Topical Review

What Is the Use of Hypothermia for Neuroprotection After Out-of-Hospital Cardiac Arrest?

Francis Kim, MD; Paco E. Bravo, MD; Graham Nichol, MD

Out-of-hospital cardiac arrest (OHCA) refers to the loss of cardiac mechanical activity with hemodynamic collapse in the out-of-hospital setting. If not treated rapidly, OHCA invariably results in death. Survival to hospital discharge after OHCA is low in many communities, ranging between 10.7% (95% confidence interval, 9.9%–11.5%) for adults treated for all rhythms and 31.7% (95% confidence interval, 28.2%–35.1%) for those resuscitated after bystander-witnessed ventricular fibrillation (VF). The most common cause of death among patients hospitalized after OHCA is neurological injury. In spite of these unmet challenges, the in-hospital mortality rate of treated patients has declined 11.8% in recent years, from 69.6% in 2001 to 57.8% in 2009. This improvement in outcomes is thought to be related in part to the advent of therapeutic hypothermia, as well as implementation of intensive care protocols for those successfully resuscitated but still comatose after OHCA.

Rationale for Hypothermia

Reperfusion injury occurs in the brain and heart during and after restoration of blood flow. It includes release of proinflammatory then anti-inflammatory cytokines, which contribute to poor capillary perfusion, tissue ischemia, and microcirculatory dysfunction. Cardiac function decreases then improves during the initial 2 days. Vascular and intestinal permeability increase during the next 3 days. Patients may experience sepsis-like hemodynamic states, neurological injury, multiple organ dysfunction, and death. The extent of reperfusion injury is associated with the duration of ischemia, and the adequacy of resuscitation. In turn, long-term prognosis is correlated with the extent of reperfusion injury.

Induction of hypothermia during ischemia prolongs the tolerance of organs to ischemia. Hypothermia after reperfusion reduces production of deleterious glutamate, oxygen-free radicals and inflammatory molecules, cerebral oxygen demand, intracranial pressure, and the final extent of neurological injury. Thus, induced hypothermia (IH), sometimes called targeted temperature management, which consists of cooling the body to reduce neurological injury and multiorgan dysfunction, is applied to patients with OHCA. The 2010 Guidelines on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care recommend that:

comatose (ie, lack of meaningful response to verbal commands) adult patients with restoration of spontaneous circulation (ROSC) after out-of-hospital VF cardiac arrest should be cooled to 32°C to 34°C (89.6°F to 93.2°F) for 12 to 24 hours (Class I, LOE B). Induced hypothermia also may be considered for comatose adult patients with ROSC 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 (Class IIb, LOE B).

These evidence-based recommendations are being reevaluated in light of recent trials of IH in patients with OHCA. Until then, we offer contemporary evidence-based recommendations for use of IH in this population.

Early Cooling

In considering the optimal timing of mild hypothermia, several animal studies suggest that cooling earlier results in more protection than cooling later. In a mouse model, IH with cooling blankets during CPR was better than IH after restoration of spontaneous circulation (ROSC). In a dog model of VF arrest, mild hypothermia with cold normal saline infusion during CPR was associated with greater survival compared with IH after resuscitation. In another dog model, mild hypothermia during arrest significantly improved cerebral function as compared with normothermia, whereas IH 15 minutes after reperfusion did not. These animal studies suggest that intra-arrest cooling or cooling within 15 minutes after ROSC is associated with better neurological recovery.

The optimal timing of the initiation of mild hypothermia in humans remains an important question. In humans, IH started 4 to 8 hours after resuscitation, is associated with improved neurological outcome compared with normothermia. A challenge in testing IH earlier than this in humans is finding a simple and safe method that paramedics can apply in the field to patients with cardiac arrest. Invasive and noninvasive hospital-based methods may not be applicable for use in

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the field. Invasive strategies using cooling catheters rapidly achieve the goal temperature, but are impractical for field application because they are placed into the inferior vena cava. External cooling techniques have the advantage of being less invasive; however, most of them, including cooling blankets or fluid pads depend on an external energy supply or external cooling unit, and are not practical for field use. Ice packs have been used13; wide application of ice packs is limited because of relatively slow induction times to temperatures <34°C compared with other methods.

Infusion of Cold Fluid

The use of intravenous infusion of ice-cold fluids is appealing because it is portable and easy to administer in the field in patients resuscitated from OHCA, and was initially popularized by the group of Bernard et al in 2003. Rajek et al16 studied the use of 40 mL/kg of normal 4°C saline solution infused >30 minutes into 9 anesthetized volunteers who received vecuronium, and demonstrated a mean temperature decrease of 2.5°C. Similar results have been demonstrated in elective surgical volunteer patients; however, healthy volunteer surgical patients or young volunteers may not be representative of patients with OHCA. In all these studies, neuromuscular blockade was used to augment the effects of infusing cold fluid.

The use of early cooling using cold intravenous fluid has been recently addressed by our group, in the largest randomized trial of IH in patients with OHCA reported to date.17 In this study, 1359 adult patients successfully resuscitated from nontraumatic OHCA (583 with VF and 776 without VF) were randomized to prehospital cooling (n=688; 292 with VF and 396 without VF) versus standard care only (n=671; 291 with VF and 380 without VF) irrespective of the presenting rhythm. The study was conducted in emergency medical service (EMS) agencies and receiving hospitals in Seattle and King County, Washington. Prehospital cooling was initiated by EMS providers via rapid infusion of ≤2 L of 4°C normal saline after ROSC. All patients received standard care on hospital arrival with mild therapeutic hypothermia protocols involving surface and intravascular cooling devices for ≤24 hours with a goal temperature of <34°C.

Temperature at randomization was not significantly different between subgroups (±36°C). The intervention group had decreased mean core temperature by 1.2°C in patients with VF (35.0°C versus 35.9°C; P=0.0001) and by 1.3°C in patients without VF (34.8°C versus 35.7°C; P=0.0001) by hospital arrival and reduced the time to achieving a temperature <34°C by >1 hour in patients with VF (4.2 versus 5.5 hours; P<0.01) and those without VF (3.0 versus 4.0 hours; P<0.01) compared with the control group (standard care alone). In the intervention group, the percentage of patients who achieved a core temperature <34°C at hospital arrival was 26% (as compared with 5% in the control group; P<0.0001) in patients with VF and 29% (versus 6% control; P<0.0001) in patients without VF. Despite these differences, survival and favorable neurological outcome at the time of hospital discharge were not significantly different in patients with (survival, 62.7% versus 64.3%; P=0.69) and without VF (survival, 19.2% versus 16.3%; P=0.30) in the intervention group compared with those in the standard care only. Similarly, the proportions of patients who either awakened from a coma or died without awakening in patients with and without VF were comparable between the intervention and control groups.

Importantly, the intervention group had a higher incidence of cardiac arrest during transport (26% versus 21%; P=0.008), longer time from first EMS dispatch to hospital arrival (51±13 versus 49±14 minutes; P=0.006), significantly lower oxygenation (PaO2, 189±135 versus 218±144 mm Hg; P=0.001), more acidosis (pH 7.16±0.23 versus 7.20±0.29; P=0.005), increased pulmonary edema on first chest x-ray (41% versus 30%; P<0.001), and greater use of diuretics during the first 12 hours of hospitalization (18% versus 13%; P=0.009) compared with the control group. However, these differences present within the first 24 hours, resolved in the following days as demonstrated by similar rates of pulmonary edema on subsequent chest x-rays, duration of mechanical ventilation, need for reintubation, and hospital length of stay between groups. Importantly, mortality in the out-of-hospital setting (1.3% versus 1.6%; P=0.61) and at the emergency department (12.8% versus 12.7%; P=0.95) did not differ between groups.

Bernard et al18,19 reported similar findings in a smaller randomized study in Australia. The authors randomized 234 resuscitated patients from VF arrest to paramedic-initiated cooling with a rapid infusion of 2 L of ice-cold lactated Ringer solution versus standard hospital-based therapeutic hypothermia (33°C) using surface cooling techniques. The intervention resulted in a modest decrease in core temperature of 0.8°C (34.4±1.2°C versus 35.2±1.0°C; P=0.001) on hospital arrival compared with the control group, although, core temperature equalized just 60 minutes after hospital arrival between groups (34.7±1.1°C versus 34.7±0.9°C; P=0.7). The primary end point defined as patients discharged directly home or to a rehabilitation facility was not significantly different between the paramedic-cooled group (47.5%) and hospital-cooled group (52.6%; P=0.043). The reported incidence of pulmonary edema and recurrent cardiac arrest during transport was not significantly different between groups.

Taking these trials together, the available data does not support the use of EMS-initiated rapid infusion of cold crystalloids as a mean to achieve faster cooling rates after ROSC in patients with or without VF arrest. These are disappointing findings because laboratory-based studies have previously suggested a relationship between early onset of therapeutic hypothermia and favorable outcomes in various animal models of cardiac arrest.10,12,20 This lack of translation from bench-to-bedside has several potential explanations.

First, in animal models, the best outcomes have been observed when cooling is achieved in ‑arrest19 or immediately after ROSC.21 In 1 animal study, a delay of only 15 minutes in the initiation of therapeutic hypothermia was enough to mitigate some of the neuroprotective benefits observed in the immediate cooling group.22 This is an important methodological difference between animal and human studies, because therapeutic hypothermia after ROSC is currently achieved after several hours in humans (3 hours in patients without VF...
and 4.2 hours in VF-arrested patients in the Seattle trial intervention group.

Congruent with these human data is a study in 258 rats exposed to 10-minute asphyxial cardiac arrest then randomized to normothermia or cooling (33°C) at 30 minutes, 1, 4, and 8 hours after ROSC and maintained for either 24 or 48 hours. IH initiated at 0 minute (45%), 1 hour (36%), and 4 hours (36%) after ROSC had similar survival, which was significantly better than that in the 8-hour group (14%) and normothermia group (17%). The Seattle and King County trial and animal data both suggest that there is no difference in survival so long as IH is initiated within 4 hours of arrest.

Second, in the Seattle and King County trial described above, the prehospital use of rapid cold saline infusion was associated with more episodes of reartert en route, acidosis, and pulmonary edema on admission. Cardiac arrest has the potential of causing further anoxic brain injury, acidosis is a known predictor of adverse outcomes and rapid cold saline infusion, at least in 1 cardiac arrest animal model, was associated with reduced coronary artery perfusion pressure compared with postresuscitation surface cooling methods. These complications related to cold saline infusion did not affect early mortality in our study, but it is conceivable that they may have manifested because increased risk of death later during the hospitalization, thus, offsetting any potential benefit of achieving earlier hypothermia by rapid cold saline infusion.

Third, many factors contribute to outcomes after resuscitation. The quality and timing of bystander CPR, the performance and training of EMSs, and care by emergency and intensive care units are all critical elements and direct determinants of survival and functional outcomes. The lack of survival benefit in our study must be interpreted in the context of the EMS and regional health system where the study was performed. We reported mortality rates of 35% for patients with VF, which are among the lowest in the United States. An important question remains whether the use of prehospital cooling might benefit patients in a less optimal EMS environment. For example, might prehospital cooling benefit patients who had a longer transit time before hospital arrival, or had longer EMS response times?

Potential Alternatives

Future outcome trials using faster, volume-sparing hypothermia methods during CPR or immediately after ROSC are clearly needed. As a preamble, Castrén et al reported the safety, feasibility, and cooling efficacy of the RhinoChill device (BeneChill, Inc, San Diego, CA) during active CPR (intra-arrest) in the Pre-ROSC IntraNasal Cooling Effectiveness study. RhinoChill is a transnasal evaporative cooling system that has been shown to improve the CPR success rate in a porcine model of cardiac arrest, explained by a higher increment in the coronary perfusion pressure compared with cooling with cold saline infusion. Moreover, transnasal evaporative cooling seems to rapidly induce preferential brain cooling as compared with the rest of the body, which is cooled at a slower rate, creating a significant brain–body temperature gradient.

This small trial suggested that intra-arrest cooling with the RhinoChill device was feasible, relatively safe, and reduced the core temperatures by nearly 2 hours compared with hospital-based cooling systems. Larger randomized trials are ongoing to assess the effect of intra-arrest IH on clinically important outcomes. If these trials do not show benefit, the strategy of early, out-of-hospital cooling should be abandoned.

Hospital-Based Cooling

Initial clinical trials focused on hospital-based target core temperature of 32°C to 34°C, commonly referred to as mild therapeutic hypothermia, for an average of 12 to 24 hours. However, the hypothermia after cardiac arrest trial was criticized because the average temperature in the nonhypothermia control group remained >37°C, and some patients even developed fever between 8 and 36 hours after ROSC. This has raised several questions of whether the improved survival and neurological outcomes seen at least in the hypothermia after cardiac arrest study were partly because of the therapeutic effects of induced mild hypothermia or the avoidance of fever/hyperthermia after the first 24 hours post OHCA. This becomes relevant because the development of hyperthermia during the first 36 to 48 hours postarrest seems to be associated with unfavorable outcomes in comatose patients with OHCA.

Therefore, investigators conducted the temperature management to a target of either 33°C or 36°C after OHCA targeted temperature management (TTM) trial. The investigators randomized a total of 939 patients with OHCA (=80% with VF) to hospital-initiated cooling to a target temperature of 33°C (n=473) or 36°C (n=466), which was achieved by ice-cold fluids, ice packs, and intravascular or surface devices and maintained for 28 hours, after which, gradual rewarming was begun, however, in unconscious patients temperature was maintained <37.5°C in both groups for 72 hours post OHCA using fever control measures.

Remarkably, the primary outcome of all-cause mortality (50% versus 48%; P=0.51) and secondary outcome of a composite of poor neurological function or death (54% versus 52%; P=0.78) through the end of the trial (180 days) were no different between the 33°C and 36°C group. The hazard ratio for death in multiple a priori subgroups, including age, time to ROSC, initial rhythm, and presence of shock at hospital admission, none of the point estimates showed a trend in the direction of a clinical benefit using 33°C as the target core temperature in the first 36 hours post OHCA resuscitation.

On the basis of these findings, the authors concluded that there was no evidence at this time to indicate that aiming for a body temperature of 33°C conferred any significant clinical benefits over a temperature of 36°C in unconscious patients admitted to the hospital after OHCA. One of the main hypotheses for this comparable clinical benefit seen with either hypothermia strategy has to do with the importance of avoiding the development of hyperthermia or fever during the active cooling intervention during the first 36 hours post cardiac arrest, and the subsequent days after the passive rewarming process.

Again, there are several plausible explanations for the lack of difference in survival or neurological outcome in the TTM trial. First, the majority of patients enrolled in the TTM had witnessed arrests, with bystander CPR initiated within a
median of 1 minute after the onset of arrest. As such, they may have had less ischemia and reperfusion injury, and, therefore, a better overall prognosis than the average patient treated for OHCA. This is corroborated by the observation that >75% of patients in either the control or intervention group had a pupillary light reflex response at the time of admission. Others have reported that ≈20% of patients resuscitated from OHCA have pupillary responses. The presence of a pupillary response is one of the strongest predictors of good neurological outcome in the presence or absence of IH/TTM. It seems plausible that the lack of difference in survival between the 33°C group and the 36°C group in the TTM trial may, in part, have been because patients in either group had a good overall prognosis and insufficient neurologic or cardiac injury to benefit from IH/TTM.

Second, the 33°C group had significantly more days receiving mechanical ventilation (median, 0.83 [0.67, 1.0] versus 0.76 [0.6, 10]; P = 0.006) and were significantly less likely to have woken before prognosis assessment (44% versus 52%; P = 0.03) compared with the 36°C group. A strength of the TTM trial was that participating clinicians used a deferred, structured approach to prognosis assessment and withdrawal of care in enrolled subjects. Unfortunately, this approach did not account for the prolonged metabolism of drugs in patients with deeper hypothermia. It seems plausible that the increased duration of ventilation and increased likelihood of unconsciousness at the time of prognosis assessment in the 33°C group compared with the 36°C group in the TTM trial was because of prolonged metabolism of sedatives.

Third, the estimated time from ROSC to achievement of a target temperature <33°C was ≈720 minutes. in the TTM trial. This was long compared with previous trials (Table). This delay in reaching target temperature (may have) negated any clinical benefit.

Finally, propofol was commonly used as a sedative in the TTM trial (TTM Investigators, unpublished data, 2014). Cardioprotection from reperfusion injury was attenuated by propofol in a trial that of cardioprotection in patients undergoing coronary artery bypass grafting. As well, in a systematic review of randomized trials of patients (n=696) undergoing bypass grafting, propofol was associated with significantly less myocardial ischemia and injury compared with sevoflurane. It seems plausible that concurrent use of propofol may have attenuated the benefit of IH in the TTM trial.

Adoption of a target temperature range of 36°C may be associated with increased shivering as 36°C is close to the normal shivering threshold. Shivering markedly increases heat production. If endovascular methods of IH are used, skin counterwarming can be used to reduce the heat production and the shivering threshold. Limited trials have not demonstrated that one pharmacological method of reducing shivering is better than another in patients with cardiac arrest or normal volunteers. Medications commonly used to reduce shivering during IH include midazolam, fentanyl, dexmedetomidine, magnesium sulfate, meperidine, and buspirone.

Neuromuscular blocking agents (NMB) are sometimes used to reduce shivering. A systematic review of randomized trials in adults with acute respiratory distress syndrome (n=431) suggested that NMB reduce mortality as compared with no NMB. A single-center randomized trial of NMB (rocuronium) in patients resuscitated from cardiac arrest has completed enrollment but not reported results (clinicaltrials.gov identifier NCT01683006). Until there is compelling evidence for or against use of NMB in patients with cardiac arrest, selection of NMB type and dose is at provider discretion.

Randomized trials completed to date have evaluated IH without other concurrent interventions. IH may have incremental benefit when combined with emergency cardiopulmonary support to improve cardiac output, or hemofiltration to remove cytokines, or xenon to increase neuroprotection. These combination therapies remain investigational.

### Conclusions

IH provides neuroprotection in animal models of cardiac arrest, but is of uncertain benefit in humans. Use of EMS-initiated rapid infusion of cold crystalloid as a means to achieve faster cooling rates after ROSC in patients with and without VF arrest did not improve survival. Whether intra arrest or volume-sparing cooling methods in the field are beneficial remain unclear. Initial trials of IH in patients hospitalized comatose after resuscitation from OHCA demonstrated benefit as compared with the control group. The lack of significant difference in survival or neurological outcome with temperature ranges of 33°C versus 36°C has increased uncertainty about which range and concurrent treatments are best.

| Table. Treatment Process and Outcome in Large Randomized Trials of Hospital-Based Hypothermia |
| Population | Temperature Target, °C | Time From Onset of Arrest to Target, min | Survival |
| Bernard et al 2015 | Control (n=34) | Out-of-hospital VF | n/a | n/a | 33 |
| Intervention (n=43) | 33°C | ≈270 | 49 |
| HACA 2016 | Control (n=138) | Witnessed out-of-hospital VF or pVT | n/a | n/a | 45 |
| Intervention (n=137) | 32–34°C | ≈500 | 59 |
| Nielsen et al 2017 | Control (n=466) | Out-of-hospital VF, PEA, or witnessed PEA | n/a | n/a | 50 |
| Intervention (n=473) | 33°C | ≈720 | 46 |

HACA indicates hypothermia after cardiac arrest; n/a, not applicable; PEA, pulseless electrical activity; pVT, pulseless ventricular tachycardia; and VF, ventricular fibrillation.
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Breathing outside the hospital (out-of-hospital cardiac arrest, OHCA) is breathing failure that occurs outside the hospital. If the patient does not receive care, OHCA inevitably results in death. Survival rates for OHCA vary among different regions, with 10.7% (95% CI, 9.9%-11.5%) for adults who receive in-hospital care and 31.7% (95% CI, 28.2%-35.1%) for those who receive resuscitation due to ventricular fibrillation (VF) witnessed by an bystander.

OHCA after hospitalization is the most common cause of death is neurological damage.

The mechanism of reperfusion damage is that perfusion is not possible during and after reperfusion, which may cause multiorgan dysfunction. After two days of regular heart function, blood circulation and organ function may improve, and the patients may suffer from sepsis or multiple organ dysfunction syndrome (MODS). The severity of reperfusion injury is related to the duration of hypoxia and the effectiveness of resuscitation.

Hypothermia (induced hypothermia, IH) is often used to reduce the severity of reperfusion injury. IH is induced to reduce body temperature to 32°C to 34°C (89.6°F to 93.2°F) for 12-24 hours. The IH cooling period is 3°C more than the recovery period. IH can reduce the severity of organ injury from cardiorespiratory arrest. The 2010 Guidelines on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care recommends this treatment for patients who survive cardiac arrest and are in a coma (e.g., no response to verbal commands).

IH is also recommended for adults who have pulseless electric activity or asystole. However, this recommendation is made based on case reports and expert opinions, and the evidence for its effectiveness is not yet available. The use of IH for OHCA should be considered on a case-by-case basis, and the decision should be made by a multidisciplinary team. The use of IH should be guided by evidence from randomized controlled trials that demonstrate its effectiveness and safety.
하여 뇌기능을 의미 있게 호전시켰는데 재관류 15분 이후에 IH는 그렇지 못했다.12 이런 동물실험들은 심정지 시에 냉각을 하거나 ROSC 발생 15분 이내에 냉각을 하는 것이 신경학적 회복이 더 좋다는 것을 시사한다.

사람에서 경도의 저체온을 시작하는 적절한 시기가 중요하다는 의문점으로 남아있다. 사람에서 소생술 완료 4~8시간 후에 IH를 하는 것은 정상 체온보다 신경학적 예후를 향상시켰고,3,4,11,12 사람에서 이보다 더 일찍 시작하는 IH의 효과를 시사한다.3,4,11,12 사람에서 경도의 저체온치료 프로토콜을 가지고 병원에 도착한 모든 환자에게 표준적인 치료를 하였다.

무작위균형 시점에서의 체온은 집단 간에 의미 있게 차이가 없었다(36°C, 중대군은 병원 도착 전까지 VF가 있는 환자에서 평균 심박온은 1.2°C 감소하였고,35.0°C 대 35.9°C: P < 0.0001), VF가 없는 환자에서 1.3°C 감소하였으며(34.8°C 대 35.7°C: P < 0.0001) 34°C 미만으로 체온을 떨어뜨리는 것이 있어서 2 L 이하의 4°C 생리식염수를 빠르게 주사하여 냉각을 유도할 수 있었다. VF가 있는 환자(4.2 대 5.5시간; P < 0.01)와 VF가 없는 환자(3.0 대 4.0시간; P < 0.0001)에서 대조군과 비교하여 1시 간 넘어 사망의 단축시켰다. 중대군에서 병원 도착 시에 34°C 미만으로 심박 체온이 떨어진 환자의 비율이 VF가 있는 환자에서 26%(대조군 3%; P < 0.0001), VF가 없는 환자에서 29%(대조군 6%; P < 0.0001)였다. 이런 차이에도 불구하고 표준적 치료만 받은 환자들은 비교하여 중대군에서의 심박과 무관한 사망률을 얻었다. VF가 있는 환자(생존율, 62.7% 대 64.3%; P = 0.30)에 의한 차이가 없었다. 전체적으로 중대군에서 VF 유무가 무관하게 환자에게 가려나는 환자의 비율과 가려나지 못하고 사망하는 환자의 비율은 비슷했다.

대조군과 비교할 때 중대군은 이송 중에 더 자주 심정지가 왔고(26% 대 21%; P = 0.008), EMS의 출동 후 병원 도착할 때까지의 시간이 더 길었으며(49±14분 대 49±14분; P = 0.006), 산소포화도 높았으며(189±135 대 218±144 mmHg; P < 0.001), 산증이 더 심하게 발생하였고(pH 7.16±0.23 대 7.20±0.29; P = 0.005), 첫 가슴방사선촬영에서 폐부종이 더 많았고(41% 대 30%; P < 0.001), 입원 후 첫 12시간 동안 이뇨제의 사용이 더 많았 다(18% 대 13%; P = 0.009)는 점이 중요하다. 그러나 오는 6시간 동안 모든 환자들은 이송 후 12시간 동안 사망하는 환자들의 비율에 관계없이 사망률 및 응급실에서의 사망률(1.3% 대 1.6%; P = 0.61)과 응급실에서의 사망률(12.8% 대 12.7%; P = 0.05)은 두 군간에 차이가 없었다.

Bernard 등18,19는 호주에서 시행한 소규모 무작위시험에서 비슷한 결과를 보고하였다. 저자들은 VF 심정지로 소생술을 시행한 234명의 환자를 응급구조사가 찬 링커서폰액(lactated Ringer solution) 2 L를 빠르게 주사하여 냉각을 유도하거나 표면냉각기법을 이용하는 표준적인 병원기반 저체온치료(33°C)를 받도록 무작위할당하였다. 이 중대군은 대조군과 비교하여 병원 도착 시에 심박온은 0.8°C (34.4±1.2°C 대 35.2±1.0°C; P = 0.001) 정도 더 떨어뜨리지 않고 병원에 도착한 후 60분이 지나서도 뇌기능을 의미 있게 호전시킨다는 것을 시사한다. VF가 있는 환자(62.7% 대 64.3%; P = 0.30) 및 VF가 없는 환자(19.2% 대 16.3%; P = 0.30)에서 응급구조사가 찬 링커서폰액(lactated Ringer solution)을 사용하는 것과 비교하여 사망률 및 응급실에서의 사망률(1.3% 대 1.6%; P = 0.61)이 두 군간에 차이가 없었다.
송 중의 심정지 재발 보고는 양 군에서 의미 있는 차이가 없었다.

이런 임상시험의 결과들을 종합적으로 보았을 때 VF 유무와 관계없이 ROSC 이후 냉각을 빨리 시작하기 위한 수단으로 EMS가 찬 정질액(crystalloid)을 빨리 주사하는 것이 유용하다고 뒷받침해 주는 증례는 없다. 과거에 다양한 심정지동물모델을 이용한 실험연구에서 절상온치료를 빨리 시작하는 것이 양호한 결과를 가져왔지만 이를 고려하면 이는 실망스러운 결과이다.11,12,20 이런 중 개개인과 실험관에 대한 이유에 대해서는 몇 가지 설명이 가능하다.

첫째, 동물모델에서 최선의 결과는 심정지 중에 또는 ROSC 직후 냉각을 하였을 때 나왔다. 한 동물연구에서 15분간 저체온 치료를 늦추어도 즉시 냉각을 한 집단에서 관찰한 신경보호 효과가 없어졌다.12 인간에서 ROSC 이후 냉각 치료에 도달하기까지 3시간이 걸리는 시애틀 임상시험 중재군에서 VF가 없는 환자에서 3시간, VF가 있는 환자에서 4.2시간) 이것은 동물연구와 인간연구에서 중요한 방법 상의 차이점이다.

258마리의 쥐를 10분 동안 질식시켜 심정지를 유발한 후 정상 체온 또는 ROSC 30분, 1시간, 4시간 후에 24시간이나 48시간동안 냉각(33°C)으로 무작위할당한 연구도 인간에서의 결과와 비슷하다.12 ROSC 직후(45%), 1시간(36%), 4시간(36%) 이후 IIH를 시작해도 모두 비슷한 생존률을 보였고 8시간 집단(14%)이나 정상 체온 집단(17%)보다는 의미 있게 좋았다. 시애틀 및 킹 카운티 임상시험과 동물데이터는 모두 IIH를 심정지 후 4시간 이내에 시작하면 생존에는 차이가 없다는 것을 시사한다.

둘째, 전술한 시험에 및 김 가오 연구에서 병원 전단계의 빠른 절식혈액투과는 이중의 심정지 재발 및 내원 시의 산증, 폐부종을 더 많이 일으켰다. 심정지 재발은 무산소성 뇌손상의 가능성을 높이고 있으므로 소개해 주는 이유로, 이 연구에서는 심정지로 인한 뇌손상의 위험을 통제하기 위한 및 매개변수를 정의하였다. 심정지 재발은 이에 영향을 미치는 것으로 considere.14

셋째, 여러 가지 요인들이 소생술 이후의 결과에 영향을 준다. 일반인에 의한 CPR의 질 및 시기, EMS의 성격과 속련도, 응급실과 중환자실의 치료 등이 모두 생존과 기능적 예후의 중요한 직접적인 결정인자들이다.22

생존에 가장 영향을 미치는 요인은 응급처치의 시간과EMS의 성격과 속련도, 응급실과 중환자실의 치료 등이 모두 생존과 기능적 예후의 중요한 요소이다.”

따라서 연구진은 targetted temperature management (TTM) 시험에서 OHCA 이후 목표 체온을 33°C 또는 36°C로 설정하였으며.22

병원기반 냉각

기초의 임상시험은 병원기반으로 심부 채온 목표를 33°C에서 34°C로 설정하여 평균 12~24시간 동안 유지하였고 보통 정도의 저체온치료라고 불리었다.13,14 그러나 저체온법을 하지 않은 대조군에서 평균 33°C를 넘었고, 어떤 환자들은 ROSC 8~36시간 후에 차이가 있겠음. 심정지 후 저체온 연구에서 생존과 신경학적 예후가 좋은 것이 OHCA 이후 72시간 동안 정도의 저체온 유도는 유도의 치료적 효과 때문에가 아닌지 아니면 일?/고체온을 예방해서인지에 대해 몇 가지 궁금증을 야기하였다. OHCA로 혼수상태인 환자에서 불량한 예후가 심정지 이후 36~48시간 동안의 고체온 발생과 관련이 있기에 가정이 있다.26,27

따라서 연구진은 targetted temperature management (TTM) 시험에서 OHCA 이후 목표 체온을 33°C 또는 36°C로 하는 체온관리를 하였다.22 연구진은 939명의 OHCA 환자(80%는 VF)를 33°C (n=473)나 36°C(n=466)을 목표 체온으로 하는 병원기반의 냉각으로 무작위할당하였다. 이는 IIH가 가관적인 이점이 OHCA 이후 72시간 동안의 저체온 유도는 유도의 치료적 효과 때문이 아니면 일?/고체온을 예방해서인지에 대해 몇 가지 궁금증을 야기하였다. OHCA로 혼수상태인 환자에서 발생하였을 수 있다. OHCA 이후 72시간 동안의 고체온 발생과 관련이 있기에 가정이 있다.26,27

일차 결과는 모든 종류의 사망(50% 대 48%; P=0.51)과 이차 결과인 불량한 신경학적 기능 또는 사망(54% 대 52%; P=0.78)
은 임상시험 중료시(180일)까지 33°C군과 36°C군에서 서로 차이가 없었다. OHCA 소생술 이후 첫 36시간 동안 목표 심부체온은 33°C로 유지하는 것이 아니라, ROSC까지의 시간, 초기의 심박, 내원 시 속의 유무 등 여러 개의 아집단에서 사망의 HR를 보였을 때 어떤 것도 임상적으로 이득이 되는 방향으로의 경향을 보이지 못했다.

이런 결과를 바탕으로 저자들은 OHCA 이후 입원한 의식불명 환자에서 목표 체온을 33°C로 하는 것이 36°C보다 임상적 이득이 있다고 하는 것은 보여주는 증거가 현재는 없다고 결론 내렸다. 두 가지 저온의 전략에서 보이는 비슷한 임상적 이득에 대한 가설은 심정지 이후 첫 36시간 동안의 적극적 냉각조절 및 수동적 신론 상승 과정 후의 멸절 동안 고체온이나 열의 발생을 예방하는 것의 중요성과 관련이 있다.

하지만 TTM 시험에서 생존이나 신경학적 예후에서 차이가 없었던 것은 몇 가지 다른 설명이 존재한다. 먼저 TTM에 등록된 환자의 대부분은 심정지 시에 목적자가 있었고 심정지 발생 후 중간 간 1분 이내에 일반인이 CPR을 시작하였다. 그 자체로 환자들은 휴혈 및 재관류 손상을 덜 받았고 따라서 OHCA로 치료받은 평균적인 환자들보다 더 좋은 체온적인 예후를 나타낼 수 있었다. 이는 대조군과 중재군에서 모두 환자의 >75%에서 동공반사반사가 있었다는 관찰에 맞받침해 준다.30 다른 연구에서는 OHCA로 소생술을 한 환자의 약 20%에서 동공반사는 있었다고 보고했다.31,32 IH/TTM을 하면33,34,35 환자들은 저체온법을 한 환자에서 약물대사가 연장되는 것을 설명해 주지 않았다는 점이다.

환자들에게 예후를 평가하고 치료를 중단할 때 일정 기간 보류가 필요했던 52%; 예후 평가를 하기 전에 깨어나는 빈도가 더 적었다(44% 대 75%; P=0.03). TTM 시험의 장점은 참여하는 의사들이 등록된 환자들의 대부분은 심정지 시에 목격자가 있었고, 33°C군과 36°C군에서 생존에 차이가 없었던 것은 TTM 시험에서 부분적으로 양 군의 환자들이 양호한 간호적인 예후를 나타내었고 IH/TTM으로 효과를 보게 될 가능성은 더 높은 신경학적 또는 심장손상을 가졌기 때문일 수 있었다.

둘째, 36°C군에 비해 33°C군은 기계 호흡을 한 일수(중간값, 0.83 [0.67, 1.0] 대 0.76 [0.6, 1.0]; P=0.006)가 의미 있게 더 걸었고 예후 평가를 하기 전에 개통하는 빈도가 더 적었다(44% 대 52%; P=0.03). TTM 시험의 장점은 참여하는 의사들이 등록된 환자들에게 예후를 평가하고 치료를 중단할 때 일정 시간 간에 보류된 조직적인 접근을 했다는 점이다.36,37 불행히도 이런 접근은 심도의 저온체온법을 한 환자에게 악랄하게 해주는 것을 설명해 주지 못한다.38,39 TTM 시험에서 33°C군과 36°C군에서 기계 호흡의 기간이 더 길고 예후 평가 시에 의사의용인 바이어가 증가한 것 은 임상적 요구가 연장되어서 가능성이 상당히 있다.

세 번째로 TTM 시험에서 ROSC 이후 33°C 미만의 목표 체온에 도달할 때까지 걸린 시간의 추정치가 약 720분이었다. 이는 기존의 시험보다 길다(Table), 목표 체온에 도달하는데 시간이 오래 걸린 것은 임상적인 이득을 상쇄하였을 것이다.

마지막으로 TTM 시험에서 프로포폴을 혼합한 치료제로 사용하였다(TTM Investigators, unpublished data, 2014). 심장동맥 우회로조성술을 받은 환자에서 심장호흡의 효과를 본 임상시험에서 프로포폴은 재관류 손상에 대한 심장보호의 효과를 약화시켰다.34,35 재관류 방御에 대한 systematic review에서 프로포폴은 세포질라린(sevoflurane)보다 의미 있게 더 적은 심근하혈과 심근손상과 관련이 있었다.35 TTM 시험에서 프로포폴의 병용은 IH의 이득을 감소시켰을 가능성이 있다.

36°C은 정상적인 휴혈 약제에 가까워 36°C로 목표 체온을 맞추면 휴혈이 증가할 것이다.36,37 휴혈은 발생을 확실하게 증가시킨다.38,39 혈관내 병용 방법의 IH를 사용하면 피부 counterwarming을 이용해서 발생 및 휴혈억제를 찾을 수 있다.40,41 소수의 임상시험들 은 심정지 환자나 정상 환자에서 다른 방법보다 더 심장질환을 줄이는 약물학적 방법이 존재한다는 것을 보여주지 못했다.42,43,44,45,46,47,48,49 IH 중에 휴혈을 감소시키기 위해 혈관사용약물은 미세조용(microemulsion), 페나탈린(fentanyl), 탱스테로디민(dexamethasone), 창산아마네스, 메베릴린(merpeditine), 부스프린(buspirone) 등이 있다.

화물 뜨이기 위해 가끔 신경근육계내계(neuromuscular blocking agent, NMB)를 사용한다. 환인 급성 호흡곤란 증후군(acute respiratory distress syndrome)의 무작위시험에 대한 systematic review (n=431)에서 NMB 사용은 사용하지 않았을 때보다 사망률을 더 감소시켰음을 보여주었다.43,44,45,46,47,48,49 심정지 후 소생술을 한 환자에서 NMB (rocuronium)를 이용한 단일기간 무작위시험은 환자 동등을 끌었으나 결과를 보고하지 않았다.
(clinicaltrials.gov identifier NCT01683006). 심장지 환자에서 NMB의 사용을 지지하거나 반대하는 강력한 증거가 나오기 전까지 NMB의 종류 및 용량에 대한 선택은 의사의 재량에 맡긴다.

현재까지 종료된 무작위시험들은 다른 중재술을 병용하지 않고 IH만을 평가했다. IH는 심박출을 증가시키는 응급심폐부유지 (emergency cardiopulmonary support)의 사이토카인을 저하시키는 혈액액체로, 심혈관계를 증가시키는 효과를 나타낸다는 맬시노(xenon)과 같이 사용할 때 효과가 더 좋아진 가능성이 있다. 이런 복합 치료는 아직 연구단계이다.

결론
IH는 심장지 동물모델에서는 신경보호효과가 있으나 인간에서는 효과가 불확실하다. VF가 있던 없던 ROSC 이후 빠르게 냉각을 시키기 위해 EMS가 찬 정질액을 빨리 주사하는 것은 생존율을 증가시키지 못 한다. 심장지 중에 냉각을 하거나 수협량을 낮추는 냉각 방법이 현장에서 도움을 금치는 불명확하다. OHCA로 인해 소생술을 한 뒤에 혼수상태로 입원한 환자에서 IH를 한 초반의 임상시험은 대조군에 비해서 이득을 보였다. 33°C의 체온이 36°C과 비교해서 생존이나 신경학적 예후에 있어서 의미 있는 차이를 보이지 못한 것은 어느 수준의 체온이 최선이고 어떤 병합 요법이 필요한지에 대해 불확실성을 증가시킨다.

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Key Words: cardiac arrest ■ hypothermia ■ reperfusion injury