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STATE-OF-THE-ART PAPER

Hypothermia Therapy

Neurological and Cardiac Benefits

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Due to its protective effect on the brain and the myocardium, hypothermia therapy (HT) has been extensively studied in cardiac arrest patients with coma as well as in patients presenting with acute myocardial infarction (MI). In the setting of cardiac arrest, randomized studies have shown that HT decreases mortality and improves neurological outcomes. Subsequent guidelines have therefore recommended cooling (32°C to 34°C) for 12 to 24 h in unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest due to ventricular fibrillation. Observational studies have also confirmed the feasibility of this therapy in clinical practice and support its early application in patients with nonventricular fibrillation cardiac arrest and in post-resuscitation circulatory shock. In patients with acute MI, available clinical evidence does not yet support HT as the standard of care, because no study to date has shown a clear net benefit in such a cohort. After a brief review of the mechanisms of action for HT, we provide a review of the clinical evidence, cooling techniques, and potential adverse effects associated with HT in the setting of post-cardiac arrest patient and acute MI. (J Am Coll Cardiol 2012;59:197–210) © 2012 by the American College of Cardiology Foundation

Mild hypothermia therapy (HT), defined as body temperature between 32°C and 35°C, has been examined in a multitude of brain injury models, such as ischemic and hemorrhagic stroke, spinal cord injury, hepatic encephalopathy, traumatic brain injury, and neonatal hypoxic-ischemic encephalopathy. Randomized clinical trials (RCTs) in the setting of cardiac arrest (1,2) and neonatal hypoxic-ischemic encephalopathy (3–5) have in turn validated the clinical applicability of such therapy. Due to its potential myocardial protective properties, the role of HT might well extend beyond its neuroprotective properties in patients presenting with coma after a cardiac arrest to patients presenting with an acute myocardial infarction (MI).

Mechanisms of Action of Hypothermia

Neuroprotection. Experimental and clinical evidence have confirmed the neuroprotective effects of hypothermia. The mechanism(s) underlying the beneficial properties of HT are multifactorial and include reductions in the cerebral metabolism of glucose and oxygen consumption (6–8); pathways mediating accumulation of excito-toxic neurotransmitters, intracellular acidosis, and the influx of intracellular calcium and oxygen free radical production (9,10); alterations in the expression of "cold shock proteins" (10–12); reduction in brain edema (13,14); minimizing the risk of thrombosis; and reducing the risk of epileptic activities through electrical stabilizing properties (10).

Cardioprotection. A number of preclinical studies have demonstrated the beneficial effects of HT in reducing infarct size, with the greatest benefit being derived when the heart is cooled before reperfusion, thereby indicating a potential correlation between the degree of myocardial salvage and the myocardial temperature at the time of reperfusion (15–23). Although the mechanisms by which HT enhances myocardial protection have not been as thoroughly elucidated as in the brain, a number of potential explanations have been proposed. These include reducing the metabolic demand of the myocardium at risk (24), enhancing cellular membrane integrity through increased adenosine triphosphate preservation (24,25), enhancing mitochondrial membrane stability (26–29), and improvements in the myocardial microvasculature blood flow (22,30–32).

HT and Cardiac Arrest

Randomized controlled clinical trials. After observational clinical studies suggesting a beneficial effect for HT in survivors of cardiac arrest (33), 2 pivotal RCTs have provided the definitive evidence for such an efficacy (Table 1) (1,2). In the first study (1), HT was shown to be associated with improvements in neurological outcome and survival at 6 months in survivors of cardiac arrest due to ventricular fibrillation (VF) or pulseless ventricular tachycardia. In the second study (2), HT initiated in the ambulance was again found to be associated with improvements in neurological

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Abbreviations and Acronyms

HT = hypothermia therapy
MI = myocardial infarction
PCI = percutaneous coronary intervention
RCT = randomized clinical trials
ROSC = return of spontaneous circulation
STEMI = ST-segment elevation myocardial infarction
VF = ventricular fibrillation

outcome as compared with normothermia. A subsequent meta-analysis concluded that the number-needed-to-treat to allow 1 additional patient to leave the hospital with improvements in neurological outcome was 6 (95% confidence interval: 4 to 13) (34). The International Liaison Committee on Resuscitation recommended HT (32°C to 34°C for 12 to 24 h), on the basis of such results, in unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest when the initial rhythm is VF (class IIa). Cooling was also recommended for survivors of non-VF cardiac arrest patients (class IIb) (35,36). These recommendations have also been incorporated in the more recently published resuscitation guidelines (37,38).

Observational studies. The feasibility and favorable neurological outcomes associated with HT have also been confirmed in a multitude of observational studies (Table 2) (39–63). In a retrospective study of unselected comatose survivors of all rhythm cardiac arrest patients, Holzer et al. (46) demonstrated that HT was associated with better survival and improvements in neurological outcome at 1 month. The ERC HACA (European Resuscitation Council Hypothermia After Cardiac Arrest) registry of 650 comatose patients after all rhythm cardiac arrest has also confirmed that HT led to a higher discharge survival rate and improvements in neurological outcome (40). Similarly, the Hypothermia Network Registry of 986 all rhythm cardiac arrest patients also confirmed the clinical efficacy of HT in this cohort of patients (51).

HT in non-VF cardiac arrest. Although the feasibility of HT in non-VF cardiac arrest patients has been confirmed (53,64), no study to date has shown either a survival or a neurological benefit with HT in this cohort of patients (62,65). One potential reason for this observation might be the poor prognosis associated with asystole, regardless of the therapeutic measure undertaken (66).

HT in post-resuscitation circulatory shock. Animal data have suggested a beneficial effect of HT in cardiogenic shock mediated through modulations in inflammation, apoptosis, and remodeling (67,68). In humans, although post-resuscitation shock is a relatively frequent complication of cardiac arrest (66), such patients have been excluded from RCTs, and the results of observational studies have been hampered by variations used to define "shock" and lack of report on outcomes in this subset of patients (Table 2). In 2 retrospective studies focusing on patients presenting with post-resuscitation shock, HT did not adversely affect the expected outcome (47,61).

HT and emergency coronary intervention. Several observational studies have shown that combining HT with immediate coronary angiography ± percutaneous coronary intervention (PCI) is feasible and might improve the outcome of comatose patients who have been successfully resuscitated from cardiac arrest due to ST-segment elevation myocardial infarction (STEMI) (49,55,58,59). In 1 of the earliest studies to address this combination, Sunde et al. (58) showed an improvement in neurological outcomes and survival at discharge after implementation of a standardized post-resuscitation care protocol including HT. In a prospective study with historical control that included 72 comatose patients successfully resuscitated from VF related to STEMI and who needed primary PCI, Knafelj et al. (49) reported greater 6-month survival and improvements in neurological outcomes in patients receiving HT without adversely affecting the symptom-to-balloon time. Other studies have also demonstrated that implementing such a strategy does not adversely influence the door-to-balloon time (59).

HT and Acute MI

Animal models of MI have suggested that HT might be an effective method in reducing infarct size (15,17,69,70). In humans, several studies have examined HT as a novel method to reduce myocardial injury in patients with STEMI (Table 3) (71–76). Upon establishment of the feasibility of such therapy by Dixon et al. (71), the COOL-MI (Cooling as an Adjunctive Therapy to Percutaneous Intervention in Patients with Acute Myocardial Infarction) and ICE-IT (Intravascular Cooling Adjunctive to Percutaneous Coronary Intervention) trials (72,77) were designed to address whether or not HT could decrease infarct size as measured by single-photon emission computed tomography imaging at 30 days in the STEMI population. However, neither study demonstrated such a benefit—although in patients presenting with anterior STEMI and who had achieved a core temperature <35°C, a favorable trend was observed. Furthermore, a sub-analysis of the ERC HACA trial (78) failed to show any significant impact of HT on such parameters as creatine kinase, creatine kinase myocardial-band, or electrocardiogram evaluation. Interestingly, patients in the HT group with a shorter time to target temperature (≤8 h) had significantly reduced levels of creatine kinase and creatine kinase myocardial-band, suggesting that early cooling rather than its duration might be a critical factor in achieving infarct size reduction (15,17,22,23,69,70).

Both experimental and clinical studies seem to suggest that, in addition to early cooling, the optimal cardioprotective effects of hypothermia might be derived at core temperatures <35°C (15,22,23,72,77). Such a hypothesis has received additional support from Götberg et al. (76), who demonstrated, in patients undergoing primary PCI for STEMI, not only that a core body core temperature of <35°C could be achieved without delaying the door-to-balloon time but that it was also associated with a 38%

Table 1 Randomized Controlled Trials of Hypothermia Therapy in Cardiac Arrest

First Author (Ref. #)	Period of Inclusion Primary Endpoint Number of Patients, H vs. C	Initial Rhythm Hemodynamic Status at Inclusion (If Reported)	Method of Cooling	Target Temp/ Cooling Duration/ Rewarming Time	Favorable Neurological Outcome* H vs. C	Survival, H vs. C	Adverse Outcomes, H vs. C
HACA study 2002 (1)	Mar 1996–Jan 2001 Favorable neurological outcome within 6 months 136 vs. 137	VF/VT Evidence of hypotension >30 min after ROSC excluded	External cooling (including cooling mattress) Time from ROSC to <34°C: 8 h	32°C–34°C 24 h Passive ≈6 h	55% vs. 39% at 6 months, p = 0.009 OR: 1.40, 95% CI: 1.80–1.81	59% vs. 45% at 6 months, p = 0.02 OR: 1.35, 95% CI: 1.72–1.05	No difference
Bernard (2)	Sep 1996–Jun 1999 Favorable neurological outcome at discharge 43 vs. 34	VF Cardiogenic shock excluded	External cooling Passive cooling started in the field by paramedics Time from ROSC to 33.5°C: 2.5 h	33°C 12 h Active within 6 h	49% vs. 26% at discharge, p = 0.04 Adjusted OR: 5.25, 95% CI: 1.47–18.76	49% vs. 32% at discharge	No difference except lower cardiac index, higher systemic vascular resistance and more hyperglycemia in H group
Kim (84)	Nov 2004–Feb 2006 In the field H vs. C: Efficacy of in-field cooling to decrease the hospital arrival core temp 63 vs. 62	All rhythm Post-resuscitated hemodynamically unstable patients excluded	In the field: cold infusion after resuscitation Decrease in temp of 1.24°C in cold infusion vs. 0.1°C in control group, p < 0.01 In-hospital cooling rate differed in both groups	33°C 24 h if cooling was continued Unknown	—	33% vs. 29% at discharge VF: 66% vs. 45% at discharge Asystole/PEA: 6% vs. 20% at discharge	No difference
Castren PRINCE trial (96)	Nov 2008–Jan 2009 In the field H vs. C: Safety, feasibility and cooling efficacy of pre-hospital intra arrest cooling using intra-nasal cooling device 93 vs. 101	All rhythm	In the field: intranasal cooling system Time to target tympanic temperature of 34°C: 102 vs. 282 min, p = 0.03 Time to target core temperature of 34°C: 155 vs. 284 min, p = 0.13 Patients in both groups were cooled upon hospital arrival	Unknown	At discharge: 34% vs. 21%, p = 0.21 For CPR within 10 min, 43% vs. 18%, p = 0.03	At discharge: 44% vs. 31%, p = 0.26 For CPR within 10 min, 56% vs. 30%, p = 0.04	18 device-related adverse events: Nasal discoloration: n = 13 Epistaxis: n = 3 Peri-oral bleeding: n = 1 Peri-orbital emphysema: n = 1

*Favorable neurological outcome was defined by a Cerebral Performance Categories scale of 1 (good recovery) or 2 (moderate disability) in the HACA (Hypothermia After Cardiac Arrest) study, by discharge home or to a rehabilitation facility in the Bernard et al. (2) study, and by the neurologically intact survival for the PRINCE (Pre-ROSC IntraNasal Cooling Effectiveness) trial.

C = control subjects; CI = confidence interval; CPR = cardiopulmonary resuscitation; H = hypothermia; m = months; MI = myocardial infarction; OR = odds ratio; PEA = pulseless electrical activity; ROSC = recuperation of spontaneous circulation; temp = temperature; VF = ventricular fibrillation; VT = ventricular tachycardia.

Table 2 Nonrandomized Clinical Studies of Hypothermia Therapy in Cardiac Arrest

First Author (Ref. #)	Study Type Period of Inclusion Number of Patients H vs. C	Initial Rhythm, H vs. C Hemodynamic Status at Inclusion (If Reported), H vs. C	Method of Cooling	Target Temp/ Cooling Duration	Favorable Neurological Outcome* H vs. C	Survival H vs. C	Adverse Outcomes H vs. C
Al-Senani (39)	Prospective (no control) Mar 2001–Sep 2002 13	Unknown	ECD	33°C 24 h	38% at 30 days	70% at 30 days	—
Kliegel (48)	Prospective (no control) Jun 2003–Apr 2004 26	Unknown Cardiogenic shock excluded	Cold infusion + ECD	33°C 24 h	50% at 6 months	54% at 6 months	—
Holzer (46)	Retrospective Aug 1991–Nov 2004 97 vs. 941	VF: 71% vs. 46%	ECD ± cold infusion	33°C 24 h	53% vs. 34% at 30 days, $p < 0.001$ Adjusted OR: 2.56, 95% CI: 1.57–4.17	69% vs. 50% at 30 days, $p < 0.001$ Adjusted OR: 1.96, 95% CI: 1.19–3.23	No difference except for bradycardia: 15% vs. 3%, $p = 0.025$
Oddo (53)	Retrospective H = Jun 2002–Dec 2004 C = Jun 1999–May 2002 55 vs. 54	VF: 77% vs. 80% Asys/PEA: 23% vs. 20% Shock on admission: 31% vs. 26%	ExC (including cooling mattress)	33°C 24 h	At discharge: Overall population: 47% vs. 20% VF group: 56% vs. 26%, $p < 0.01$ Non-VF group: 17% vs. 0%, $p = NS$ Cardiogenic shock on admission: 29% vs. 0%, $p = 0.03$	At discharge Overall population: 51% vs. 33% VF group: 60% vs. 44%, $p = 0.28$ Non-VF group: 17% vs. 9%, $p = NS$ Cardiogenic shock on admission: 29% vs. 21%, $p = NS$	No difference
Busch (44)	Retrospective H = Jun 2002–Nov 2003 C = Jan 2001–Jun 2002 27 vs. 34	VF: 74% vs. 62% Cardiogenic shock excluded	ExC	33°C 12–24 h (≈10 h)	41% vs. 26% at discharge, $p = 0.21$	59% vs. 32% at discharge, $p = 0.05$	No difference except for hypokalemia: 81% vs. 33%, $p < 0.01$ and insulin resistance: 19% vs. 0%, $p = 0.02$
Scott (56)	Prospective (no control) Aug 2003–Sep 2005 49	Unknown	Cold infusion + ExC (± garment-type cooling device)	33°C 24–36 h	33% at discharge	39% at discharge	—
Haugk (45)	Prospective (no control) Jul 2004–Aug 2005 27	Unknown Patients with hypotension excluded	ExC (including garment-type cooling device)	33°C 24 h	33% at 6 months	52% at 6 months	—
Arrich (40)	Prospective/control subjects in same period May 2003–Jun 2005 462 vs. 123	VF/VT: 68% vs. 37% Asys/PEA: 27% vs. 59%	ECD (75%) Or ExC (including cooling blanket) + cold infusion (25%)	33°C 24 h	Overall population: 45% vs. 32% at discharge, $p = 0.02$ Non-VF group: 19% vs. 19% at discharge, $p = 0.98$	Overall population: 57% vs. 32% at discharge, $p < 0.01$ Non-VF group: 35% vs. 19% at discharge, $p = 0.02$	—
Sunde (58)	Prospective/historic control subjects IG† vs. C IG = Sep 2003–May 2005 C = Feb 1996–Feb 1998 58 vs. 61	VF: 90% vs. 84% Comatose after cardiac arrest: 85% vs. 90%, Only 40 in 52 comatose patients was cooled in IG	ECD and/or ExC (including garment-type cooling device) + cold infusion	33°C 24 h	56% vs. 26% at discharge, $p < 0.01$	56% vs. 31% at discharge, $p < 0.01$ Same at 1 year	No difference

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Table 2 Continued

First Author (Ref. #)	Study Type Period of Inclusion Number of Patients H vs. C	Initial Rhythm, H vs. C Hemodynamic Status at Inclusion (If Reported), H vs. C	Method of Cooling	Target Temp/ Cooling Duration	Favorable Neurological Outcome* H vs. C	Survival H vs. C	Adverse Outcomes H vs. C
Laish-Farkash (50)	Prospective (no control) Feb 2002–Sep 2006 51	VF Cardiogenic shock excluded	ExC (including garment-type cooling device) ± cold infusion	32°C–34°C 24 h	61% at discharge	63% at discharge	—
Hovdenes (47)	Retrospective (no control) Apr 2003–Apr 2005 50 Comparison IABP (n = 23) vs. no IABP (n = 27)	VF Shock on admission: 74% IABP: 46%	ExC (including garment-type cooling device) ± cold infusion	32°C–34°C 24 h	68% at 6 months Comparison IABP vs. no IABP: 61% vs. 74%, p = NS	82% at 6 months Comparison IABP vs. no IABP: 74% vs. 89%, p = 0.17	—
Belliard (42)	Prospective/historic control subjects H = Jan 2003–Dec 2005 C = Jan 2000–Dec 2002 32 vs. 36	VF Hypotension after resuscitation: 34% vs. 22%	ExC	32°C–34°C 24–48 h	41% vs. 17% at discharge, p = 0.02	56% vs. 36% at discharge, p = 0.04	No difference
Knafelj (49)	Prospective/historical control subjects H = Nov 2003–Dec 2005 C = Jan 2000–Oct 2003 40 vs. 32	VF related to STEMI who needed PPCI	Cold infusion + ExC	32°C–34°C 24 h	55% vs. 16% at discharge, p < 0.01 Same at 6 months	75% vs. 44% at discharge, p < 0.01 Same at 6 months	More positive tracheal aspiration in H group (93% vs. 72%, p = 0.04) Trend to more antimicrobial treatment (90% vs. 72%, p = 0.07)
Oksanen (54)	Prospective 2004–2005 407	VT/VF	ExC or ECD or both methods	Unknown	—	55% at 6 months	—
Wolfrum (59)	Prospective/historical control subjects H = 2003–2004 C = 2005–2006 16 vs. 17	Rhythm unknown but cardiac arrest due to STEMI who needed PPCI	ExC (including cooling mattress) + cold infusion	32°C–34°C 24 h	69% vs. 47% at 6 months, p = 0.30	75% vs. 65% at 6 months, p = 0.71	Trend toward more overall bleeding in H group: 56% vs. 24%, p = 0.08 More transfusions in H group: 38% vs. 6%, p = 0.04 More infections: 62% vs. 24%, p = 0.04
Oddo (52)	Prospective (no control) Dec 2004–Oct 2006 74	VF: 51% Asys/PEA: 49% Post-resuscitation shock: 46% Cardiogenic shock: 14%	ExC (including cooling mattress)	33°C 24 h	32% at discharge VF group: 55% Non-VF group: 8.3% Post-resuscitation shock: 26%	39% at discharge VF group: 60% Non-VF group: 17% Post-resuscitation shock: 35%	—

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Table 2 Continued

First Author (Ref. #)	Study Type Period of Inclusion Number of Patients H vs. C	Initial Rhythm, H vs. C Hemodynamic Status at Inclusion (Ff Reported), H vs. C	Method of Cooling	Target Temp/ Cooling Duration	Favorable Neurological Outcome* H vs. C	Survival H vs. C	Adverse Outcomes H vs. C
Storm (63)	Retrospective/historical control subjects H = Jan 2006–Jan 2007 C = 2003–2005 52 vs. 74	VF/VT: 65% vs. 58% Asys/PEA: 35% vs. 42%	Cold infusion +ExC (including garment-type cooling device)	33°C 24 h	61% vs. 23% at discharge, $p < 0.01$	At discharge: 71% vs. 58%, $p = 0.19$ At 1 yr: 55% vs. 31%, $p = 0.013$	No difference
Schefold (55)	Prospective/historical control subjects H = Dec 2005–Dec 2006 C = 2002 to 2005 31 vs. 31	All rhythm due to acute MI VF: 81% vs. 81% Asys/PEA: 19% vs. 19%	ExC (including cooling blanket) + cold infusion	33°C 24 h	61% vs. 19% at discharge, $p < 0.01$	68% vs. 68% at discharge, $p = NS$	No difference
Bro-Jeppesen (43)	Prospective/historical control subjects H = Jun 2004–May 2006 C = Jun 2002–May 2004 79 vs. 77	VT/VF: 66% vs. 73%	ExC (including garment-type cooling device) + cold infusion	33°C 24 h	In VT/VF patients: 63% vs. 48% at discharge	In VT/VF patients: 65% vs. 68% at discharge 57% vs. 56% at 30 months	Bradycardia, recurrent VT more common in H group
Nielsen (51)	Prospective (no control) Oct 2004–Oct 2008 986	VT/VF: 70% Asys/PEA: 29% Cardiogenic shock: 18% Intra-aortic balloon pump: 12%	ExC (± device) and/or cold infusion and/or ECD	33°C 24 h	44% at discharge VT/VF: 53% Asys/PEA: 22% 46% at 6–12 months VT/VF: 56% Asys/PEA: 22%	56% at discharge VT/VF: 67% Asys/PEA: 30% 46% at 6–12 months VT/VF: 61% Asys/PEA: 25%	—
Ferreira (60)	Retrospective/historical control subjects H = Jan–Sep 2005 C = Oct–Dec 2006 9 vs. 26	VT/VF: 96% vs. 94% Asys: 4% vs. 6% Shock under supporting measures excluded	ExC (n = 25) Oct–Feb 2006 or ECD (n = 24) Mar–Dec 2006	33°C 24 h	51% vs. 19% at discharge, $p < 0.01$ No difference between 2 cooling methods	67% vs. 42% at discharge, $p = 0.04$ No difference between 2 cooling methods	—
Don (62)	Retrospective/historical control subjects H = Nov 2002–Dec 2004 C = Jan 2000–Nov 2002 204 vs. 287	VT/VF: 39% vs. 32% Asys/PEA: 60% vs. 66%	ExC (including cooling blanket or garment-type cooling device)	32°C–34°C 24 h	VT/VF: 35% vs. 15% at discharge, $p < 0.01$ Adjusted OR: 2.62, 95% CI: 1.10–6.27 Asys/PEA: 11% vs. 9% at discharge, $p = 0.44$ Adjusted OR: 0.92, 95% CI: 0.37–2.32	VF group: 54% vs. 39% at discharge, $p = 0.04$ Adjusted OR: 1.71, 95% CI: 0.85–3.46 Non-VF group: 21% vs. 19% at discharge, $p = 0.65$ Adjusted OR: 0.82, 95% CI: 0.41–1.60	—
Skulec (61)	Retrospective Nov 2002–Nov 2006 56 Comparison shock (n = 28) vs. no shock (n = 28):	VF: 60% Asys/PEA: 36% Cardiogenic shock: 50%	ExC + cold infusion	33°C 12 h	Overall population: 53% Shock vs. no shock: anytime during hospital stay: 68% vs. 82%, $p = 0.35$, at discharge: 39% vs. 71%, $p = 0.031$	Overall population: 62% Shock vs. no shock: 43% vs. 79% at discharge, $p = 0.013$	No difference between shock and no shock in terms of major bleeding, infection and malignant arrhythmia

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Table 2 Continued

First Author (Ref. #)	Study Type Period of Inclusion Number of Patients H vs. C	Initial Rhythm, H vs. C Hemodynamic Status at Inclusion (If Reported), H vs. C	Method of Cooling	Target Temp/ Cooling Duration	Favorable Neurological Outcome* H vs. C	Survival H vs. C	Adverse Outcomes H vs. C
Batista (41)	Retrospective H = 2002–2009 90 Comparison PCI (n = 20) vs. no PCI (n = 70)	VF/VT: 47% Asys/PEA: 53% Shock on admission: 24%	ExC (± device)	32°C–34°C 24 h	24% at discharge	29% at discharge VT/VF: 37% PEA/Asys: 22% Comparison PCI vs. no PCI: 60% vs. 70%, p = 0.4	No difference between PCI and no PCI group in terms of arrhythmia
Storm (57)	Retrospective/historical control subjects H = 2005–2007 C = 2002–2004 107 vs. 98	Rhythm unknown	ExC (including garment-type cooling device)	Unknown 24 h	60% vs. 24% at discharge, p < 0.01	55% vs. 34% at 2 yrs, p = 0.03 Adjusted HR: 1.43, 95% CI: 2.2–1.04	—
Dumas (65)	Prospective/control subjects in same period Jan 2000–Dec 2009 718 vs. 427	VF/VT: 63% vs. 59% Asys/PEA: 36% vs. 41% Post-resuscitation shock: 37%	ExC (forced cold air)	32°C–34°C 24 h	VF/VT: 44% vs. 29% at discharge, p < 0.001 Adjusted OR: 1.90, 95% CI: 1.18–3.06 Asys/PEA: 15% vs. 17% at discharge, p = 0.48 Adjusted OR: 0.71, 95% CI: 0.37–1.36	—	VT/VF: More infections in H group: 60% vs. 44%, p < 0.001 Asys/PEA: More infections in H group: 57% vs. 39%, p < 0.001

All patients were reported comatose after successful resuscitation from cardiac arrest, apart from Sundle 2007, who included patients with sustained ROSC in the emergency department (ED) after out-of-hospital cardiac arrest of cardiac etiology with or without coma. *Neurological function were assessed by those Cerebral Performance Categories scale (favorable neurological outcome = Cerebral Performance Categories scale 1 [good recovery] or 2 [moderate disability]) except for 5 studies, which used Glasgow outcome score (Al-Senami et al., Belliard et al.), Glasgow outcome coma scale (Scott et al.), modified Rankin Scale (Batista et al.), and their own neurological outcome scale (Don et al.). †Protocol including: hypothermia therapy; percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI); and controls of hemodynamic status, blood glucose, ventilation, and seizures.

Asys = asystole; ECD = endovascular cooling device; ExC = external cooling device; HR = hazard ratio; IABP = intra-aortic balloon pump; IG = intervention group; MAP = mean arterial pressure; PPCI = primary percutaneous coronary intervention; SBP = systolic blood pressure; other abbreviations as in Table 1.

Table 3 Clinical Studies of Hypothermia Therapy in Patients With STEMI

First Author (Ref. #)	Study Type Period of Inclusion Number of Patients H vs. C	Indications	Method of Cooling	Target Temp/ Cooling Duration	Outcomes H vs. C	Adverse Outcomes H vs. C
Dixon COOL-MI Pilot (71)	RCT, primary endpoint: MACE (death, re-MI, TVR) Feb–Jul 2001 21 vs. 21	STEMI <6 h from the symptom onset/PPCI Awake patients	Endovascular cooling device started in cath lab or ED Shivering suppressed by skin warming, oral buspirone, and IV meperidine	33°C 3 h after reperfusion	MACE at 30 days: 0% vs. 10%, p = NS SPECT infarct size at 30 days: 2% vs. 8% of LV, p = 0.8	No difference
O'Neill COOL-MI trial TCT (77) (abstract)	RCT, primary endpoint: SPECT infarct size 177 vs. 180	STEMI <6 h from the symptom onset/PPCI Awake patients	Endovascular cooling device started in cath lab or ED Shivering suppressed by skin warming, oral buspirone, and IV meperidine	33°C 3 h	Infarct size at 30 days: 17.9% vs. 19.2% of LV, p = 0.92 MACE (death, re-MI, TVR) at 30 days: 6.2% vs. 3.9%, p = 0.45 In anterior MI with temp <35°C at reperfusion, infarct size: 9.3% vs. 18.2%, p = 0.05	More incidence of shock in the H group Trend toward higher rate of vascular bleeding, deep venous thrombosis, and pulmonary edema in H group
Grines ICE-IT TCT (72) (abstract)	RCT, primary endpoint: SPECT infarct size 114 vs. 114	STEMI <6 h from the symptom onset/PPCI Awake patients	Endovascular cooling device started in cath lab or ED	33°C 6 h	Infarct size at 30 days: 13.5% vs. 14.2%, p = 0.77 MACE (death, re-MI, stroke, severe CHF, cardiogenic shock) at 1 yr: 13.7% vs. 10%, p = 0.53 In anterior MI with temp <35°C at reperfusion, infarct size: 12.9% vs. 22.7%, p = 0.09	Trend toward higher rate of "any general adverse effect"
Kandzari LOWTEMP study (75)	Prospective/no control Oct 2002–Apr 2003 18	STEMI <6 h from the symptom onset/PPCI Awake patients	Endovascular cooling device Shivering suppressed by oral buspirone and/or IV meperidine ± skin warming	32 to 34°C ≈ 6 h	SPECT infarct size at 30 days: 4% of LV	—
Ly NICAMI study (74)	Prospective/no control Mar–Sep 2003 9	STEMI <6 h from the symptom onset/PPCI Awake patients	External cooling (garment-type cooling device) Shivering suppressed by IV meperidine	34.5°C 3 h at target	SPECT infarct size at 30 days: 23% of LV	—
Götberg RAPID-MI-ICE trial (76)	RCT, primary endpoint: safety and feasibility of inducing hypothermia therapy before reperfusion Mar–Oct 2009 9 vs. 9	STEMI <6 h from the symptom onset/PPCI Awake patients	Cold infusion and endovascular cooling device started in cath lab Shivering suppressed by skin warming, oral buspirone, and IV meperidine	33°C 3 h	Door-to-balloon time 43 vs. 40 min, p = 0.12 Infarct size normalized to myocardium at risk assessed by cardiac magnetic resonance at 4 days: 29.8% vs. 48.0%, p = 0.041	No difference

AUC = area under the curve; cath = catheterization; CHF = cardiac heart failure; CK = creatinine kinase; LV = left ventricle; MACE = major adverse cardiac event(s); RCT = randomized control trial; SPECT = single-photon emission computed tomography; TVR = target vessel revascularization; other abbreviations as in Tables 1 and 2.

reduction in the infarct size as assessed by cardiac magnetic resonance imaging (CMRI). Although relatively small in sample size, this was the first such study demonstrating a beneficial effect of HT in this population. The achievement of a body core temperature <35°C and the use of CMRI, currently the "gold-standard" for infarct assessment (79–81), have been proposed as potential explanations for the observed benefits. In contrast to single-photon emission computed tomography, which has been used in the majority of the aforementioned studies, CMRI has the advantage that it provides information not only on geometrical information such as ventricular volume but also segmental wall motion abnormalities and left ventricular function as well as remodeling.

However, despite such encouraging results, the optimal method and timing of HT in the STEMI population would

require an adequately powered RCT, and until such data become available, the utility of HT will remain conjectural and cannot be recommended in routine, daily clinical practice for this cohort of patients.

Cooling Techniques

The currently available cooling methods have been largely developed in the setting of post-cardiac arrest comatose survivors and are detailed in the following text (82–96).

Cold infusion. The infusion of cold fluid has been shown to be an effective technique to cool patients, especially for the induction phase, rendering it a readily accessible strategy in an out-of-hospital environment. Different protocols have been proposed, such as the infusion of 30 ml/kg of ice-cold (4°C) lactated Ringers solution intravenously over 30 min (83) or the use of 500 to 2,000 ml of 4°C normal saline as soon as possible after resuscitation (84). The latter protocol has been validated in an RCT showing that cold infusion initiated in the field is effective in lowering arrival hospital temperature without adverse consequences in terms of blood pressure, heart rate, arterial oxygenation, risk of pulmonary edema or re-arrest (84). Although the cold fluid intravenous infusion seemed to be effective, safe, and quick to induce HT, it does not seem sufficient to be used alone for the maintenance phase of HT and needs the additional use of either external cooling techniques or endovascular cooling devices (85,86).

External cooling techniques. External cooling therapy is a simple, inexpensive, easy-to-implement technique achieved with the application of ice packs to the groin, torso, axillae, and neck and/or ice water-soaked towels and fanning. This method can be considered for both the induction and maintenance phases in the intensive care unit but suffers from the inability to control the rate of de-cooling as well as the extreme vigilance and experience required to prevent over-cooling (87). A number of commercially available cooling devices are now available, including cooling mattresses, air-filled or water circulating cooling blankets, and garment-type surface cooling devices (88). In addition to a tight thermoregulatory capacity, these devices have the distinct advantage of reducing the risk of over-cooling during the induction phase, but they are expensive and associated with rare adverse skin reactions (skin erythema and mottling underneath the cooling pads) (89).

Non-cold infusion endovascular cooling techniques. Initially developed to cool non-intubated awake patients, to decrease cold discomfort and shivering, this method has been used in the post-cardiac arrest setting over the last few years (71,75). 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 (90). As a consequence, the device allows the rapid and accurate establishment of the target temperature, is effective in maintaining a stable temperature after induction, and allows an efficient control of the re-warming phase (60,91–93). The main drawbacks limiting the routine use of this technique are the requirement for central venous cannulation, venous thrombosis, infection, and the cost of the device. Furthermore, the U.S. Food and Drug Administration has also requested additional data from adequately powered RCTs before recommending this device in inducing mild hypothermia in comatose survivors of cardiac arrest (brief Summary from the Circulatory System Devices Panel Meeting, March 17, 2005). Although it is likely that the various cooling techniques exert a class effect, this can only be addressed in an RCT, but whether this can be achieved in the current financial turmoil remains to be determined.

Novel cooling techniques and devices. A number of novel noninvasive cooling techniques have been proposed as alternatives to the more conventional techniques that are currently available. These include iced saline gastric lavage (94), cooling helmets (64), a total cold water immersion system (95), as well as a trans-nasal cooling device (96) that allows rapid induction of hypothermia to a core temperature of 34°C. More novel cooling techniques are also being considered in such studies as the CHILL-MI (Efficacy of Endovascular Catheter Cooling Combined With Cold Saline for the Treatment of Acute Myocardial Infarction) trial sponsored by Philips Innercool.

Establishment of HT

The establishment of HT can be divided into 3 steps: induction, maintenance, and re-warming phase (Fig. 1).

Complications of HT and Its Management

Hypothermia therapy is associated with a number of common physiological changes and potential complications (Table 4) (10,88).

Shivering. Shivering is a natural physiological response to hypothermia and can impede both the induction and maintenance phases of HT by generating heat and increasing the oxygen consumption and metabolic demands of tissues (97). After peripheral vasoconstriction, shivering seems to be the "last resort" response against cold as the core temperature falls below 35.5°C.

Numerous pharmacological strategies have been developed to counteract such a response (90). In the post-cardiac arrest setting, a widely adopted combination is that of benzodiazepines for sedation, opioid analgesic, and systemic neuromuscular blockade for muscle relaxation (2). By contrast, the combination of meperidine (± buspirone) and skin warming to reduce the shivering threshold and avoid

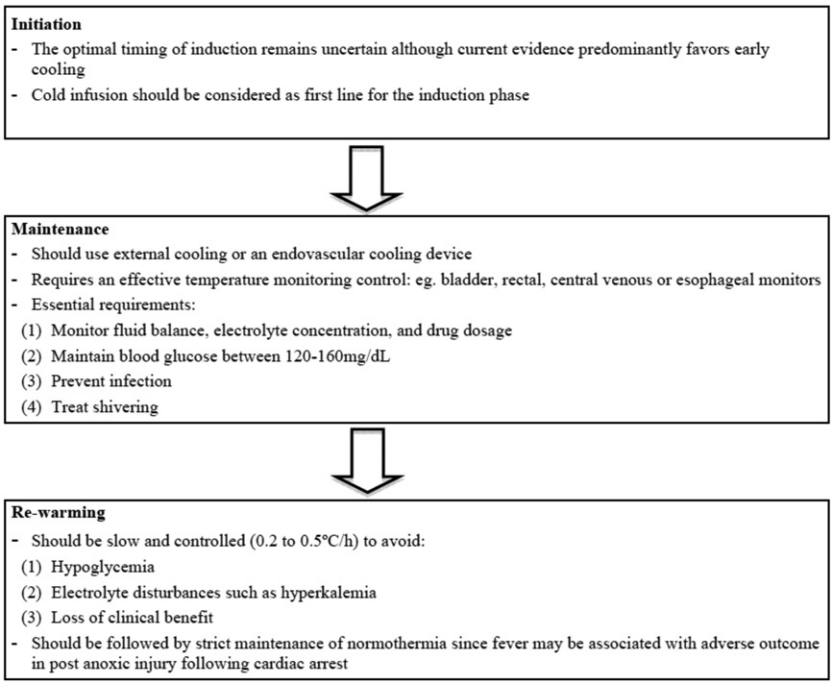

Figure 1 Hypothermia Therapy Flow Chart

thermal discomfort has become the standard of care in awake patients (71,74–77).

Cardiovascular manifestations of HT. The cardiovascular effects of hypothermia are complex and have been summarized in Table 4 (10,88). After the induction phase, HT might be accompanied by bradycardia and an increase in myocardial contractility (88,98). This reduction in heart rate might in turn give rise to a reduction in cardiac output, although this is not sufficiently severe enough to lead to hemodynamic compromise (10,88). At this stage, the hypothermia-induced vasoconstriction of peripheral arteries and arterioles might increase the systemic vascular resistance and lead to a slight increase in the arterial pressure (88,99,100). However, cardiac arrest patients who have been cooled also develop a hypotensive response as a consequence of the "post-cardiac arrest syndrome," which is characterized by myocardial dysfunction, a systemic ischemia-reperfusion response, as well as a systemic inflammatory response (66). Furthermore, such a hypotensive response might be further exacerbated by the underlying cause of cardiac arrest, such as MI, ventricular arrhythmia, and the "cold diuresis" that can accompany HT through several mechanisms, such as increased venous return due to peripheral vasoconstriction, misbalance in diuretic hormones, and tubular dysfunction (10). Although HT has not been associated with the development of arrhythmia in RCTs or in observational studies, persistent arrhythmia can develop as a consequence of over-cooling (≤32°), electrolyte imbalance, or tubular dysfunction (10).

Infection. Although HT might increase the rate of infection as a consequence of hypothermia-induced impairment of cellular and humoral immunity (101), the message from clinical studies does not provide a uniform answer as to whether this hypothetical risk is of clinical significance. Several studies have indicated an increased clinical risk (46,59), whereas others have refuted such findings (53,58,102).

Bleeding. Hypothermia might result in an increased risk of bleeding as a result of impaired platelet function, thrombopenia, and impairment of the coagulation cascade (88). However, such risks have not been observed in clinical practice when HT has been used in isolation or in combination with PCI.

Alterations in drug metabolism. Hypothermia leads to a slowing of a number of hepatic enzymes including the cytochrome P450. Therefore, drugs that are metabolized by the liver, such as sedative and neuromuscular blocking agents, will require dose modification (103).

Conclusions

Hypothermia therapy should be considered, on the basis of current evidence, as the standard of care in post-cardiac arrest patients irrespective of the initial rhythm as recommended by the guidelines. However, many unanswered questions remain, such as the optimal duration of hypothermia, depth of cooling, rate of re-warming, best cooling method, and cost effectiveness. In patients presenting with

Table 4 Common Physiological Changes Occurring During Hypothermia

Body Systems	Physiological Changes	Medical Treatment
Cutaneous and muscular	Cutaneous vasoconstriction, Shivering (≤35°C–30°C)	Prevent bedsores Prevent and treated shivering (pharmacologic treatment ± skin warming in awake patients)
Cardiovascular		
HR	Tachycardia (≥36→35°C, briefly for induction): related to the increase in venous return to the heart caused by a shift in circulatory volume from peripheral to core compartment, leading to a reflex increase in HR might be exacerbated when patient is not sedated enough and/or shivering response not overcome Bradycardia (≤35°C): further pronounced as core temperature drop (at 33°C, normal HR will be 45 to 55 beats/min) caused by a decrease in the rate of diastolic repolarization in the cells of the sinus node as well as prolongation of the duration of action potentials and a mild decrease in the speed of myocardial impulse conduction Slight hypertension (≤34°C, ≈10 mm Hg more): due to hypothermia-induced vasoconstriction of peripheral arteries and arterioles Association with hypotension due to: hypovelemia related to "cold diuresis" post-cardiac arrest syndrome and its systemic inflammatory response	None unless symptomatic
Blood pressure	Primary cardiac cause	Wean vasopressors, administer analgesics and sedation if needed
	Increase when HR decreased (mild HT)	Avoiding or correcting hypovolemia by fluid administration
	Decrease when temp <30°C or artificial HR increased (chronotropic drugs or pacing)	± Vasopressors
	Decrease in cardiac output (≤35°C) in relation with HR decrease	± Etiologic treatment
	Increase central venous pressure (≤35°C)	Prevent overcooling and avoid excessive heart stimulation
Myocardial contractility	Mild arrhythmia in some patients (≤32°C) Tachyarrhythmias beginning by atrial fibrillation (≤28°C–30°C)	None unless symptomatic or hypotensive
Cardiac output	Prolonged PR, QRS, and QT intervals (≤33°C)	
	Rare Osborne's J waves in mild hypothermia	
Arrhythmia		Prevent overcooling and electrolytes disorders
		Re-warm slowly to avoid hyperkalemia in rewarming phase
ECG changes		None
Immunologic	Impaired neutrophil function, suppression of pro-inflammatory mediator release (≤35°C)	Take measure to prevent infection (especially pneumonia); antibiotic prophylaxis
	Leukopenia and impaired leukocyte function (≤33°C)	
Hematologic	Thrombopenia, thrombopathy Impaired coagulation cascade (≤35°C)	Usually none
Metabolic	Decrease metabolic demands (30°C–35 °C): Decrease carbon dioxide production Decrease oxygen consumption	Frequent blood gases (used temperature corrected value) especially in induction phase and ventilation parameters management
Endocrine	Insulin resistance (≤35°C)	Insulin administration to maintain appropriate glucose level
Gastrointestinal	Decrease motility (≤35°C)	Delayed feeding after HT
Neurological	Decrease consciousness (≤30°C–31°C) in awake patient	
Renal	Increase diuresis, tubular dysfunction (≤35°C) Electrolytes loss and disorders (≤35°C)	Monitor urine output and replace fluid if needed Prevent and monitor blood electrolytes disorders (usually every 6–8 h)
Drug metabolism	Reduce in cytochrome P450 activity Slowing of numerous liver enzymes Usually reduced clearance of numerous medications such as sedative or neuromuscular blocking agents (≤35°C)	Adjust infusion rates, use preferentially bolus dose rather than increasing infusion dose

Adapted, with permission, from Polderman et al. (10,83).
ECG = electrocardiographic; HR = heart rate; HT = hypothermia therapy.

acute MI not associated with cardiac arrest, the available evidence is currently not sufficiently strong enough to recommend the routine implementation of HT into clinical practice.

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