Heart Mirror Journal
From Affiliated Egyptian Universities and Cardiology Centers

Vol. 6, No. 1, 2012
ISSN 1687-6652

EDITORIAL

Hypothermia Therapy; the Last Chance!

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The new techniques of cardiac resuscitation after cardiac arrest caused by any etiology have saved many lives. However, there is usually a narrow window of no more than 3 minutes before brain damage starts to be irreversible. Cooling the brain has been noticed to reduce or completely abolish these changes. The idea came from observing the complete recovery of near drowning victims in iced water who were successfully resuscitated after more than 3 minutes (1).

Hypoxic-ischemic encephalopathy is the most important cause of morbidity and mortality after resuscitation, and its severity is affected by cardiac arrest duration and resuscitation effectiveness (2, 3). Evidence exists of neurological insult in nearly half of all patients after successful resuscitation (3).

Hypothermia therapy (HT) started since the early nineties. The idea was to reduce the body core temperature to 28 to 34 C. The technique was not much encouraged due to the high nature of the mortality of the involved patients with cardiac arrest. Recently, two important articles were publish in 2 major cardiovascular journals which lead to reviving its importance (4, 5).

Terms used to describe hypothermia are not clearly defined. A temperature below 28°C is consider severe hypothermia, while moderate as 28°C to 34°C, and mild as 34°C to 36°C (6).

In experimental animal subjected to global brain ischemia, the effect of hypothermia depends on ischemia duration and time between ischemia and onset of hypothermia (7).

In infants suffering from hypoxic-ischemic encephalopathy, hypothermia of 33.5°C for 72 hours proved to be safe, reduced fatality, and improved neurodevelopmental outcome (8).

HT After Cardiac Arrest

HT was mainly used for out-of-hospital cardiac arrest (OHCA) or patients who remained unresponsive after return of spontaneous circulation. Ventricular fibrillation/tachycardia or any electromechanical dissociation of the heart, are the main etiology of the complete pump shut-down or cardiogenic shock. The underlying etiology of cardiac arrest was mainly due to coronary artery disease, dilated cardiomyopathy and to a less extent other etiologies (9).

Overall survival to hospital discharge was 56%, and 92% of survivors were discharged with a positive neurological outcome (Cerebral Performance Category1 or 2) (Table 1) (4, 10). Improved outcome was observed with longer hypothermia time and possibly when time from collapse to return of spontaneous circulation was <25 minutes (11).

Table 1: Cerebral Performance Categories Scale CPC Scale (10):

Note: If patient is anesthetized, paralyzed, or intubated, use "as is" clinical condition to calculate scores.
CPC 1. Good cerebral performance: conscious, alert, able to work, might have mild neurologic or psychologic deficit.
CPC 2. Moderate cerebral disability: conscious, sufficient cerebral function for independent activities of daily life. Able to work in sheltered environment.
CPC 3. Severe cerebral disability: conscious, dependent on others for daily support because of impaired brain function. Ranges from ambulatory state to severe dementia or paralysis.
CPC 4. Coma or vegetative state: any degree of coma without the presence of all brain death criteria. Unawareness, even if appears awake (vegetative state) without interaction with environment; may have spontaneous eye opening and sleep/awake cycles. Cerebral unresponsiveness.
CPC 5. Brain death: apnea, areflexia, EEG silence, etc.

Subsequent guidelines have therefore recommended cooling (32°C to 34°C) for 12 to 24h in unconscious adult patients with spontaneous circulation after OHCA due to ventricular fibrillation (5).

Mechanisms

Hypothermia decreases the cerebral metabolic rates of glucose and oxygen and slows ATP breakdown (12), with reduction of brain oxygen consumption of about 5% for every degree fall in body temperature (13). It also reduces glutamate release, intracellular calcium rises (14), inflammation, and free radical generation, suppresses nitric oxide and peroxynitrite formation leading to limited edema formation, and interrupted necrosis/apoptosis (15, 16).

Abbreviations and Acronyms	
HT	: Hypothermia Therapy
OHCA	: Out-of-Hospital Cardiac Arrest
CPC	: Cerebral Performance Category
STEMI	: ST Elevation Myocardial Infarction
IS	: Infarct Size

Method of Body Cooling

1. **Surface cooling;** it was used for many years in the treatment of fever and heat stroke. It included convective air blankets, water mattresses, alcohol bathing, cooling jackets, and ice packing. The COOL-AID study used these techniques in both cardiac arrest and the neonatal asphyxia (17). Its main disadvantage is that it requires many hours to reach and maintain a temperature below 35°C, this is due to vasoconstriction of the cooled skin which reduces the heat exchange in cooled patients, making temperature control very difficult. Recently, new machines are used to cool skin pads more rapidly and keeping it on the desired temperature (Figure 1).

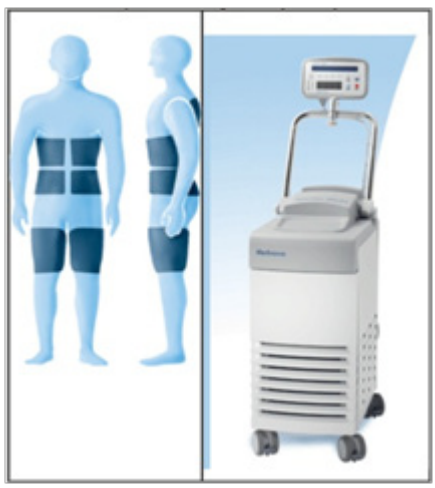

Figure 1: Noninvasive surface cooling device; a circulating chilled water in pads directly adhered to the patient's skin. The machine computer program regulates the water pads temperature according to the desired patient's temperature needed.

2. **Endovascular cooling;** the technique started by intravenous infusion of chilled saline. It was not practical in cardiac patients due to the need of infusing large amounts of fluid (18). Now a newly developed catheters with antithrombotic coverings that can be inserted into the central venous system and allow cooling via indwelling heat transfer devices (19). Endovascular cooling allows rapid cooling toward target temperature and allows skin warming during cooling and in turn, reduces shivering.

Cooling the Heart for Intervention

The idea of rapid reperfusion for ST elevation myocardial infarction (STEMI) is to reduce infarct size (IS) and associated complications. However, reperfusion in itself may cause irreversible damage to the myocardium, referred to as reperfusion injury (20).

Experimental studies have shown that mild hypothermia, induced before reperfusion of acute coronary occlusion, reduces infarct size and limits microvascular injury (21, 22).

However, hypothermia has failed to reduce IS if initiated after the onset of reperfusion (23).

The 2 major clinical trials investigating mild hypothermia using endovascular cooling catheters as an adjunct therapy in AMI failed to show a reduction in IS (24). It is believed to be mainly because therapeutic temperature was not reached before reperfusion in the majority of the patients. To overcome any delay of coronary intervention by cooling techniques, Götberg et al. combined rapid cooling by cold saline and endovascular cooling before reperfusion in patients with ST-elevation myocardial infarction. After reperfusion, the myocardium at risk as measured by cardiac magnetic resonance was reduced by 38% in the hypothermia group compared with the control group with significant decrease in both peak and cumulative release of Troponin (23).

Hypothermia and Shivering

The most uncomfortable feeling to conscious and semi-conscious patient is shivering. Also, the recent studies on patients suffering from acute stroke treated with HT showed that general anesthesia and subsequent artificial ventilation was not convenient to assess and follow the patient neurological condition (25). Shivering can be reduced with centrally active substances. Most anesthetics and narcotics change thermoregulatory control (26).

Meperidine is the most widely used drug to inhibit thermoregulatory responses (27, 28). The antishivering action of meperidine decreases the shivering threshold twice as fast as the vasoconstriction threshold and can be achieved at blood levels that do not lead to severe respiratory depression or sedation.

A low dose of meperidine (25mg IV), which does not affect alertness or respiratory function, decreases the shivering threshold by 2°C (29). Buspirone showed a synergistic effect with meperidine. The combination of both in a low-dose reduces the shivering threshold to 33.4°C (30). Pancuronium (0.1 mg per kilogram) every 2 hours was also given in another multicenter trial (31).

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In conclusions; OHCA in patients who remained comatosed after return of spontaneous circulation carries the highest mortality rate, HT proved to improve the outcome and saved lives. HT should be integrated in resuscitation guidelines, training of paramedical and medical personnel. Also, a central HT-capable hospital can be attached to a regional network of hospitals for patient transfer.

Future studies will need to investigate the effect of hypothermia on clinical outcome, the safety in combination with thrombolysis, and its potential use in conjunction with coronary intervention techniques.

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