Invited Editorial / *Davetli Editöryal Yorum*

Targeted temperature management, or therapeutic hypothermia, in post-resuscitation care

Resüsitasyon sonrası bakımda hedefli ısı yönetimi veya terapötik hipotermi

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Targeted temperature management, previously known as therapeutic hypothermia (TH), is well recognized and accepted as a part of post-resuscitation care. It involves active treatment that aims to achieve and maintain a specific body temperature (33°–36°C) for a specific duration (at least 24 hours), in an effort to improve neurologic outcome following cardiac arrest (CA).[1]

Known since the time of Hippocrates, the first study to address TH in patients with severe head injury was published in 1945. Use of TH following CA in humans was first described in the 1950s. Use of TH as a tool to reduce cerebral oxygen demand and improve neurologic outcomes following CA was supported by studies in dogs. After 1998, interest in TH increased, and the first clinical studies in humans with CA were published.[2,3]

Following the publication of 2 landmark studies in 2002,[4,5] TH was increasingly used in post-resuscitation care. The trials demonstrated that mild TH (32–34°C) improved neurologic outcome and decreased mortality in patients with return of spontaneous circulation following ventricular fibrillation in cases of out-of-hospital CA. These initial trials were followed by numerous nonrandomized studies that demonstrated improved outcomes when TH was introduced, even in cases of non-ventricular fibrillation in patients with out-of-hospital CA and in-hospital CA, and with any initial rhythm.[6,7] Following a targeted temperature management trial published in 2013,[8] which demonstrated similar rates of survival in 2 groups who had undergone temperature management (33°C *vs* 36°C), the American Heart Association, the European Resuscitation Council, and the International Liaison Committee on Resuscitation updated post-resuscitation guidelines and recommendations. These recommendations are summarized in Table 1.

Abbreviations:

TH *Therapeutic hypothermia*
CA *Cardiac arrest*

Mechanisms of therapeutic hypothermia

Hypothermia reduces cerebral metabolic rate for oxygen by 6–10% for every reduction in temperature of 1°C. Hypothermia is likely to lower lactate and other wastes from the anaerobic metabolism, decreasing cellular acidosis. While cellular acidosis decreases, cell apoptosis and cell death also diminish in neural tissue. Hypothermia significantly reduces extracellular levels of excitatory neurotransmitters, including dopamine and glutamate. Production of free radicals is associated with oxidative damage that is minimized at lower temperatures. Hypothermia also delays the induction of pro-inflammatory cytokines. In addition,

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Table 1. Recent guidelines and recommendations for the use of therapeutic hypothermia following cardiac arrest

Guidelines	Recommendations
2015 American Heart Association (AHA) Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care[9]	* Comatose (i.e.,lack of meaningful response to verbal commands) adult patients with return of spontaneous circulation after out-of-hospital ventricular fibrillation or pulseless ventricular tachycardia cardiac arrest should undergo targeted temperature management with goal temperature 32–36°C (89.6–96.8°F) for at least 24 hours (class I, level of evidence B). * Comatose adult patients with return of spontaneous circulation after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electric activity or asystole should undergo targeted temperature management with goal temperature 32–36°C (89.6–96.8°F) for at least 24 hours (class I, level of evidence C).
2015 Recommendations from the International Liaison Committee on Resuscitation (ILCOR)[10]	* Targeted temperature management with goal temperature 32–36°C (89.6–96.8°F) for at least 24 h should be part of a standardized treatment strategy for comatose survivors of cardiac arrest.
2015 European Resuscitation Council (ERC) Guidelines for Resuscitation[11]	* Targeted temperature management is recommended for adults after out-of-hospital cardiac arrest with an initial shockable rhythm who remain unresponsive after return of spontaneous circulation (strong recommendation, low-quality evidence). * Targeted temperature management is suggested for adults after out-of-hospital cardiac arrest with an initial non-shockable rhythm who remain unresponsive after return of spontaneous circulation (weak recommendation, very low-quality evidence). * Targeted temperature management is suggested for adults after in-hospital cardiac arrest with any initial rhythm who remain unresponsive after return of spontaneous circulation (weak recommendation, very low-quality evidence). * If targeted temperature management is used, it is suggested that the duration is at least 24 hours (weak recommendation, very low-quality evidence).

dysregulation in cerebral blood flow following ischaemia is normalized by hypothermia, which reduces immediate hyperemia and delayed hypoperfusion.[12]

Cooling Techniques

Cold infusion: The infusion of cold fluid has been proven effective, particularly in out-of-hospital environments and at the induction phase. Various protocols have been proposed, including the intravenous infusion of 30 ml/kg of ice-cold (4°C) lactated Ringers solution over 30 min, or the use of 500-2000 ml of 4°C normal saline as soon as possible following resuscitation. Although cold fluid intravenous infusion seemed to be an effective, safe, and quick means of inducing TH, it has been found insufficient when used alone during the maintenance phase of TH, requiring additional use of external cooling techniques or endovascular cooling devices.

External cooling techniques: Certain external cooling therapies are simple, inexpensive, and easy-to-apply, such as the application of ice packs to the groin, torso, axillae, and neck, and/or the application of towels soaked in ice water and fanning. These

methods may be considered for both the induction and maintenance phases in the intensive care unit. However, this approach cannot achieve control of the rate of cooling, and requires extreme alertness and experience if over-cooling is to be prevented.

A number of external cooling devices are now commercially available, including cooling mattresses, air-filled or water-circulating cooling blankets, and garment-type surface-cooling devices. In addition to a tight thermoregulatory capacity, these devices have the advantage of reducing risk of over-cooling during the induction phase. However, they are expensive and associated with rare adverse skin reactions (skin erythema and mottling beneath the cooling pads).

Endovascular cooling techniques

The endovascular cooling method consists of an endovascular cooling catheter that is commonly inserted percutaneously into the inferior vena cava and connected to an automatically guided temperature cooling system. This system extracts heat directly from the core and is not impaired by thermoregulatory skin vasoconstriction. As a consequence, the device allows for the rapid and accurate establishment of target temperature, is effective in maintaining a stable temperature after induction, and allows for an efficient control of the rewarming phase. The main limitations in the routine use of this technique are the risks of venous thrombosis or infection, the cost of the device, and the requirement of central venous cannulation.

Novel cooling techniques and devices

A number of novel cooling techniques have been proposed as alternatives to the more conventional techniques currently available. These include iced saline gastric lavage, cooling helmets, a total cold water immersion system, and a trans-nasal cooling device that allows for the rapid induction of hypothermia. Cooling by peritoneal, pleural, or bladder lavage is possible, though these approaches are invasive and are not generally used. Therapies involving cooling by extracorporeal circulation, including cardiopulmonary bypass, extracorporeal membrane oxygenation, or continuous renal replacement, are rarely used.[12–14]

An optimal technique has not yet been defined, and selection of appropriate method of cooling is dependent on local factors. In particular, the choice between invasive or non-invasive methods depends upon availability of trained personnel. Because TH therapy consists of 3 distinct phases (induction, maintenance, and rewarming), an ideal cooling device should achieve each. Ideally, cooling should be initiated as quickly as possible (within 6 hours). The maintenance phase should be achieved using a regulating device or by closely monitoring body temperature. Optimal duration of cooling must last more than 24 hours. The rewarming phase can be achieved either passively or actively, but rate of rewarming should not exceed 0.25–0.5°C per hour. Following this phase, hyperthermia should be actively avoided. In order to detect rapid changes in body temperature, more central temperature monitoring sites, such as the esophagus, bladder, rectum, pulmonary artery, central venous, or tympanic membrane should be used. Lowering of core temperature during TH results in shivering, which should be suppressed using the administration of analgesia, sedation, muscle relaxants, or neuromuscular blockers.[12–14]

Adverse effects of therapeutic hypothermia

The most frequently reported complications of TH include hypokalemia, hypophosphatemia, hypomagnesemia, hypocalcaemia, hyperglycemia, hypotension, haemodynamic instability, thrombocytopenia, bleeding, pneumonia, sepsis, pancreatitis, decreased gastrointestinal motility, renal failure, pulmonary oedema, seizures, and arrhythmias. Hypokalemia induced by TH is caused by influx of potassium into cells and increased diuresis. Regular checks of serum electrolytes are necessary during TH. On the other hand, aggressive supplementation of potassium during TH may result in hyperkalemia during rewarming. TH reduces insulin sensitivity and insulin secretion. Both may lead to hyperglycemia. Hypothermia may result in increased risk of bleeding as a result of impaired platelet function, thrombocytopenia, and impairment of coagulation cascades. It is necessary to be alert to bleeding, which indicates interruption of TH. Conflicting results regarding incidence of arrhythmia during hypothermia have been published. Arrhythmias generally occur due to overcooling or electrolyte imbalance. Hypothermia leads to the slowing of a number of hepatic enzymes, including cytochrome P450. Therefore, drugs that are metabolized by the liver such as sedative and neuromuscular blocking agents require dose modification.[12,15]

Most adverse events related to TH are mild and can be easily controlled by properly administered in-

tensive care. Monitoring principles of patients undergoing TH are shown in Figure 1.

In the current issue of the Archives of the Turkish Society of Cardiology is a study in which TH performed by Aruğaslan and his colleagues is described.[16] Aruğaslan et al. conducted a prospective study in which 13 patients underwent TH. Each had in- or out-of hospital CA due to myocardial infarction. Initial non-shockable rhythm occurred in only 2 patients. The study group was younger (39.6±9.4 years), and cardiopulmonary resuscitation duration (32.9±20.1 minutes) and door-to-cooling time (286.1±182.3 minutes) were longer. TH was performed by intravascular cooling following coronary procedure. Patients were cooled to 33°C, and temperature was maintained for 24 hours. Rewarming was achieved by controlled normothermia. While serious side effects (bleeding, sepsis, pneumonia) developed in 9 patients due to TH, good clinical results were obtained. One patient died in hospital and 1 patient had poor neurologic outcome (dependent, with severe neurologic dysfunction), but 11 patients had normal neurologic status (no neurologic disability) at 1 year.

Although TH has been recommended in post-resuscitative care by all cardiopulmonary resuscitation guidelines since 2010, it is not commonly utilized in

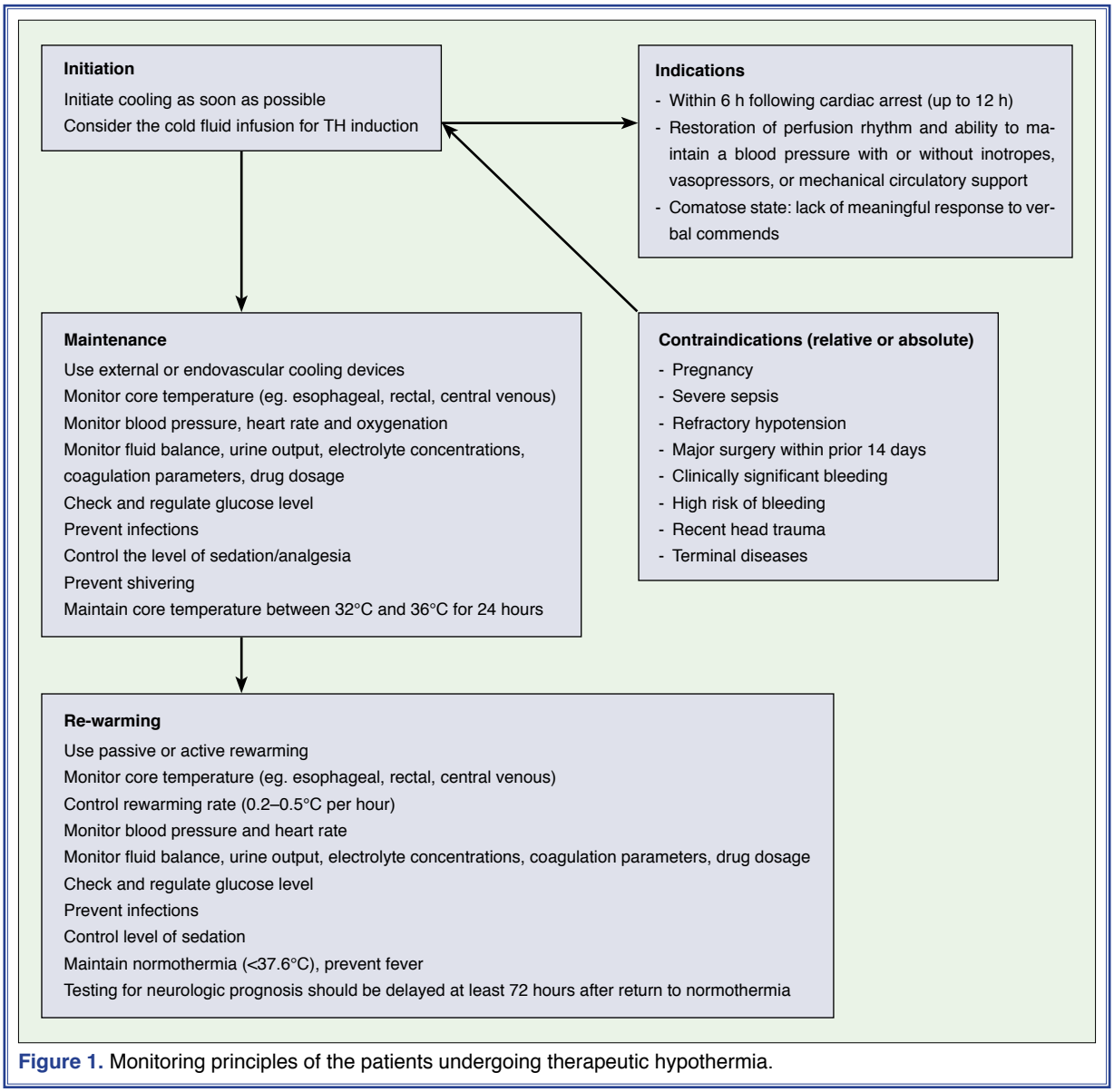

Figure 1. Monitoring principles of the patients undergoing therapeutic hypothermia.

Turkey. TH is a difficult and troublesome process, but if applied as in the Aruğaslan study, results are gratifying. This study was well-conducted, demonstrating that TH can be applied with success in our country.

Several limitations affected the study. The population was small and its members were young. No control group was utilized. The population was not homogeneous (including in- and out-of-hospital CA patients and patients transferred from other hospitals). Initial rhythm is important in the prognosis of TH. Admission with shockable rhythm is a good prognostic criterion, and most patients were admitted with shockable rhythms. Nevertheless, I believe that this study is important in the national promotion of TH following CA.

As a result, the use of TH following return of spontaneous circulation in post-CA patients as a part of routine post-resuscitation care improves survival and neurologic outcomes. While no clear answers can address certain questions (regarding best timing, optimal duration, depth of cooling, rate of rewarming, preferred cooling method, and cost-effectiveness), TH should be used in clinical practice in Turkey.

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