MANAGEMENT OF OUT-OF-HOSPITAL CARDIAC ARRESTS WITH INDUCED HYPOTHERMIA

ANAESTHESIA TUTORIAL OF THE WEEK 206

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SELF ASSESSMENT

1) According to ILCOR guidelines, to what temperature should patients be cooled?
    a. 30 - 32 ºC
    b. 30 - 34 ºC
    c. 32 - 34 ºC
    d. 32 - 36 ºC

2) What cardiovascular complications of cooling are most common?
    a. Bradycardia and hypotension
    b. Bradycardia and hypertension
    c. Tachycardia and hypotension
    d. Tachycardia and hypertension

3) By what percentage can shivering increase basal consumption of oxygen?
    a. 0 - 10%
    b. 0 - 40%
    c. 40 - 50%
    d. 40 - 100%

4) How can we adjust pH readings for temperature?
    a. Add 0.12 for every 1 ºC below 37 ºC
    b. Add 0.012 for every 1 ºC below 37 ºC
    c. Take away 0.12 for every 1 ºC below 37 ºC
    d. Take away 0.012 for every 1 ºC below 37 ºC

BACKGROUND

Out-of-hospital cardiac arrest (OOHCA) kills 90% of its victims before they reach hospital and is likely to become a more frequent event with an increasingly ageing population. In 2002 randomised control trials from Europe[1] and Australia,[2]showed that, in a defined patient population, therapeutic hypothermia improves neurological outcome in those who reach hospital. In 2002the Advanced Life Support (ALS) Task Force of the International Liaison Committee on Resuscitation (ILCOR) made the following recommendations:[3]

- Unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32-34°C for 12 to 24 hours when the initial arrest rhythm was ventricular fibrillation (VF).
- Such cooling may also be beneficial for other rhythms or in-hospital cardiac arrest.
- The 2010 iteration of the guidelines suggested that therapeutic hypothermia may also be useful in cases where the initial rhythm was non-shockable or after in-hospital arrest.

DEFINITIONS

Induced hypothermia	An intentional reduction of a patient's core temperature to less than 36°C.
Therapeutic hypothermia	Induced hypothermia, normally between 32°C and 35.9°C, with the control or suppression of potentially harmful adverse effects.

THE EVIDENCE

The criteria for entry into both the European[1] and theAustralian[2] trials were similar; a return of spontaneous circulation (ROSC) in intubated, ventilated patients, with persistent coma after out-of-hospital cardiac arrest due to VF. Both studies excluded arrests that were likely due to non-cardiac aetiology and patients with severe cardiogenic shock.

The European Study[1]

This multi-centre randomised clinical trial, took place in 9 centres in 5 European countries. 275 patients were recruited into the study and were randomly assigned to a hypothermia group or a control group. The median Glasgow Coma Scale score (GCS) on hospital admission in both groups was 3, with an interquartile range of 3-4 in the hypothermia group and 3-5 in the normothermia group. Ten patients were recruited after in-hospital cardiac arrest.

Additional entry criteria were:
- Age 18–75 years,
- Witnessed cardiac arrest,
- Estimated 5-15 minutes from patient collapse to first resuscitation by emergency personnel
- Interval of less than one hour from collapse to ROSC.

Treatment assignments were randomly generated by computer in blocks of 10, with stratification according to the centre.

*Interquartile range:*A 'mini' range, focusing on the spread of the middle 50% of the data. The data are ranked in order and the points at 25%, 50% and 75% of the distribution are identified. These are known as the quartiles and the median is the second quartile. The interquartile range is between the 1st and 3rd quartiles and is not influenced by outlying values

All patients received standardised care in an intensive care unit, according to a strict protocol, including sedation and neuromuscular blockade. The temperature on admission was measured with an infrared tympanic thermometer and afterwards with a bladder thermistor temperature probe. Those assigned to the hypothermia group were cooled to a target temperature of 32-34°C by a specifically designed mattress that delivered cold air and with ice packs where necessary. The aim was to reach the target temperature within 4 hours of ROSC and to maintain it for 24 hours. This was then followed with *passive* re-warming.

The physicians responsible for assessing the neurological outcome within the first 6 months after the cardiac arrest were blinded to the treatment assignments. 75 of the 136 patients (55%) in the hypothermia group, for whom data was available had a favourable neurological outcome and were able to live independently at 6 months, compared to 54 of 137 (39%) in the normothermia group. At 6 months, there were 56 deaths in the hypothermia group (41%), compared with 76 in the normothermia group (55%). The absolute risk reduction (ARR) if this therapy was 14% in this study (the risk of death in the normothermia group, minus that of the group treated with hypothermia. The relative risk reduction (RRR), is the absolute risk in the hypothermia group (treated) divided by the absolute risk in the normothermia (control or untreated) group and is calculated to be 74.5% (41% / 55%). This demonstrates that there is an association between therapeutic hypothermia and survival and that it is protective.

The Australian Study[2]

This study was performed at four hospitals in Melbourne. Men under 18 years and women under 50 years (because of the possibility of pregnancy), patients with cardiogenic shock, or a possible cause of coma other than cardiac arrest were excluded. Patients were allocated to the hypothermia and normothermia groups according to the day of the month.

Hypothermia was initiated in the field by paramedics, through the application of ice packs, for those patients allocated to hypothermic management. This was continued following admission to hospital, aiming to achieve until a temperature of 33°C within 2 hours of ROSC. Hypothermia was maintained for 18 hours followed by *actively* rewarming over the next 6 hours. The temperature was monitored via tympanic or bladder thermometers. Again, patients in both groups received a standard care bundle, including sedation and neuromuscular blockade.

The primary outcome measure was survival to hospital discharge, with sufficient neurological function to be sent home or to a rehabilitation facility. 77 patients were enrolled in the study. Despite more patients in the normothermia group receiving bystander CPR, 49% of the patients in the hypothermia group had a good outcome (moderately disabled or better), compared with 26% of the normothermia group. The ARR was 23% (a poor outcome of 74% in the normothermia group minus a poor outcome of 51% in the hypothermia group). The RRR was 68.9% in this study (51% / 74%), demonstrating a protective association between hypothermia and a poor outcome.

TIMING OF COOLING

The optimal timing of hypothermia remains has not been defined. It seems logical that the earlier the cooling is instigated, the greater the benefit. The European study cooled patients within 4 hours of cardiac arrest and maintained therapeutic hypothermia for 24 hours,[1] whereas the Australian study cooled patients within 2 hours and maintained hypothermia for 12 hours.[2] Both studies demonstrated a significantly improved neurological outcome compared to a normothermic group and current recommendations suggest that patients should be cooled for 12-24 hours.[3]

Induction phase

Aim to reduce the core body temperature to the 32-34°C as quickly as possible. A small overshoot (≤1°C) should be regarded as acceptable. Avoid temperatures below 30°C.

Maintenance phase

When the target temperature as been achieved, aim to control core temperatures tightly within a narrow range, with no, or minor, fluctuations (maximum 0.2-0.5°C).

Re-warming phase
Re-warm to normothermia slowly. The target rate should be 0.2-0.3°C per hour, but the maximum acceptable rate is 0.5°C per hour.This can usually be achieved with passive re-warming. Rapid re-warming after therapeutic hypothermia can "re-trigger" harmful processes,such as rebound hyperthermia. This can adversely affect outcome by causing the physiologically opposite of the protective mechanisms detailed below.

COOLING METHODS

There are a varietyof ways to cool a patient, but the most effective methods are less simple to implement. External cooling methods are easy to use, but reduce core temperature more slowly than more invasive methods, such as cooling by peritoneal or pleural lavage, or the use of an intravascular heat exchange device.

Simple external cooling methods include the application of ice packs to the groin, axillae and neck, the use of cooling blankets, the use of wet towels and fanning and also the use of a cooling helmet.A recent innovation is the use of specialised cooling jackets and pads (e.g. ArcticGel™pads, Medivance) which make cooling to target temperature achievable within 40 minutes (http://www.medivance.com/html/products_arcticgel.htm). An example of a more invasive technique is the Alsius Coolguard 3000®, an intravascular catheter balloon that provides precise, rapid cooling and rewarming (http://www.alsius.com/products/coolgard.html). It is possible to cool patients using an intravenous infusion of 30ml.kg^{-1} crystalloid at 4°C over 30 minutes. Anti-pyretic agents, such as paracetamol can be used as an adjunct, although their central effects are recognised to be low. The Australian study used the immediate application of ice-packs in the field, which was continued upon admission to hospital and the European group used a cooling mattress, with the addition of ice packs if the target temperature was not achieved within 4 hours of admission to hospital.Core temperature, measured using an oesophageal or bladder temperature probe, should guide therapy.

THERAPEUTIC MECHANISMS OF ACTION OF COOLING

1. **Reduced intracranial pressure**
2. **Decreased cerebral metabolic rate ($CMR-O_2$)**– there is a reduction of 6-7% for every 1°C decrease in temperature.
3. **Suppresses many chemical actions associated with reperfusion injury, e.g.**
   - Excitatory amino acid production,
   - Free radical release,
   - Calcium shifts, which can lead to mitochondrial damage and apoptosis.

POTENTIAL SIDE EFFECTS OF COOLING

Circulatory	Through a hypothermia-induced cold diuresis, causing hypotension.
Cardiovascular	Predominantly bradycardias and hypertension**.** Other arrythmias, although these appear only clinically significant if the core temperature is less than 30°C**.** Mild diastolic dysfunction is seen in some patientsand there are variable effects of myocardial contractility.

Elecrolyte disorders	Urinary loss and intracellular shift of potassium, magnesium and phosphate during cooling phase**.** Extracellular shift and hyperkalaemia during re-warming phase.
Hyperglycaemia	Due to insulin resistance and decreased secretion.
Shivering	Increases oxygen consumption by 40-100% and reduces rate of cooling, but is less marked below temperatures of 34°C.
Skin injuries / bedsores	Direct exposure of skin to ice packs can cause burns, which can be exacerbated by vasoconstriction.
Infection	Due to immunosuppressive effects of hypothermia, such as neutropenia.
Clotting disorders	This is thought to be primarily due to inhibition of the clotting cascade and is often accompanied by a thrombocytopaenia and decreased platelet function.

PRECAUTIONS TO TAKE WHEN COOLING PATIENTS

Cool and warm in an appropriate setting

Although it may be necessary to initiate cooling measures prior to admission to the ICU, many of the associated side-effects are best prevented, monitored and managed in an ICU setting.

Use appropriate sedation and analgesia

This promotes cooling through vasodilatation and inhibition of shivering**.**Animal studies suggest loss of protective effects with insufficient sedation. This is due to the increased cerebral metabolic rate and oxygen consumption seen with both the stress response and with shivering.

Adjust drug dosage

Drug clearance (especially by the liver) is reduced, prolonging the action of sedatives, opiates and paralysing agents.Use boluses during the induction phase and avoid high maintenance doses.

Remember that blood gas analysis and clotting studies are affected by cooling

Warm samples to 37°C or adjust for patients' core temperature:

- pH - add 0.012 points for every 1°C below 37°C,
- $PaO_{2,}$ - subtract 5mmHg (0.93kPa) for every 1°C below 37°C
- $PaCO_{2,}$ - subtract2mmHg (0.27kPa) for every 1°C below 37°C.

Adjust ventilator settings

Cooling causes reduced O_2 consumption and CO_2 production.

Avoid unnecessary treatment of normal physiology

Mild lactic acidosis, bradycardias, elevated liver enzymes and elevated amylase levels are a normal effect of hypothermia.

Avoid long-term paralysis

Paralysis can mask inadequate sedation and seizuresand increase the risk of critical illness polyneuropathy or myopathy.Use alternatives to control shivering, such as magnesium sulphate, fast-acting opiates, propofol or benzodiazepines.

Adjust feeding rate

Cooling reduces metabolism by 7-10% for every 1°C below 37°C.

Monitor for infections closely and treat aggressively
As mentioned previously, hypothermia has an immunosuppressive effect.

Consider platelet administration prior to invasive procedures
This may attenuate a hypothermia associated clotting disorder.

OTHER THERAPIES TO CONSIDER IN THE OOHCA PATIENT

Management of the cause of arrest
The majority of OOHCAs are caused by myocardial infarction. It is therefore important to manage the causative disease alongside instigating therapeutic hypothermia. Things to consider following MI include:

- Discussion with a cardiologist and consideration of thrombolysis or rescue PCI.
- Treatment with a loading dose of aspirin and a GPIIb/IIIa antagonist, alongside a low molecular weight heparin e.g. (aspirin 300mg, clopidogrel 300mg, enoxaparin 1mg.kg^{-1}).
- The use of nitrates in ongoing or subsequent episodes of ischaemia seen on ECG monitoring.
- Future treatment with a beta-blocker and ACE inhibitor.
- A 12-hour troponin level (although this is likely to be raised anyway following CPR).
- Echocardiography to assess myocardial function and likely prognosis.

Cerebral protection
It is important to implement cerebral protective measures following a potentially anoxic brain injury. These are the same as those required by a patient who has suffered a head injury and include:

- Keep the head up at 30-45º and the neck straight to avoid venous congestion,
- Tape, rather than tie ETTs, to avoid venous constriction,
- Maintain normal blood pressure and a MAP $\geq$ 90mmHg,
- Ventilate to normocapnia and avoid hypocapnia ($PaCO_2 \geq 3.5$ kPa),
- Maintain tight glycaemic control,
- Maintain adequate sedation and analgesia,
- Control shivering with neuromuscular blockers where required.

CONCLUSIONS

There is increasing evidence to suggest that temperature can significantly improve neurological outcome in patients who suffer an out-of-hospital cardiac arrest due to ventricular fibrillation. Use of therapeutic cooling is now recommended by leading international resuscitation committees, for appropriate patients. There are many potential side effects and pitfalls associated with therapeutic hypothermia, but provided that they are acknowledged and acted upon appropriately, it is relatively well tolerated. Although therapeutic cooling is only recommended for use in a small subset of patients, temperature should be monitored and controlled in all critically ill patients, especially those with neurological injuries. The role of this therapy is likely to expand even further in the future.

REFERENCES

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ANSWERS TO SELF-ASSESSMENT

1) c
2) b
3) d
4) b