47 (95% CI 1.09–1.82). The overall 6-month mortality was also significantly better in the hypothermic compared with the normothermic group (41% versus 55%; $P = 0.02$). Although sepsis was more commonly seen in the hypothermic group, there was no overall difference in complications between the two groups [12].

The other major randomized controlled trial was performed by Barnard *et al.* [16] for adult patients with out-of-hospital cardiac arrest from ventricular fibrillation. Patients with ROSC were randomized to hypothermic and normothermic groups. All patients were intubated, sedated and paralyzed and received standard critical care treatment. Patients in the hypothermic group were cooled with ice packs as soon as possible with the goal of reaching a core temperature of 33°C. This temperature was maintained for 12 h when the patients were actively rewarmed over 8 h. Outcome was assessed at discharge and 49% (21/43) of patients in the hypothermic group had a good neurologic outcome compared with 26% (9/34) in the normothermic group ($P = 0.046$). The odds ratio for a good outcome was 5.25 (confidence interval (CI) 1.47–18.76; $P = 0.011$). The mortality was 51% in the hypothermic group and 68% in the normothermic group ($P = 0.145$) [16].

In a small feasibility study using a helmet device to induce hypothermia, Hachimi-Idrissi *et al.* [17] studied 30 patients who were unconscious following ROSC after cardiac arrest with asystole or pulseless electrical activity. It took 3 h for the patients to reach the target temperature of 34°C. Three of 16 patients in the hypothermia group and one of 14 patients in the normothermic group left the hospital alive. No adverse effects due to hypothermia treatment were noted.

Holzer *et al.* [11•] did a metaanalysis of mild therapeutic hypothermia for comatose patients with ROSC after cardiac arrest. They found that more patients in the hypothermia group had favorable neurologic outcome than the normothermic group with a risk ratio of 1.68 (96% CI 1.29–2.07). The number needed to treat for one additional patient to have a favorable neurologic outcome was six with a 95% CI of 4–13.

Hypothermia postcardiac arrest guidelines

As a result of these studies, organizations have supported the use of mild therapeutic hypothermia for adult patients who are comatose after resuscitation from cardiac arrest. The International Liaison Committee on Resuscitation (ILCOR) [18] issued an advisory statement in 2003 recommending ‘Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C for 12 to 24 hours when the initial rhythm was ventricular fibrillation (VF). Such cooling may be beneficial for other rhythms or in-hospital cardiac arrest’.

In the 2005 International Emergency Cardiac Care Guidelines [3**], the authors concluded ‘mild hypothermia may be beneficial to neurologic outcome and is likely to be well tolerated without significant risk of complications. In a select subset of patients who were initially comatose but hemodynamically stable after a witnessed VF arrest of presumed cardiac etiology, active induction of hypothermia was beneficial. Thus, unconscious adult patients with ROSC after out-of-hospital cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours when the initial rhythm was VF (Class IIa). Similar therapy may be beneficial for patients with non-VF arrest out of hospital or for in-hospital arrest (Class IIb)’.

Despite the general consensus from the leaders in resuscitation science that hypothermia could benefit a subset of patients who have ROSC but remain comatose, it is used in only a minority of patients. In a survey of 265 physicians, 87% responded that they had not used mild therapeutic hypothermia in their clinical practice [19]. A number of barriers exist to implementation of therapeutic hypothermia. Like many treatments for patients in cardiac arrest, hypothermia requires a well coordinated

team effort that crosses many medical specialties. It is not something that one physician can implement for a single patient. Cooling will usually begin in the emergency department and then continue through the critical care admission. An order set developed by a multidisciplinary team including cardiology, emergency medicine, critical care intensivists, cardiothoracic surgeons, neurologists as well as nursing staff could be invaluable to standardize care and assure appropriate monitoring. If the patient cannot be closely monitored for core temperatures below 32°C when significant complications can occur, it may be best not to implement cooling measures. A hypothermia protocol and order set could guide physicians, nurses and health care professionals how best to institute cooling and rewarming procedures, as well as monitoring for complications.

Future directions

The clinical use of mild hypothermia is the only treatment that has been proven efficacious in randomized clinical trials for improving neurologic outcome. Mild hypothermia should be implemented, whenever feasible, in addition to standard supportive and critical care. Yet, there remain unanswered questions that will need to be addressed in future studies.

What is the best method for inducing hypothermia? Ice packs and cooling blankets have been used in some settings. There are also commercial devices which work through surface cooling. Endovascular devices are available to implement core cooling. One advantage of the cooling devices is that they usually monitor the patient's core temperature and adjust the cooling rate to prevent an overshoot of the target temperature. When the temperature reaches the target, they switch to maintenance cooling and will rewarm the patient at a set rate. There are no studies demonstrating which method of cooling and rewarming is best for patient outcome. Therefore, clinicians must decide which cooling method best fits their needs and provides safe and effective cooling for patients at their institution. The standard cooling protocol and order set will help to ensure uniformity and safety.

Is therapeutic hypothermia efficacious for patients with initial rhythms other than ventricular fibrillation? The clinical studies have focused on out-of-hospital ventricular fibrillation cardiac arrest. These patients have a better prognosis than patients with asystole or pulseless electrical activity (PEA). Cerebral global ischemia from cardiac arrest, however, would not be expected to be different for patients with asystole or PEA than patients with ventricular fibrillation. Therefore, published guidelines encourage health care professionals to consider the use of this method in patients who have ROSC but are comatose with PEA or asystole as the initial rhythm. Similar questions surround the use of mild therapeutic

hypothermia for patients who are comatose following in-hospital cardiac arrest. In-hospital patients may have different etiologies of their arrest compared with out-of-hospital arrest. If they are comatose from global ischemia, however, mild therapeutic cooling may be of benefit.

How long should hypothermia be continued for? In the two clinical studies, therapeutic hypothermia was continued for 24 h in one and 12 h in the second with overall neurologic improvement in both [12,16]. How rapidly should the cooling take place? How rapidly should warming take place?

When should mild hypothermia be started? In the clinical studies, it appears to have some effect even 4–6 h after the arrest. There is some evidence that earlier institution of hypothermia may be more beneficial. Abella *et al.* [20] showed that cooling during treatment of a cardiac arrest in an animal model produced significantly better survival and neurologic outcome compared with animals who received delayed cooling. Kim *et al.* [21] showed that cooling can be rapidly induced with the infusion of 2 l of normal saline in 20–30 min in a peripheral vein. The infusion had little effect on hemodynamics and cardiac function and produced a temperature drop of 1.4°C at 30 min. Should cooling measures be started as part of the out-of-hospital resuscitation treatment? In a pilot study, Bernard *et al.* [22] began cooling measures for 22 comatose patients following resuscitation from out-of-hospital cardiac arrest by a rapid infusion of 30 ml/kg of 4°C of Ringer's lactate solution over 30 min. This infusion resulted in a significant decrease in core body temperature from 35.5 to 33.8°C with no adverse effects. Of note, 57% (eight of 14) of patients with ventricular fibrillation arrest and 25% (two of eight) of patients with other rhythms were discharged alive. There is potential for rapid cold solution infusions to become a standard part of care by medics prior to arrival in the hospital.

These studies bring up key clinical questions. Can we differentiate those patients who will benefit from mild hypothermia and those who will not? Patients who wake up soon after the arrest and patients who have irreversible cerebral dysfunction do not need to be cooled. Future research may provide answers to these clinical problems.

Conclusion

The survival of patients who suffer cardiac arrest and have ROSC requires careful management of the postresuscitation syndrome. Neurologic injury suffered during the arrest can be devastating. Over the past 5 years, there is new evidence from two randomized clinical trials that when mild hypothermia is applied to comatose survivors who have ROSC from ventricular fibrillation arrest, this will significantly improve neurologic outcome. Clinicians should work to institute protocols for mild hypothermia

treatment for such patients as a part of their critical care treatment.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 283).

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