Topical Review

Section Editors: Kyra J. Becker, MD, and Emanuela Keller, MD

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 by bystander-witnessed ventricular fibrillation (VF). The most common cause of death among patients hospitalized after OHCA is neurological injury.2,3 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 2009.4 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.5

Rationale for Hypothermia

Reperfusion injury occurs in the brain6 and heart6 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,7 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.8 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 that9:

- 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).10 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.11 In another dog model, mild hypothermia during arrest significantly improved cerebral function as compared with normothermia, whereas IH 15 minutes after reperfusion did not.12 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.13,14 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...
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 used\textsuperscript{13}; 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\textsuperscript{15} in 2003. Rajek et al\textsuperscript{16} 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.\textsuperscript{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 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 3% 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 nearest 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 (PaO$_2$, 189±135 versus 218±144 mmHg; $P=0.001$), 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 al\textsuperscript{18,19} 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.\textsuperscript{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-a-renal,\textsuperscript{10} or immediately after ROSC.\textsuperscript{12} 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.\textsuperscript{12} 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.20 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 rearest 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 EMSSs, and care by emergency and intensive care units are all critical elements and direct determinants of survival and functional outcomes.22 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 al23 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.24 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.25

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.13,14 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.26,27

Therefore, investigators conducted the temperature management to a target of either 33°C or 36°C after OHCA targeted temperature management (TTM) trial.28 The investigators randomized a total of 939 patients with OHCA (n=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 neurological 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 awoken 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). Untill 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.
Sources of Funding

This study was supported by R01HL089554, National Heart Lung Blood Institute, Bethesda, MD (Drs Kim and Nichol).

Disclosures

Dr Nichol reports receiving research support from Philips Healthcare Inc, Andover, MA; Physio-Control Inc, Redmond, WA; and ZOLL Corporation, Chelmsford, MA; and serving as coprincipal investigator of the Velocity Pilot Study of Ultrafast Hypothermia in Patients with ST-segment-elevation myocardial infarction (Velomedix, Inc, Menlo Park, CA; waived personal compensation). The other authors report no conflicts.

References


51. Talpe P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. *Anesthesiology*. 1997;87:835–841.


**Key Words:** cardiac arrest ■ hypothermia ■ reperfusion injury
What Is the Use of Hypothermia for Neuroprotection After Out-of-Hospital Cardiac Arrest?
Francis Kim, Paco E. Bravo and Graham Nichol

*Stroke.* 2015;46:592-597; originally published online January 6, 2015;
doi: 10.1161/STROKEAHA.114.006975
*Stroke* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/2/592

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2016/04/07/STROKEAHA.114.006975.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Stroke* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to *Stroke* is online at:
http://stroke.ahajournals.org//subscriptions/
병원 밖에서 발생한 심정지(out-of-hospital cardiac arrest, OHCA)는 병원 밖에서 심장의 기계적 활동이 없어지고 혈액학적 허탈이 오는 것이다. 빨리 치료하지 않으면 OHCA는 필연적으로 사망으로 이어진다. 여러 지역사회에서 OHCA 발생 후에 퇴원 시까지 생존할 확률은 낮아서 심박에 무관하게 치료 받은 환자의 경우 10.7% (95% CI, 9.9%-11.5%)이며, 일반인이 목격한 심실세동(ventricular fibrillation, VF)으로 소생술을 받은 환자의 경우 31.7% (95% CI, 28.2%-35.1%)에 이른다.1 OHCA 이후 입원한 환자의 사망의 가장 흔한 원인은 신경학적 손상이다.2,3 이러한 해결되지 않은 문제에도 불구하고 치료 받은 환자의 원내사망률은 2001년의 69.6%에서 2009년의 57.8%로, 또한 최근에는 11.8%로 감소하고 있다.1 OHCA 이후 성공적으로 소생시켰으나 아직 흔발성환은 환자에 대한 집중치료 프로토콜 및 저체온치료의 도입이 부분적으로 예후의 호전과 관련이 있는 것으로 생각한다.4

저체온법의 원리

혈류가 돌아오는 동안 그리고 그 이후에 뇌와 심장에 재관류 손상이 생긴다. 이는 전염증성(proinflammatory) 및 항염증성 사이토카인이 분비되어 모세혈관관류(capillary perfusion) 악화, 조직 허혈, 미세순환기능이상(microcirculatory dysfunction) 등을 일으키는 것을 포함한다. 뒷 뒷 동안에는 심장 기능이 감소했다가 좋아진다. 이후 3일 동안 혈관 및 장의 투과성이 증가한다. 환자는 페혈증과 비슷한 혈액학적 상태가, 심장기능이상(multiple organ dysfunction), 사망 등을 겪을 수 있다. 재관류 손상의 정도는 혈류의 기간 및 소생술의 적절성과 관련이 있다. 다음에는 장기간의 약화가 재관류 손상의 정도와 관련이 있는지 정리한다.

허혈 중의 저체온은 허혈에 대한 재관류 순상의 치유를 증가한다. 재관류 이후 저체온법은 혈로운 글루타민산염(glutamate), 산소자유기(oxygen-free radical), 염증성 반응의 생성, 뇌산소 요구도, 두개내압, 신경학적 손상의 최종 정도 등을 감소시킨다.6 따라서 저체온 유도(induced hypothermia, IH)는 때로는 목표 체온관리(targeted temperature management)라고 불리는데 신경학적 손상과 다발 기관기능이상 등을 줄이기 위해 퇴원 이래로는 시도한 OHC4 환자에게 적응한다. 2010 Guidelines on Cardiopulmonary Resuscitation (CPR) and Emergency Cardiovascular Care는 다음과 같이 권유한다:7

전외 VF 심정지 이후 자연순환으로의 회복(restoration of spontaneous circulation, ROSC)이 온 혼수상태(예를 들면 구두 지시에 대한 의미 있는 반응이 없음)의 성인 환자는 32°C에서 34°C (89.6°F에서 93.2°F)로 12-24시간 냉각해야 한다(Class I, LOE B). 저체온 유도는 초기 심박무관해로 원내심정지 이후 또는 pulseless electric activity 또는 무수축(asystole)의 초기 심박명한 원외심정지 이후 ROSC가 온 혼수환자에서도 고려할 수 있다(Class IIb, LOE B). 이 연구의 중심의 근본은 OHCA가 있는 환자에서 IH의 효과를 본 최근의 임상시험의 간단에서 재평가하고 있다. 재평가가 나오기 전이므로 우리가 이 연구결과에서 IH의 사용에 대한 근거 중심의 최신 권고안을 제공해 보겠다.

초기 냉각

경도의 저체온법의 적절한 시기를 고려할 때 몇몇 동물실험은 초기에 냉각하는 것이 나중에 냉각하는 것보다 더 보호를 잘 한다는 것을 보여주었다. 생쥐모델에서 CPR 동안 냉각담보(cooling blanket)를 이용해 IH를 하는 것은 ROSC 이후에 IH를 하는 것보다 더 좋았다.10 VF 심장정지의 개 모델에서 CPR을 하는 동안 찬 생리식염수로 경도의 저체온법을 하는 것은 소생술 이후에 IH를 하는 것보다 생존율이 더 높았다.10 다른 개 모델에서 심정지 시에 경도의 저체온법을 하는 것에 대한 세부화 비교

From the Department of Medicine, Harborview Medical Center, University of Washington, Seattle.
Correspondence to Graham Nichol, MD, University of Washington-Harborview Center for Prehospital Emergency Care, PO Box 359727, 325 Ninth Ave, Seattle, WA 98104. E-mail nichol@uw.edu
© 2015 American Heart Association, Inc.
한 수액의 주사

OHCA 이후 소생한 환자에게 한 수액을 정맥주사하는 것은 현장에서 응급처치를 시작하는 적절한 시기에 중요한 의문점으로 남아있다. 한수액 주사 시에 보고된 결과들로는 심정지 시에 냉각을 하거나 ROSC 발생 후 15분 이내에 냉각을 하는 것이 신경학적 회복이 더 좋다는 것을 시사한다.

이런 동물실험들은 심정지 시에 냉각을 하거나 ROSC 발생 15분 이내에 냉각을 하는 것이 신경학적 회복이 더 좋다는 것을 시사한다. 12

사람에서 경도의 저체온법을 시작하는 적절한 시기는 중요한 의문점으로 남아있다. 사람에서 뇌기능을 의미 있게 호전시켰는데 재관류 15분 이후에 IH를 하는 것은 그렇지 못했다. 13,14

사람에서 경도의 저체온치료를 시작하는 적절한 시기는 중요한의문점으로 남아있다. 사람에서 소생술 완료 4-8시간 후에 IH를 하는 것은 정상 체온보다 신경학적 예후를 향상시켰다. 15

사람에서 경도의 저체온치료를 시작하는 적절한 시기는 중요한의문점으로 남아있다. 사람에서 소생술 완료 4-8시간 후에 IH를 하는 것은 정상 체온보다 신경학적 예후를 향상시켰다.

이러한 동물실험들은 심정지 시에 냉각을 하거나 ROSC 발생 15분 이내에 냉각을 하는 것이 신경학적 회복이 더 좋다는 것을 시사한다.

사람에서 경도의 저체온법을 시작하는 적절한 시기는 중요한의문점으로 남아있다. 사람에서 소생술 완료 4-8시간 후에 IH를 하는 것은 정상 체온보다 신경학적 예후를 향상시켰다.

사람에서 경도의 저체온치료를 시작하는 적절한 시기는 중요한의문점으로 남아있다. 사람에서 소생술 완료 4-8시간 후에 IH를 하는 것은 정상 체온보다 신경학적 예후를 향상시켰다.

사람에서 경도의 저체온치료를 시작하는 적절한 시기는 중요한의문점으로 남아있다. 사람에서 소생술 완료 4-8시간 후에 IH를 하는 것은 정상 체온보다 신경학적 예후를 향상시켰다.
송 중의 심정지 재발 보고는 양 군에서 의미 있는 차이가 없었다.

이런 임상시험의 결과들을 종합적으로 보면 VF 유무와 관계없이 ROSC 이후 냉각을 빨리 시작하기 위한 수단으로 EMS가 찬 정질액(crystalloid)을 빨리 주사하는 것이 유용하다고 뒷받침해 주는 증거는 없다. 과거에 다양한 심장정지동물모델을 이용한 실험연구에서 체온은 냉각을 빨리 시작하는 것이 양호한 결과를 가져왔던 것을 고려하면 이는 실망스러운 결과이다.11,12,20 이러한 연구결과는 실험실에서의 결과는 환자에서의 결과와는 다르다고 할 수 있다.

초기의 연구결과로는 심장정지 동물모델에서의 빠른 비침습적 저체온치료가 효과가 있는 것으로 보였지만, 이는 사람에게는 적용이 어려웠다.13,14 이것은 동물모델에서의 결과와 사람의 결과가 다르게 나타나는 것을 보여주고 있다.13,14 실험연구에서의 저체온치료 효과를 입증하기 위한 임상시험은 필요하다.

楨이나, 저체온치료에 대한 희망을 지지한 여러 연구결과는 많으나, 아직까지는 사람의 생명을 구하는 데 도움이 되는 효과가 없는 것으로 보여진다.15,16

소규모 임상시험에서의 저체온치료의 효과는 아직도 논의의 대상이지만, 치열한 논의가 이어지고 있다.17-19

병원기반 냉각

초기에 의상시험은 병원기반으로 실부 체온 목표를 35°C에서 33°C로 설정하여 평균 12-24시간 동안 유지하였고 보통 정도의 저체온치료라고 불리었다.13,14 그러나 저체온치료를 하지 않은 대조군에서 평균 37°C를 넘었고, 어떤 환자들은 ROSC 8-36시간 후에 심지어 발열이 있기도 하여 심정지 후의 저체온치료 시험은 비판을 받았다.14 이는 심장정지 후 저체온 연구에서 생존율과 신경학적 예후가 좋아진 것이 아니라, 비정상 체온이 원인이라 할 수 있다.13,14

따라서 연구진은 targeted temperature management(TTM) 시험에서 OHCA 이후 목표를 33°C 또는 36°C로 하여 체온관리를 하였다.20,21 연구진은 939명의 OHCA 환자(약 80%는 VF)를 33°C (n=473)나 36°C (n=466)를 목표 체온으로 하는 병원기반의 냉각으로 무작위할당하였는데 이는 찬 수액, 얼음찜질, 혈관내 또는 표면 장치를 이용하여 28시간 동안 유지한 후 점차 체온을 올려주었다.20,21 연구진은 939명의 OHCA 환자 중 90%가 36시간 이내에 사망하고, 이는 높은 사망률을 보였다.20,21

일차 결과인 모든 종류의 사망률(50% 대 48%; P=0.51)과 이차 결과인 불량한 신경학적 기능 또는 사망(54% 대 52%; P=0.78)
은 임상시험 종료시(180일)까지 33°C군과 36°C군에서 서로 차이가 없었다. OHCA 소생술 이후 첫 36시간 동안 목표심부체온은 33°C로 유지하는 것은 아니고, ROSC까지의 시간, 초기의 심박, 내원 시 숙의 유무 등 여러 개의 아집단에서 사망의 HR를 보았을 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 것을 보여주는 증거가 현재는 없다고 결론 내렸다. 두 가지 저온에 전략에서 보이는 비슷한 임상적 이득에 대해 가설은 심장지 이 후 첫 36시간 동안의 적극적 냉각중재 및 수동적 체온 상승 과정 후의 메릴 동안 고체온이나 열의 발생을 예방하는 것이 중요성과 관련이 있다.

다시 말하지만 TTM 시험에서 생존이나 신경학적 예후에서 차이가 없었던 것은 몇 가지 그림같은 실현이 존재한다. 먼저 TTM에 등록된 환자들의 대부분은 심장지 시에 목표가 있었고, 심장지 발생 후 중간 값 1분 이내에 발동인이 CPR를 시작하였다. 그 자체로 환자들은 혼합 및 재관류 손상을 덜 받았고 따라서 OHCA로 치료받은 평균적인 환자들보다 더 좋은 전체적인 예후를 나타낼 것이다. 이는 대조군과 중재군에서 모두 환자의 >75%에서 동공반응이 있었다는 관찰이 뒷받침해 준다.38 다른 연구에서는 OHCA로 소생술을 한 환자의 약 20%에서 동공반응이 있었다고 보고했다.39IH/TTM을 하기30,31 하지 않아32,33 동공반응의 존재는 앙호한 신경학적 예후를 예측하는 가장 강력한 인자 중에 하나이다. 33°C군과 36°C군에서 생존에 차이가 없었던 것은 TTM 시험에서 부분적으로 양 군의 환자들이 앙호한 천연적인 예후를 나타내었고IH/TTM로 효과를 보기는 불충분한 신경학적 또는 심장손상을 가졌기 때문일 수 있다.

둘째, 36°C군에 비해서 33°C군은 기계 호흡을 하였던 하루(중간 값, 0.83 [0.67, 1.0]) 때 0.76 [0.6, 10]; P=0.006)가 의미 있게 더 길었고 예후 평가를 하기 전에 개내는 빈도가 더 적었다(44% 대 52%; P=0.03). TTM 시험의 장점은 참여하는 의사들이 동록된 환자들에게 예후를 평가하고 치료를 중단할 때 일정 시간 보류된 조직적인 접근을 했다는 점이다.30 심호흡도 역시 이런 접근은 심도의 저체온법을 한 환자에서 약물대사가 연장되는 것을 예방해 주지 않는다는 것이다.35,36 TTM 시험에서 33°C군과 36°C군에서 기계 호흡이 더 길고 예후 평가 시에 의식불명이 비율이 증가한 것은 심장성의 대사가 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 혼합히 치료제로 사용하였다(TTM Investigators, unpublished data, 2014). 심장지에 우회로성맥을 받은 환자에서 심장보호의 효과를 본 임상시험에서 프로포폴은 재관류 손상에 대한 심장보호의 효과를 약화시켰다.34,35 AHA가 우회로 이식술을 받은 환자들(n=686)에 대한 무작위시험들에 대한 systematic review에서 프로포폴은 세포פש류란(sevoflurane)보다 의미 있게 더 적은 심근혼합과 심근손상과 관련이 있었다.39,40 TTM 시험에서 프로포폴의 복용은 IH의 이득을 감소시키는 가능성이 있다.

36°C는 정상적인 임상盼望에서 가깝기에 36°C로 목표 체온을 맞추면 임상이 증가할 것이다.36,37 맥락은 병원을 확실히 증가시킨다.38,39 이론적 방법의 IV를 사용하면 피부 counterwarming을 이용해서 병원 및 환경적 변경을 낮추기 수 있다.40,41 소수의 임상시험들은 심장지 환자나 정상 지원자에서 다른 방법보다 더 맥락을 줄이는 약물학적 방법이 존재한다는 것을 보여주지 못했다.42,43–51 IH 중에 맥락을 감소시키기 위해 혈중 사용하는 약은 마디로기(microlax), 벤자린(fentanyl), 메스테노디미덱(dexametomidine), 황산마그네슘, 메페리딘(meperidine), 부스피론(buspirone) 등이 있다.

맥락을 줄이기 위해 가끔 신경근육차단제(neuromuscular blocking agent, NMB)를 사용한다. 성인 급성 호흡곤란 중추군(acute respiratory distress syndrome)의 무작위시험에 대한 systematic review(n=433)에서 NMB 사용은 사용하지 않았을 때보다 사망률을 더 감소시켰음을 보여주었다.52 심장지 후 소생술을 한 환자에서 NMB (rocuronium)를 이용한 단일기관 무작위시험은 환자 동통 등을 끌어냈으나 결과를 보고하지 않았다.
결론

IH는 심장지동모델에서는 신경보호효과가 있으나 인간에서 는 효과가 불확실하다. VF가 있긴 없던 ROSC 이후 빠르게 냉각 을 시키기 위해 EMS가 찬 정제액을 빨리 주사하는 것은 생존율을 증가시키지 못 한다. 심장지 중후부 냉각을 하거나 수액량 낮 추는 냉각 방법이 현장에서 도움이 될지는 불분명하다. OHCA로 인해 소생술을 한 뒤에 혼수상태로 입원한 환자에서 IH를 한 초 기의 임상시험은 대조군에 비해서 이득을 보였다. 33°C의 체온이 36°C과 비교해서 생존이나 신경학적 예후에 있어서 의미 있는 차 이를 보이지 못한 것은 어느 수준의 체온이 최선이고 어떤 병합 요법이 필요한지에 대해 불확실성을 증가시킨다.

Sources of Funding
This study was supported by RO1HL089554, National Heart Lung Blood Institute, Bethesda, MD (Drs Kim and Nichol).

Disclosures
Dr Nichol reports receiving research support from Philips Healthcare Inc, Andover, MA; Physio-Control Inc, Redmond, WA; and ZOLL Corporation, Chelmsford, MA; and serving as coprincipal investigator of the Velocity Pilot Study of Ultrafast Hypothermia in Patients with ST-segment-elevation myocardial infarction (Velomedix, Inc, Menlo Park, CA; waived personal compensation). The other authors report no conflicts.

References


10.1213/01.ANE.0000180198.13467.DF.


51. Talke P, Tayefeh F, Sessler DI, Jeffrey R, Noursalehi M, Richardson C. Dexmedetomidine does not alter the sweating threshold, but comparably and linearly decreases the vasoconstriction and shivering thresholds. *Anesthesiology.* 1997;87:835–841.


---

Key Words: cardiac arrest ■ hypothermia ■ reperfusion injury