Devices for rapid induction of hypothermia

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Summary
In industrial countries it is estimated that the incidence of out-of-hospital sudden cardiac arrest lies between 36 and 128 per 100,000 inhabitants per year. Almost 80% of patients who initially survive a cardiac arrest present with coma lasting more than 1 h. Current therapy during cardiac arrest concentrates on the external support of circulation and respiration with additional drug and electrical therapy. Therapeutic hypothermia provides a new and very effective therapy for neuroprotection in patients after cardiac arrest. It is critical that mild hypothermia has to be applied very early after the ischaemic insult to be effective, otherwise the beneficial effects would be diminished or even abrogated. There are numerous methods available for cooling patients after ischaemic states. Surface cooling devices are non-invasive and range from simple ice packs to sophisticated machines with automatic feedback control. Other non-invasive methods include drugs and cold liquid ventilation. The newer devices have cooling rates comparable to invasive catheter techniques. Invasive cooling methods include the administration of ice-cold fluids intravenously, the use of intravascular cooling catheters, body cavity lavage, extra-corporeal circuits and selective brain cooling. Most of these methods are quite invasive and are still in an experimental stage. The optimal timing and technique for the induction of hypothermia after cardiac arrest have not yet been defined, and it is currently a major topic of ongoing research. The induction of hypothermia after cardiac arrest needs to be an integral component of the initial evaluation and stabilization of the patient.

Keywords: CARDIAC ARREST; HYPOTHERMIA; EQUIPMENT AND SUPPLIES; OUTCOME.

Introduction
In industrial countries, it is estimated that the incidence of out-of-hospital sudden cardiac arrest lies between 36 and 128 per 100,000 inhabitants per year. In these cases, resuscitation efforts are made in 34–86% and return of spontaneous circulation as well as admission to a hospital can be achieved in 17–49%. Unfortunately, full cerebral recovery is still a rare event. Almost 80% of patients who initially survive a cardiac arrest present with coma lasting more than 1 h. Admitted patients are discharged with a poor neurological outcome in 2–13%, good neurological recovery can be achieved in 11–48% of the cases. The rest of the patients die during their hospital stay [1].

Current therapy during cardiac arrest concentrates on the external support of circulation and respiration with additional drug and electrical therapy [2]. However, after restoration of circulation, which is important to restore cellular function, reoxygenation may also provoke deleterious chemical cascades during this phase. This secondary damage of the brain after primary successful resuscitation was termed 'Postresuscitation Disease' by Negovsky [3].

Therapeutic hypothermia provides a new and very effective therapy for neuroprotection in patients after cardiac arrest. It is critical that mild hypothermia be applied very early after the ischaemic insult in order to be effective, otherwise
the beneficial effects would be diminished or even abrogated [4,5].

It is well known that postischemic hypothermia reduces the number of cell death in certain brain regions [6]. The multifactorial processes of hypothermia leading to cell protection include slowing of destructive enzymatic processes and fluidity protection of lipid membranes, which appear to be stiffened by hypothermia, beneficial effects on low-flow regions during reperfusion by reducing oxygen needs without impairing microvasculatory blood flow [7—9], inhibition of the accumulation of lipid peroxidation [10], and attenuation of brain oedema [11] and of intracellular acidosis [12].

Cooling methods

The optimal timing and technique for the induction of hypothermia after cardiac arrest have not yet been defined, and are currently a major topic of ongoing research. The induction of hypothermia after cardiac arrest needs to be an integral component of the initial evaluation and stabilization of the patient.

Core temperature must be continuously and accurately monitored when induction of hypothermia is planned. There is a minimal temperature gradient between the brain, the bladder and the rectal temperature and it is usually most convenient to monitor bladder temperature after arrival at hospital. Tympanic temperature monitoring may be used pre-hospital, but is less accurate, particularly when the head is surrounded by ice packs during surface cooling. For rapid induction of therapeutic hypothermia more central temperature monitoring sites, like oesophageal or central venous temperature should be used, as temperature in the bladder and rectum can show a considerable delay in response during rapid cooling. If these slower sites are used, a dangerous cooling overshoot in the central compartment could be overlooked.

The rapid lowering of core temperature in an adult patient after cardiac arrest requires that shivering be suppressed with the administration of sedation and/or muscle relaxants, while heat is concurrently removed from the body.

Surface cooling

A very simple technique for cooling after cardiac arrest is the extensive application of ice packs to the head, neck and torso of the patient. This technique was effective but provided for relatively slow core cooling (approximately 0.9°C h⁻¹) [13]. It was also considered very time consuming and inconvenient.

The European (Hypothermia After Cardiac Arrest (HACA)) study of hypothermia after cardiac arrest used surface cooling with cold air [14]. However, this was also found to be a very slow technique, with a decrease in core temperature of only 0.3°C h⁻¹.

A combination of alcohol and a cooling cover filled with water was used by Yanagawa and coworkers [15] in order to cool survivors after cardiac arrest to a core temperature of 33°C to 34°C over 48 h. The target temperature was achieved after 336 ± 180 min. This corresponded to a cooling rate of 0.25°C h⁻¹. Nevertheless, cooling blankets are a feasible and safe approach to the induction of mild hypothermia [16].

More recently, developments in cooling technology have made surface cooling much more efficient. One system uses large adhesive pads applied around the trunk and limbs (Arctic Sun; Medivance, Louisville, CO, USA). With adhesive pads, cooled by water at a controlled temperature, the patients are automatically cooled to the target temperature. An automatic feedback control system allows for very accurate control of patient core temperature. Although published data on patients after cardiac arrest is limited, this system has been demonstrated to provide improved temperature control compared with traditional surface cooling blankets in febrile patients in a neurological ICU [17]. This system has the particular advantage of being non-invasive and can be readily applied by nursing staff.

A different cooling device, which is a further development of the one used in the HACA trial, is the DeltaTherm® system by KCI Medicals (Houten, The Netherlands). This machine also uses cold air for cooling the patient. However, the air volume was increased and the efficiency was further increased by a recirculation of the air. In a recently accomplished clinical pilot study in 11 patients, the median cooling rate was 1.25°C h⁻¹. This device also offers the possibility of automatically adjusting body temperature by automatic feedback of the bladder temperature. Therefore it is also possible to rewarm the patient with specifically defined rewarming rates.

Surface heat loss could also be achieved with evaporative techniques using fans and alcohol. However these are time consuming and impractical in most emergency and critical care units.

The surface cooling method with the fastest rate is complete patient immersion in an ice-water bath [18]. This approach results in a rapid decrease in a core temperature of 9.7°C h⁻¹, but is regarded as impractical for critically ill patients. A device overcoming the practical issues in critical care patients (Thermosuit System, Life recovery Systems, Kinnelon, NJ, USA) is currently under clinical investigation. Preclinical data in small (30 kg) pigs.
yielded promising results with cooling rates up to 24°C h⁻¹ [19].

It has been proposed that cooling helmets may be more efficient than cooling blankets, since the skin of the torso and limbs may be poorly perfused in the early post-cardiac arrest period, while brain blood flow is preserved. In one study investigating this approach, 14 patients with neurological injury were assigned to either a cooling helmet or no cooling [20]. The temperature just below the surface of the brain was measured directly and compared with the patients' core temperatures. Within 1 h of helmet application, a 1.8°C brain surface temperature reduction (range 0.9-2.4°C) was observed. However, it required a mean of 3.4 h to achieve a brain temperature lower than 34°C (0.9°C) and over 6 h before systemic hypothermia (<36°C) occurred.

In a second study of a cooling helmet device, the tympanic temperatures of 16 patients who were cooled after cardiac arrest were compared to 14 normothermic controls [21]. The median tympanic temperature on admission to hospital in both groups was 35.5°C. In the cooling helmet group, the core target temperature of 34°C was achieved after a median time of 180 min after resuscitation (0.5°C h⁻¹). These studies indicate that cooling helmets are relatively slow to provide systemic hypothermia in adults and probably have no advantage over surface cooling with ice packs and/or cooling blankets.

Because of the relative size of the head compared with the torso, helmet cooling might be more efficient in neonatal patients. After 45 min of global hypoxic-ischaemic insult [22] in piglets, the animals were cooled for 7 h using a cap wrapped around the head with circulating cold water (median 8.9°C). To warm the body during cerebral cooling, radiant overhead heating was used. During the 7-h cooling period the mean deep-brain temperature was 31.1°C, while rectal temperature remained stable at 38.8°C.

This technique was then used in a clinical trial of hypothermia in neonates with hypoxic-ischaemic encephalopathy [23]. The cooling cap (Cool Care System; Olympic Medical, Seattle, WA, USA) was placed around the head of the neonate for 72 h. The system consists of a thermostatically controlled cooling unit and a pump that circulates water (median 8°C) through the cap. The infants were also nursed under a radiant overhead heater, which was servo-controlled to the infant's abdominal skin temperature and adjusted to maintain the rectal temperature at 34-35°C. This study demonstrated improved outcomes in neonates with moderate, but not severe, hypoxic-ischaemic encephalopathy.

A very promising cooling device for pre-hospital cooling was also examined in an animal model [24]. In this study, six pigs were cooled with precooled (-10°C) mattresses, consisting of a latex wrapping incorporating a mixture of water/graphite, which was glued to the skin of the animals (EMCOOLSPad®, Emcools, Vienna, Austria). The target temperature of 33.5°C was achieved within 30 ± 5 min, which corresponded to a cooling rate of 9.3 ± 1.4°C h⁻¹. In a clinical pilot study using the same device, a cooling rate of 3.3°C (2.6-3.5°C) h⁻¹ could be obtained [25].

Drug cooling

Neurotensin is an endogenous tridecapeptide with specific receptors throughout the central nervous system (CNS) and induces hypothermia by activation of these receptors in the brain.

Recently, a neurotensin analogue has been developed, which can be administered intravenously (i.v.). The application of neurotensin may provide a practical method for rapidly inducing hypothermia within minutes without the need for sedation or general anaesthesia. In addition, when neurotensin degrades over 24 h, the core temperature returns to normal without the need for external application of heat. The use of neurotensin has been studied in a rat model of asphyxial cardiac arrest [26]. The animals with neurotensin-induced hypothermia had improved neurological outcome comparable to prolonged external cooling. However, the feasibility and safety of this drug in human beings is unknown at this time.

The instillation into the lungs of a large volume of ice-cold perfluorocarbon would be expected to provide rapid core cooling, while still allowing adequate oxygenation and ventilation. However, this has only been studied in animal models at this stage [27].

Large volume ice-cold i.v. fluid

A simple, inexpensive technique for the induction of mild hypothermia is the rapid infusion of a large volume (40 mL kg⁻¹) of ice-cold (4°C) i.v. fluid. The fluids used in clinical trials to date have included lactated Ringer's solution and normal saline.

In a study of 22 patients in an Emergency Department, 30 mL kg⁻¹ of ice-cold lactated Ringer's solution was rapidly infused i.v., together with a large dose of a long-acting neuromuscular blocker to prevent shivering [13]. This infusion decreased core temperature by 1.6°C and increased blood pressure, without any patient developing pulmonary oedema.

In another study, cardiac arrest patients received 2000 mL of large volume ice-cold i.v. fluid to
initiate hypothermia prior to endovascular cooling [28]. The core temperature decreased from 35.6 ± 1.3°C on admission to 33.8 ± 1.1°C. The target temperature (<34°C) was reached in a mean of 185 min after return of spontaneous circulation and 135 min after start of infusion. There were two patients with radiographic signs of mild pulmonary oedema, but no other complications that could be attributable to the large volume ice-cold i.v. fluid infusion.

The cardiac effects of large volume ice-cold i.v. fluid were studied in cardiac arrest patients following hospital admission [29]. Just before and 1 h after the infusion of large volume ice-cold i.v. fluid, transthoracic echocardiography was used to assess cardiac function. The infusion resulted in a mean core temperature drop of 1.4°C and there were no significant changes in vital signs, electrolytes, arterial blood gases or coagulation parameters. The initial mean cardiac ejection fraction was 34%, and the fluid infusion did not affect ejection fraction, central venous pressure, pulmonary pressures or left atrial filling pressures.

Large volume ice-cold i.v. fluids have also been used for the pre-hospital induction of hypothermia. In one study, 30 mL kg⁻¹ of lactated Ringer's solution was infused at a rate of 100 mL min⁻¹ into an antecubital vein of 13 adult patients who were resuscitated from cardiac arrest [30]. The mean core temperature decreased from 35.8 ± 0.9°C at the start of infusion to 34.0 ± 1.2°C on arrival at hospital. No serious adverse haemodynamic effects were observed.

The technique of large volume ice-cold i.v. fluid has also been tested in a laboratory study during cardiac arrest [31]. In this study, 20 piglets were subjected to 8 min of ventricular fibrillation, followed by cardiopulmonary resuscitation (CPR). They were randomized into two groups, one given a 50 mL kg⁻¹ infusion of 4°C Ringer's solution at 1.33 mL kg⁻¹ min⁻¹, starting after 1 min of CPR and the other given the same infusion volume at room temperature. After 9 min, defibrillation was used to achieve a return of spontaneous circulation. The mean temperatures in the large volume ice-cold i.v. fluid animals were significantly reduced by a mean of 1.6°C compared with 1.1°C in the control group. There was no difference in cortical cerebral blood flow or haemodynamic variables and no adverse effects of the infusion.

On the other hand, there may be some concern that hypothermia induced during cardiac arrest decreases the effectiveness of defibrillation. This has been studied by Boddicker and colleagues [32], in a swine model of cardiac arrest. First-shock defibrillation success was higher in the moderate-hypothermia group. These data suggest that mild hypothermia in fact facilitated defibrillation.

Possible contra-indications to large volume ice-cold i.v. fluid include the presence of fulminate pulmonary oedema and/or the patient with chronic renal failure. In these patients, the i.v. infusion of a small volume of a much colder liquid might be useful. Recently, ice 'slurry', comprising smoothed 100 μm ice particles at a sub-zero temperature, has been developed. The effects of a rapid infusion of this slurry (50 mL kg⁻¹) were studied in swine [33]. Compared with the normothermic control animals, brain temperatures of the slurry and saline groups dropped by 5.3°C and 3.4°C (P = .009), respectively.

The use of large volume ice-cold i.v. fluid is an effective approach to rapidly cooling patients after cardiac arrest, and should be administered as soon as possible after resuscitation. For further maintenance of hypothermia, additional cooling techniques are required, as rewarming of the core temperature occurs in 85% of the patients [34].

**Body cavity lavage**

Plattner and colleagues [18] compared a number of these cooling techniques with surface cooling in volunteers. In addition to surface cooling techniques (ice-water immersion) described previously, Plattner and colleagues also studied gastric lavage (500 mL iced water every 10 min) and bladder lavage (300 mL iced Ringer's solution every 10 min). The first volunteer developed abdominal cramping and diarrhoea after gastric lavage and this technique was not used again. On the other hand, bladder lavage decreased core temperature by 0.8°C h⁻¹. The use of bladder lavage may therefore be a useful adjunct to cooling, but does require considerable additional nursing time to maintain the fluid exchanges.

Peritoneal lavage has been studied by Xiao and colleagues [35] in a dog model. Ringer's solution, 2 L, at 10°C was instilled into the peritoneal cavity, left for 5 min, and then drained. Tympanic membrane temperature decreased by a mean of 0.3°C min⁻¹. In addition, pulmonary artery temperature decreased by a mean of 0.8°C min⁻¹. However, peritoneal cooling has not been studied in post-cardiac arrest patients.

**Endovascular cooling**

With this cooling technique, a catheter is placed in the venous circulation (usually into the inferior vena cava via the femoral vein) and contains circulating saline at a controlled temperature. The fluid is
Patients with neurological injury after cardiac arrest were included. Continuous temperature and cooling rate were studied during primary percutaneous coronary intervention (PCI) for acute myocardial infarction [37]. Conscious patients were randomized to primary PCI with either normothermia or cooling using an endovascular cooling catheter (Icy Catheter; Alsius, Irvine, CA, USA) in patients with neurological injury and fever. There was a 64% reduction in 'fever burden' (area under the temperature chart) compared to the conventional group.

In the 'Cool-MF' study, the use of a cooling catheter was studied during primary percutaneous coronary intervention. Unselected survivors of cardiac arrest. Consecutive randomized to primary PCI with either normothermia or cooling were only cooled with endovascular cooling. The cooling was well tolerated, with no haemodynamic instability or increase in the incidence of arrhythmia. Although the median infarct size was not significantly smaller in patients who received cooling compared with the control group, the study demonstrated the safety and efficacy of the cooling technology.

Endovascular cooling has also been used in patients with neurological injury after cardiac arrest [38]. Thirteen patients were enrolled with a mean age of 60 years and were cooled to a target of 33°C for 24 h, followed by controlled rewarming. The rate of cooling averaged 0.8°C h⁻¹. No procedure-related adverse events occurred.

In a retrospective cohort study, the efficacy and safety of endovascular cooling was investigated in unselected survivors of cardiac arrest. Consecutive comatose survivors of cardiac arrest, who were either cooled for 24 h to 33°C with endovascular cooling, or treated with standard post-resuscitation therapy, were included. Continuous temperature and cooling data were available only for the endovascular-cooling group. Admission tympanic temperature was 35.4 ± 1.1°C. Of the 97 patients who were cooled with endovascular cooling, 41 received additional cold Ringer's lactate during induction of hypothermia. The bladder temperature at start of cooling, 95 (interquartile range (IQR) 67-156) min after restoration of spontaneous circulation, was 35.3 ± 1.0°C. It took 253 (IQR 170-345) min from restoration of spontaneous circulation to reach the target temperature of 33°C in the patients who were only cooled with endovascular cooling. The cooling rate was 1.2°C (IQR 0.7-1.5°C) h⁻¹. In 14 of the 97 patients, cooling was terminated prematurely due to haemodynamic instability, bleeding at the catheter insertion site, transfer to the operation theatre, obvious signs of brain death, multiple organ failure and subarachnoid haemorrhage.

Temperature control was effective and safe with this device [39]. However, the use of an endovascular cooling catheter is limited to the hospital setting. The heat exchanger and catheters are also expensive and the latter require insertion by a physician with additional training. This delays the induction of hypothermia for some time after hospital arrival. Nevertheless, these devices appear to provide excellent temperature control during maintenance and rewarming from hypothermia.

**Extra-corporeal circuits**

Extra-corporeal circulation consists of large intravascular (usually i.v.) catheters, a blood pump and an in-line heat exchanger. These circuits allow very accurate and rapid control of core temperature. The rapid rate of cooling with veno-venous cooling was studied in large swine [40]. Here, cooling reduced brain temperature from 38.0°C to 33.0°C in a mean time of 41 min compared with endovascular cooling which took a mean time of 126 min. None of the animals developed significant haemolysis, arrhythmias or bleeding.

Clinical experience with extra-corporeal circuits to induce hypothermia has been limited to only one report in patients with cardiac arrest [41]. After the return of spontaneous circulation, patients received mild hypothermia (34°C for 2 days) induced successfully by extra-corporeal haemodialysis coil cooling.

**Selective brain cooling**

To avoid possible systemic complications of hypothermia, isolated brain cooling was suggested. Cannulation of the carotid vessels and the infusion of cooled blood into the cerebrum have been studied in a swine model of cardiac arrest [42]. Animals received selective brain hypothermia (32°C) for 12 h using femoral/carotid bypass. This study demonstrated significant improvement in the neurohistology scores in the selective brain-cooled animals as compared with those of the normothermic control. However, given the modest side-effects of systemic hypothermia, and the potential complications of cannulating the carotid arteries under emergency conditions, this approach is unlikely to be used in the near future.

**Intra-aortic flush cooling during cardiac arrest**

It was shown in mice [43] and rats [44] that induction of hypothermia during cardiac arrest,
before start of resuscitation, improves outcome as compared to hypothermia induced after successful resuscitation. Similarly, it was shown in myocytes that injury to ischaemic cells takes place mainly after reperfusion, but not during ischaemia itself, by initiating several cascades leading to cell death [45]. When ischaemic myocytes were made hypothermic before reperfusion, injury to the cells was less, even if the duration of ischaemia was prolonged as compared to cells with normothermic reperfusion [46].

Therefore rapid cooling methods, which could be used during cardiac arrest no-flow, are sought.

One possible approach was shown by Nozari and colleagues [47] in dogs, where induction of hypothermia during cardiac arrest was done with veno-venous extra-corporeal cooling. Dogs were cooled via veno-venous extra-corporeal cooling to tympanic temperatures of 27°C or 34°C with ongoing chest compressions for 20 min. Then 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. In the normothermic groups, all dogs achieved spontaneous circulation, but remained comatose and died within 58 h with multiple organ failure. In the hypothermia groups, all dogs survived to 96 h without gross extra-cerebral organ damage.

Another approach for induction of hypothermia during CPR is the rapid infusion of large amounts of cold saline into the aorta.

In one study of exsanguination cardiac arrest in dogs, an aortic flush with 100 mL kg⁻¹ saline at 2°C decreased tympanic temperature to approximately 28°C within 4 min [48] with a corresponding brain temperature of 18°C. When an aortic flush adding vasopressin, which increased the arterio-venous pressure gradient, was applied in a 30 kg swine after achieving spontaneous circulation, but remained via veno-venous extra-corporeal cooling to tympanic venous extra-corporeal cooling. Dogs were cooled compared to cells with normothermic reperfusion, achieved 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.

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