

Role of hypothermia in cerebral protection after cardiac arrest

Charles David Gomersall

Abstract

Two randomized controlled studies have shown a meaningful improvement in outcome in survivors of out of hospital cardiac arrest who were treated with therapeutic hypothermia. At present proof of benefit is restricted to those with persistent coma after out of hospital arrest due to ventricular fibrillation or pulseless ventricular tachycardia. Important exclusion criteria are shock and primary

coagulopathy (but not thrombolysis). In these patients the adverse effects of hypothermia (which include arrhythmias, infection and coagulopathy) are more likely to, at least partially, offset the benefits. At present external cooling is the recommended method of cooling but the use of rapid infusion of cold intravenous fluids may be useful in patients with good respiratory function.

Keywords: Heart Arrest; Death, Sudden, Cardiac; Hypothermia, induced; Ventricular fibrillation

Introduction

A number of therapies have been proposed in an attempt to decrease anoxic cerebral damage after cardiac arrest. Most of these have only been successful if applied prior to cardiac arrest and none have been widely accepted in clinical practice. Therapeutic hypothermia has been tested in animals, with success, and two recent clinical trials indicate that it is beneficial in patients who suffer an out-of-hospital cardiac arrest due to ventricular fibrillation [1,2].

Mode of action

The exact mechanism by which therapeutic hypothermia results in reduced cerebral damage is unclear. In the normal brain the cerebral metabolic rate for oxygen decreases by 6-7% for each 1°C decrease in temperature. Although this might result in a reduction in the imbalance between oxygen supply and demand in areas of ischaemic brain, mild hypothermia did not significantly reduce the cerebral metabolic rate for oxygen after cardiac arrest in dogs [3]. Mild hypothermia may exert its beneficial effect by

suppression of free radical production, release of excitatory amino acids or calcium shifts, all of which are associated with reperfusion and can lead to cell death [4].

Human studies

A large multicentred European study recruited 275 patients with witnessed out of hospital cardiac arrest [2]. Inclusion criteria were ventricular fibrillation or pulseless ventricular tachycardia as the initial cardiac rhythm, presumed cardiac origin of the arrest, a 5-15 minute delay between collapse and attempted resuscitation by emergency medical personnel and restoration of spontaneous circulation in <60 mins. Exclusion criteria included spontaneous hypothermia (<30°C), drug induced coma prior to cardiac arrest, pregnancy, terminal illness, coagulopathy, response to verbal commands, and hypotension or hypoxaemia after return of spontaneous rhythm and prior to randomization. All patients were sedated, paralyzed and mechanically ventilated. Those randomly assigned to the hypothermia group were cooled to a target bladder temperature of 32-34°C for a period of 24 hours from the start of cooling. This was followed by a period of passive rewarming. Cooling was carried out using a cooling mattress, with the addition of ice packs if the target temperature was not achieved within 4 hours. At 6 months significantly more patients in the hypothermia group (55%) than in the normother-

Address requests for reprints to:

Charles David Gomersall, MD.
Dept of Anaesthesia & Intensive Care, The Chinese University of Hong Kong,
Prince of Wales Hospital, Shatin, Hong Kong.
Tel. +852 2632 2734. Fax. +852 2637 2422.
E-mail: gomersall@cuhk.edu.hk

mia group (39%) had a favourable outcome (good recovery or moderate disability on the Pittsburgh cerebral-performance scale). Mortality was also lower in the hypothermia group (41 vs. 55%). There was a trend to more complications, in particular pneumonia, bleeding and sepsis, in the hypothermia group but the proportion of patients with any specific complication did not differ between groups.

A similar Australian study randomized 77 patients into hypothermia and normothermia groups [1]. Inclusion criteria were ventricular fibrillation as the initial cardiac rhythm, return of spontaneous rhythm in the field and persistent coma. Exclusion criteria included age <18 years, female aged <50 years (because of the risk of pregnancy), cardiogenic shock and other possible causes of coma. For patients in the hypothermia group attempts at cooling were initiated in the field and were continued for 12 hours after admission to hospital. The target was a temperature of 33°C within 2 hours of return of spontaneous circulation. For both groups targets were set for arterial partial pressure of oxygen and carbon dioxide, mean arterial pressure, blood glucose and serum potassium. All patients received a bolus dose of lidocaine followed by an infusion for 24 hours. Patients with an ECG suggestive of acute myocardial infarction and no contraindication received thrombolysis, while those with an ECG suggestive of ischaemia without infarction received intravenous heparin. Again, significantly more patients in the hypothermia group than in the normothermia group had a good outcome (moderate disability or better) despite more patients in the normothermia group receiving bystander cardiopulmonary resuscitation. At the time of hospital discharge 49% of patients in the hypothermia group and 26% of the normothermia group were moderately disabled or better. The incidence of complications was not reported. Although the randomization method was sub-optimal (allocation was based on the day of the month), the only important difference in baseline characteristics was that more patients in the normothermia group received bystander cardiopulmonary resuscitation.

Although these studies provide compelling evidence of the benefit of therapeutic hypothermia after cardiac arrest it should be noted that the proportion of patients eligible for inclusion was small. In the European study 3551 patients were screened to recruit 275 patients [2] while in the Australian study only 84 suitable patients were admitted to four centres over a period of 33 months [1]. In addition the apparent lack of a significant difference in complications between the hypothermia and normothermia groups in the European study may simply be a reflection of a study that was not powered to detect a difference in the incidence of complications [2].

Methods of cooling

A number of different methods are available to cool patients. External methods such as application of cooling blankets, application of ice packs, use of wet towels and fanning are simple but are slow in reducing core temperature. In the European study, which used a cooling mattress, the target temperature could not be achieved in approximately 15% of patients and the interquartile range for the time to achieve the target temperature was 4-16 hours [2]. This may, however, be related to the decision not to use ice packs unless the target temperature was not achieved within 4 hours. Animal data show that the sooner cooling is initiated after reperfusion the better the outcome [5]. Therefore the benefit may be even greater than that shown by the studies discussed above, if it is possible to cool patients more rapidly. Rapid intravenous infusion of large volumes of ice-cold (4°C) fluid may be a useful technique. Studies have demonstrated a rapid fall in temperature following infusion of 30-40 ml/kg of crystalloid solution over 30 minutes in volunteers [6] and survivors of out-of-hospital cardiac arrest [7]. In the latter study infusion of cold fluid also resulted in an increased mean arterial pressure, improved renal function and acid-base status. No patients developed pulmonary oedema but there was a dramatic fall in oxygenation associated with infusion of the fluid. Other techniques which may be used include use of extracorporeal and intravascular cooling devices [8]. The invasive nature and cost of these devices, however, are likely to restrict their use to a few specialized centres. Regardless of the method used for cooling it is important to prevent shivering with the use of neuromuscular blockage and sedation [5].

Conclusion

Although the mechanism by which hypothermia decreases cerebral injury after cardiac arrest remains elusive, data from two randomized controlled trials shows that in a highly selected group of patients institution of mild hypothermia (core temperature 32-34°C is associated with lower mortality and a better neurological outcome. At present proof of benefit is restricted to those with persistent coma after out of hospital arrest due to ventricular fibrillation or pulseless ventricular tachycardia. Although there is one small study which was not restricted to patients with these rhythms, 17 out of 22 patients had ventricular fibrillation and the outcome was compared to historical controls [9]. Important exclusion criteria are shock and primary coagulopathy (but not thrombolysis). In these patients the

adverse effects of hypothermia (which include arrhythmias, infection and coagulopathy) are more likely to, at least partially, offset the benefits. At present external cooling is

the recommended method of cooling but the use of cold intravenous fluids may be useful in patients with good respiratory function.

References

1. Bernard SA, Gray TW, Buist MD, et al: Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med* 2003; 346:557-563
2. The Hypothermia after Cardiac Arrest Study Group: Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med* 2003; 346:549-556
3. Oku K, Sterz F, Safar P, et al: Mild hypothermia after cardiac arrest in dogs does not affect postarrest multifocal cerebral hypoperfusion. *Stroke* 1993; 24:1590-1597
4. Colbourne F, Sutherland G, Corbett D: Postischemic hypothermia. A critical appraisal with implications for clinical treatment. *Mol Neurobiol* 1997; 14:171-201
5. Nolan JP, Morley PT, Vanden Hoek TL, et al: Therapeutic hypothermia after cardiac arrest: an advisory Statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation* 2003; 108:118-121
6. Rajek A, Greif R, Sessler DN, et al: Core cooling by central venous infusion of ice-cold (4 degrees C and 20 degrees C) fluid: isolation of core and peripheral thermal compartments. *Anesthesiology* 2000; 93:629-637
7. Bernard S, Buist M, Monteiro O, et al: Induced hypothermia using large volume, ice-cold intravenous fluid in comatose survivors of out-of-hospital cardiac arrest: a preliminary report. *Resuscitation* 2003; 56:9-13
8. Bernard SA, Buist M: Induced hypothermia in critical care medicine: a review. *Crit Care Med* 2003; 31:2041-2051
9. Bernard SA, Jones BM, Horne MK: Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann of Emerg Med* 1997; 30:146-153