Feature

Optimal Management of Shivering During Therapeutic Hypothermia After Cardiac Arrest

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Both pharmacological and nonpharmacological methods are used to control shivering in therapeutic hypothermia. An evidence-based protocol based on the most current research has been developed for the management of shivering during therapeutic hypothermia. Meperidine is the drug of choice and provides the greatest reduction in the shivering threshold. Other effective pharmacological agents recommended for reducing the threshold include dexmedetomidine, midazolam, fentanyl, and magnesium sulfate. In addition, skin counterwarming techniques, such as use of an air-circulating blanket, are effective nonpharmacological methods for reducing shivering when used in conjunction with medication. As a last resort, neuromuscular blocking agents are considered appropriate therapy for management of refractory shivering. (*Critical Care Nurse.* 2011;31[6]:e18-e30)

A 46-year-old handyman at a hotel and an active cigarette smoker, Mr P was admitted to the cardiac intensive care unit at Yale New Haven Hospital, New Haven, Connecticut, via the emergency department. He had experienced chest pain while eating dinner. As his wife called 911, Mr P became unresponsive. Emergency medical personnel initiated cardiopulmonary resuscitation and determined that Mr P was in ventricular tachycardia and ventricular fibrillation. They defibrillated him twice into a normal sinus rhythm.

An electrocardiogram showed ST-segment elevation myocardial infarction. Mr P was taken directly to the cardiac catheterization laboratory. A marked occlusion of the left anterior descending coronary artery was revealed, and a stent was placed. Mr P's hemodynamic status continued to be unstable, and an intra-aortic balloon pump was inserted for cardiac support. At this time, Mr P had not regained consciousness. A decision was made to begin therapeutic hypothermia.

Therapeutic hypothermia incorporates either external devices or intravascular catheters to cool a patient to a temperature of approximately 33°C. After about 24 hours, patients are rewarmed at a controlled rate by regulating the external device or the intravascular catheters. Therapeutic hypothermia can increase the likelihood of survival and improve neurological outcomes in survivors of sudden cardiac arrest.[1] However, implementation of therapeutic hypothermia protocols varies among institutions, and optimal management of adverse sequelae, such as shivering, has yet to be determined.

According to the American Heart Association,[2] cardiac arrest affects 236 000 to 325 000 persons in the United States each year. Only approximately one-quarter (14%-40%) of those who have a cardiac arrest and are resuscitated have return of spontaneous circulation and are

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admitted to a hospital.[1] In addition, only 7% to 30% of those admitted to a hospital are eventually discharged with a good neurological outcome.[1]

On the basis of evidence from several randomized controlled clinical trials, the International Liaison Committee on Resuscitation (ILCOR)[3] incorporated the use of therapeutic hypothermia into resuscitation guidelines for comatose survivors of a cardiac arrest. Brain injury is a common complication after cardiac arrest, resulting in increased morbidity and mortality[3]; this injury is due to impaired cerebrovascular autoregulation, cerebral edema, and postischemic neurodegeneration.[2] Implementation of mild hypothermia (32°C-34°C) for 12 to 24 hours after a cardiac arrest has resulted in improved survival and neurological recovery.[2]

Implementation of therapeutic hypothermia has its advantages, although complications are associated with its use. Shivering is a common complication that occurs during the induction and rewarming phases of therapeutic hypothermia.[3] Strategies for preventing and managing shivering vary across protocols. Many protocols recommend use of sedative drugs and neuromuscular blockers to prevent and manage shivering during the induction, maintenance, and rewarming phases of therapeutic hypothermia.[3] However, side effects are associated with the use of these agents. Assessment of sedation levels becomes challenging in patients who are receiving both sedatives and neuromuscular blockers. In addition to the adverse side effects of pharmacological management, clearance of sedative drugs and neuromuscular blockers is diminished up to 30% at temperatures of 34°C and below.[3] Adjunct methods to combat shivering during therapeutic hypothermia, such as application of a forced-air warming blanket or counterwarming mitts, should be evaluated for efficacy.

The optimal approach to the management of shivering is yet to be determined. In this article, we examine evidence for the use of pharmacological and nonpharmacological strategies for management of shivering in patients undergoing therapeutic hypothermia after cardiac arrest.

Sudden Cardiac Arrest

Epidemiology

Sudden cardiac arrest has an incidence of 0.1% to 0.2% per year and is a prevalent public health issue; coronary artery disease is the major contributing factor.[4] The American Heart Association[2] estimates that 95% of patients with sudden cardiac arrest die before reaching a hospital. Among patients who are successfully resuscitated, the median survival-to-discharge rate is only 8.4% for cardiac arrest initially treated by emergency medical services personnel. The majority of patients who survive sudden cardiac arrest and are admitted to a hospital have residual neurological impairment or die before discharge.[2]

Pathophysiology of Postcardiac Arrest Syndrome

ILCOR[3] coined the term "postcardiac arrest syndrome" to describe the complex pathophysiological processes that occur after the return of spontaneous circulation after a cardiac arrest. The most critical period for establishing aggressive treatment is during the intermediate phase of postcardiac arrest, which begins between 6 to 12 hours and lasts up to 72 hours after the return of spontaneous circulation.[3]

The pathophysiological responses after a cardiac arrest are due to the sustained systemic ischemia, which in turn causes extensive tissue and organ injury, and to reperfusion injuries.[3] When cerebral blood flow is restored after cardiac arrest and resuscitation, resultant neurological injury is due to cellular excitotoxicity, impaired calcium homeostasis, and increased formation of free radicals.[3] Calcium influx within neuronal cells causes a buildup of oxygen free radicals and activation of degradative enzyme pathways, causing cell death.[5] Disrupted cerebral microcirculatory reperfusion, even when cerebral perfusion pressure is sufficient,

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causes ischemia and infarctions that lead to diffuse brain injury.[3] Conditions that potentiate impaired cerebral oxygenation and cause further brain injury are hypotension, hypoxemia, disrupted cerebrovascular autoregulation, and brain edema.[3] The clinical indications of postcardiac arrest brain injury often include coma, seizures, myoclonus, neurocognitive dysfunction, and brain death. Coma and decreased state of arousal are the most common acute manifestations of the brain injury.[3]

Therapeutic Hypothermia

Use of therapeutic hypothermia in comatose survivors of a sudden cardiac arrest has been clinically effective in the treatment of postcardiac arrest syndrome, with outcomes of increased neurological function and survival rates.[3] The neuroprotective effects of therapeutic hypothermia are thought to be due to inhibition of the biosynthesis, release, and uptake of catecholamines and of glutamate and dopamine neurotransmitters involved in the generation of free radicals and cellular mediators responsible for the multifocal neurological damage.[1] Other beneficial effects of therapeutic hypothermia include conservation of the blood-brain barrier, maintenance of adenosine triphosphate stores, restoration of cerebral microcirculation, decreased intracranial pressure, and increased cerebral blood flow.[1]

Arrich et al[1] performed a systemic review and meta-analysis of current research to assess the effectiveness of therapeutic hypothermia in patients after cardiac arrest. The outcome parameters examined included neurological outcomes, survival rates, and adverse events. The investigators concluded that patients receiving therapeutic hypothermia had better neurological outcomes and increased survival rates. In addition, differences in adverse events between the patients and a normothermia control group were not significant. On the basis of the results of randomized clinical trials, the American Heart Association[2] also concluded that therapeutic hypothermia can improve outcomes in comatose survivors of out-of-hospital cardiac arrest.

Evidence From Clinical Trials and ILCOR Recommendations

In 2002, publication of the results of 2 breakthrough randomized clinical trials[5,6] paved the way for use of therapeutic hypothermia in comatose survivors of sudden cardiac arrest by indicating improved survival and neurological recovery. Bernard et al[5] found that the use of a hypothermia protocol in which a core temperature of 33°C was maintained for 12 hours was significantly associated with survival with a good outcome, meaning that the patient was discharged home or to a rehabilitation facility. The Hypothermia After Cardiac Arrest Study Group[6] found that at 6 months neurological outcome and mortality rate were significantly better in the hypothermia group than in the normothermia group. The occurrence of complications did not differ significantly between the 2 groups.

ILCOR[3] recommends therapeutic hypothermia as part of a standardized treatment strategy for comatose survivors of cardiac arrest. The recommendation is based on the results of the clinical trials[5,6] and on a meta-analysis[1] that indicated that in-hospital induction of mild hypothermia (33°C-34°C) for 12 to 24 hours in comatose patients who had ventricular fibrillation and survived resuscitation improved survival and neurological recovery.

Shivering

Induction of therapeutic hypothermia is associated with several complications, including shivering.[3] Normal thermoregulatory physiological responses to the application of therapeutic hypothermia include vasoconstriction and shivering.[7] Core temperature is normally maintained within the range of 36.5°C to 37.5°C. Temperatures less than this threshold trigger vasoconstriction and shivering.[8]

Thermoregulation involves integration of (1) peripheral and central thermoreceptor signals by the hypothalamus control center and (2) the efferent response via the autonomic and behavioral systems.[8] Skin, mucous membrane, and visceral receptors provide thermal input; the mean skin temperature accounts for approximately 20% of the total thermoregulatory input.[9] The spinal cord and brain stem modulate the thermal inputs and integrate afferent information within the hypothalamus.[8] Differences between the set-point temperature and thermoreceptor feedback lead to vasoconstriction, piloerection, and shivering in response to cold. This shivering increases heat production 2- to 5-fold.[8] For successful induction and maintenance of therapeutic hypothermia, the thermoregulatory responses of vasoconstriction and shivering must be controlled.

The numerous consequences and adverse effects of shivering influence the outcome of the induction of therapeutic hypothermia. Shivering can cause thermal discomfort as well as sympathetic nervous system activation resulting in tachycardia and hypertension.[10] Shivering results in increased resting energy expenditure and oxygen consumption, impeding the induction of hypothermia and eliminating any potential benefits.[11] When shivering is uncontrolled, consequences include increased tissue ischemia. In addition, uncontrolled shivering counteracts the neuroprotective benefits of therapeutic hypothermia due to the reduction of cerebral metabolism.[11]

For therapeutic hypothermia to be beneficial, shivering must be monitored frequently and controlled during the induction, maintenance, and rewarming phases of the therapy. Shivering is not always visible. Early indications of shivering may be detected by palpating the mandible for vibration or by identifying, on the bedside monitor, electrocardiographic artifacts due to skeletal muscle. Additionally, resistance to cooling and inability to reach a target cooling temperature within the expected time frame may indicate heat generation due to shivering.

A grading scale, such as the Bedside Shivering Assessment Scale (Table 1) developed and validated by Badjatia et al,[11] can also be useful in monitoring and controlling shivering. By assessing the correlation between the score on the scale and systemic metabolic stress defined by indirect calorimetric measurements, Badjatia et al determined that the score accurately represented the metabolic impact of shivering. The scale was an accurate predictor of all energy expenditure measures and had a high level of interobserver reliability. Badjatia et al concluded that the 4-point scale was a simple and reliable tool for the evaluation of shivering during therapeutic hypothermia.

Table 1 The Bedside Shivering Assessment Scale[a]

Score	Definition
0	None: no shivering noted on palpitation of the masseter, neck, or chest wall
1	Mild: shivering localized to the neck and/or thorax only
2	Moderate: shivering involves gross movement of the upper extremities (in addition to neck and thorax)
3	Severe: shivering involves gross movements of the trunk and upper and lower extremities

[a] Based on information from Badjatia et al.[11]

Management of Shivering During Therapeutic Hypothermia

Research and hospital protocols have incorporated the use of both pharmacological and nonpharmacological methods to control shivering during therapeutic hypothermia. Pharmacological methods typically include a drug cocktail of sedative and hypnotic agents, plus analgesics, and, occasionally, various neuromuscular blocking agents. Nonpharmacological methods have had limited use in hospitals. However, research[12-15] has shown that the use of skin counterwarming techniques is beneficial as an adjunct therapy in the management of shivering during therapeutic hypothermia.

Pharmacological Methods

Numerous pharmacological agents[7,10,16-25] (Table 2) that reduce the vasoconstriction and shivering thresholds have been used to manage shivering during therapeutic hypothermia. According to the ILCOR,[3] sedative and hypnotic agents are often used to decrease metabolic demand and facilitate mechanical ventilation in comatose patients who lack signs of awakening within the first 5 to 10 minutes after return of spontaneous circulation. Sedation will reduce both oxygen consumption and the shivering threshold.[3]

Sedatives and Hypnotics. Common sedatives used during therapeutic hypothermia to reduce the shivering threshold include propofol, dexmedetomidine, midazolam, and diazepam. Chamorro et al[26] conducted a systematic literature review and found that midazolam and propofol, in that order, were the sedative agents used most often. Doses of 2.5 to 10 mg of midazolam are moderately effective in reducing shivering, although the drug also has a high sedative effect and a low risk of hypotension.[27] Matsukawa et al[25] reported that propofol linearly reduced the shivering threshold by 0.7°C (SD, 0.1°C) per microgram per milliliter, to a shivering threshold of 34.4°C to 31.5°C with doses of 2 to 8 µg/mL, respectively. However, a limitation in the use of propofol is the risk of hypotension.[27] Dexmedetomidine is a drug not commonly used during therapeutic

Table 2 Studies of pharmacological agents for reduction of shivering

Reference, year	Drug and dose	Study design, cooling method, number of participants	Results/reduction in shivering threshold	Other outcomes/ adverse affects
Taniguchi et al,[16] 2010	Nefopam • 17-mg dose, plasma concentration 50 ng/mL • 32-mg dose, plasma concentration 100 ng/mL	Randomized, crossover design Intravenous infusion of cold (4°C) lactated Ringer solution and forced-air whole-body cover and circulating-water mattress for skin temperature of 31°C 7 healthy volunteers	0.3°C, to 35.2°C (SD, 0.3°C) (P=.004) 0.6°C, to 34.9°C (SD, 0.3°C) (P=.004)	Significant reduction in the gain of shivering with high dose of nefopam (P=.03)
Alfonsi et al,[10] 2009	Nefopam, 45-mg dose, plasma concentration 100 ng/mL Clonidine, 2.51 µg/kg Combination of nefopam, plasma concentration 100 ng/mL, and clonidine, 2.51 µg/kg Alfentanil, plasma concentration 150 ng/mL Combination of nefopam, plasma concentration 100 ng/mL, and alfentanil, plasma concentration 150 ng/mL	Randomized, crossover design, single-blind study Intravenous infusion of cold (4°C) lactated Ringer solution and cool ambient room temperature for mean skin temperature of 30°C 15 healthy male volunteers	0.6°C (SD, 0.3°C), to 35.9°C (SD, 0.3°C) (P<.05) 0.5°C (SD, 0.3°C), to 36°C (SD, 0.3°C) (P<.05) 0.7°C (SD, 0.4°C), to 35.7°C (SD, 0.2°C) (P<.05) Interaction less than additive (P=.03) 1.0°C, to 35.5°C (SD, 0.7°C) (P<.05) 1.8°C (SD, 0.6°C), to 34.5°C (SD, 0.7°C) (P<.05) Interaction was additive (P=.55)	Significantly more nausea with infusion of nefopam (P<.05) Significantly more dry mouth, bradypnea, and pruritus associated with alfentanil use (P<.05)
Hostler et al,[17] 2009	Diazepam • 20-mg dose • 10-mg dose	Randomized controlled Intravenous infusion of cold (4°C) 0.9% saline 15 healthy volunteers	1.5°C (SD, 0.2°C) (P=.007) 1.4°C (SD, 0.2°C) (P=.007)	High dose reduced shivering threshold without an increase in oxygen consumption (P<.001)
Lenhardt et al,[18] 2009	Buspirone, 60 mg orally Dexmedetomidine plasma concentration 0.6 ng/mL Combination of buspirone, 60 mg orally, and dexmedetomidine, plasma concentration 0.6 ng/mL	Randomized, crossover design, single-blind study Intravenous infusion of cold (3°C) lactated Ringer solution, and mean skin temperature maintained at 31°C via circulating water garments and forced-air warmers 8 healthy men	0.7°C, to 35.9°C (SD, 0.4°C) (P<.001) 2°C, to 34.7°C (SD, 0.5°C) (P<.001) 2.5°C, to 34.1°C (SD, 0.4°C) (P<.05) Combination was additive (P=.80)	Combination of buspirone and dexmedetomidine caused minimal sedation according to observer's assessment of alertness/ sedation (P<.05) Neither oxygen consumption nor the maximum intensity of shivering was reduced by dexmedetomidine or buspirone
Komatsu et al,[19] 2005	Doxapram, plasma concentration 2.6 (SD, 1.1) µg/mL	Randomized, crossover design, single-blind study Ambient room temperature of 21°C 9 healthy volunteers	0.5°C, to 35.7°C (SD, 0.7°C) (P=.01)	No significant change in sweating or vasoconstriction thresholds (P=.29, and P=.11, respectively)

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Table 2 *Continued*

Reference, year	Drug and dose	Study design, cooling method, number of participants	Results/reduction in shivering threshold (°C)	Other outcomes/ adverse affects
Wadhwa et al,[20] 2005	Magnesium sulfate 80 mg/kg and infusion 2 g/h	Randomized, crossover design, double-blind study Intravenous infusion of cold (4°C) lactated Ringer solution and circulating-water blanket and forced-air blanket to maintain mean skin temperature at 31°C 9 healthy men	0.3°C, to 36.3°C (P=.04)	No effect on gain of shivering (P=.34) No significant sedation or reduction in muscle strength
Zweifler et al,[7] 2004	Meperidine 50-100 mg Meperidine and buspirone 30-60 mg orally Meperidine and ondansetron, 8-16 mg bolus Meperidine and ondansetron, 8-16 mg bolus, and magnesium sulfate, 4-6 g intravenous bolus, 1-3 g/h infusion	Randomly assigned to control and experimental groups Circulating water 22 healthy volunteers	Magnesium sulfate administration decreased time to achieve 35°C by 17 min (P=.04)	Magnesium group had significantly higher comfort scores (P<.001) No adverse events associated with the addition of magnesium sulfate to the meperidine regimen Vasodilatation 88% for magnesium group vs 29% for all other groups (P=.02)
Doufas et al,[21] 2003	Meperidine, plasma drug level 0.3 µg/mL Dexmedetomidine, plasma level of 0.4 ng/mL Meperidine, 0.3 µg/mL, and dexmedetomidine, 0.4 ng/mL	Randomized, crossover design Intravenous infusion of cold (4°C) lactated Ringer solution and circulating-water and forced-air warmers to maintain mean skin temperature of 31°C 10 healthy men	1.2°C, to 35.5°C (SD, 0.6°C) (P<.001) 0.7°C (SD, 0.5°C), to 36°C (SD, 0.5°C) (P<.001) 2.0°C (SD, 0.5°C), to 34.7°C (SD, 0.6°C) (P<.001) Interaction was additive (P=.19)	Minimal sedation with either drug alone or in combination Respiratory rate and end-tidal Pco_2 preserved
Mokhtarani et al,[22] 2001	Buspirone, 60 mg Meperidine, plasma concentration 0.8 µg/mL Combination of buspirone 30 mg and meperidine 0.4 µg/mL plasma concentration	Randomized, crossover design Intravenous infusion of cold (4°C) lactated Ringer solution and circulating-water and forced-air warmers to maintain mean skin temperature of 32°C 8 healthy men	0.7°C, to 35°C (SD, 0.8°C) 2.3°C, to 33.4°C (SD, 0.3°C) 2.0°C, to 33.4°C (SD, 0.7°C) Interaction was synergistic (P=.006)	Combination caused little sedation or toxic respiratory effects

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hypothermia, most likely because of its high cost. However, studies[18,21,24] have indicated its effectiveness. In a study of 8 healthy men, Lenhardt et al[18] found that the combination of buspirone and dexmedetomidine additively reduced the shivering threshold by 2.5°C, to 34.1°C (SD, 0.4°C), and caused only minimal

Table 2 *Continued*

Reference, year	Drug and dose	Study design, cooling method, number of participants	Results/reduction in shivering threshold (°C)	Other outcomes/ adverse affects
Kurz et al,[23] 1997	Meperidine, plasma concentration 0.6 μg/mL (40 mg/h) Meperidine, plasma concentration 1.8 μg/mL (120 mg/h)	Randomized, crossover design Forced-air warmer/cooler and circulating-water mattress 9 healthy men	6.1°C (SD, 3.0°C) (P = .001)	Meperidine increased sweating threshold by 0.5°C (SD, 0.8°C), decreased vasoconstriction threshold by 3.3°C (SD, 1.5°C), and reduced shivering threshold twice as much as it did the vasoconstriction threshold (P = .001) Mild sedation with meperidine, plasma concentration of 0.6 μg/mL Deep sedation with meperidine plasma concentration of 1.8 μg/mL
Talke et al,[24] 1997	Dexmedetomidine, plasma concentration 0.4 ng/mL Dexmedetomidine, plasma concentration 0.8 ng/mL	Randomized, double blind, cross-over design Forced-air warmer/cooler and circulating-water mattress 9 healthy men	2.4°C (SD, 0.9°C) per ng/mL, to 34°C (SD, 0.9°C)	Increased sweating threshold by 0.5°C (SD, 0.4°C) at low dose and decreased vasoconstriction threshold by 1.6°C (SD, 0.8°C) per ng/mL Subjects mildly sedated at low dose and deeply sedated at high dose (0.8 ng/mL) Reduction in heart rate of 10/min and 20 mm Hg decrease in systolic blood pressure
Matsukawa et al,[25] 1995	Propofol, plasma concentrations of 2, 4, and 8 μg/mL	Randomized, crossover design Circulating-water mattress and forced-air warmer/cooler 5 healthy men	0.7°C (SD, 0.1°C) per μg/mL, to 33.6°C (SD, 0.7°C)	Mild sedation at 2 μg/mL, deep sedation at 4 μg/mL, and fully anesthetized at 8 μg/mL Decreased vasoconstriction 0.6°C (SD, 0.1°C), to 34°C (SD, 0.9°C) Slightly increased the sweating threshold (P = .04)

sedation. Also in healthy volunteers, Hostler et al[17] showed that a high dose (total dose, 20 mg) of intravenous diazepam alone significantly reduced core body temperature by 1.5°C (SD, 0.2°C) without an associated increase in oxygen consumption and caused less discomfort than a lower dose or no diazepam did, as indicated by the thermal sensation index.

Analgesics and Opioids. Many opioid medications are also used in therapeutic hypothermia because they affect thermoregulatory processes and reduce the shivering

threshold. Meperidine has been the most beneficial agent,[7,21-23] with reductions in the shivering threshold of 1.2°C to 6.1°C, to a level 33°C. Meperidine is unique among opioids in that it decreases shivering and vasoconstriction thresholds through its κ-receptor activity.[8] Disadvantages of meperidine use include risk of respiratory suppression, nausea and vomiting, and seizure potential with prolonged drug administration.[8]

Recently, in a study[22] of combinations of drugs, meperidine and dexmedetomidine additively reduced the shivering threshold. However, a combination of buspirone and meperidine was even more beneficial in reducing the threshold because of the synergistic relationship of the drugs.

Alfonsi et al[10] found that the combination of nefopam and clonidine reduced the shivering threshold by 0.7°C (SD, 0.4°C), to 35.7°C (SD, 0.2°C). This drug combination was no better than either drug alone, but the combination of nefopam and alfentanil additively reduced the shivering threshold by 1.8°C (SD, 0.6°C), to 34.5°C (SD, 0.7°C). Although the research supports the combined use of nefopam and alfentanil in reducing the shivering threshold during therapeutic hypothermia, nefopam can induce seizures and anaphylactic reactions.[27] Also, nefopam is not currently available in the United States.

Research on other analgesic and opioid medications has had varied results. Chamorro et al[26] found that fentanyl and morphine, in that order, were the most common analgesics used during therapeutic hypothermia after cardiac arrest. Both drugs effectively reduce shivering and cause moderate sedation; however, morphine has a greater risk of causing hypotension.[27]

Paralytics. When shivering occurs regardless of optimal sedation, many therapeutic hypothermia protocols recommend use of a paralytic agent (ie, a neuromuscular blocker) to control shivering.[3] Chamorro et al[26] found that pancuronium was the most common paralytic agent used during therapeutic hypothermia after cardiac arrest. However, in a study by Dupuis et al,[28] vecuronium was preferred over pancuronium for reduction of shivering because the former did not increase myocardial work and was associated with fewer complications. Frequent monitoring of sedation, neurological signs, and seizures is required when paralytic agents are used. Of note, the duration of action of neuromuscular blockers is prolonged during hypothermia.[3]

Other Medications. Several other medications with unique modes of action have been effective in reducing shivering. Zweifler et al[7] found that a bolus and then continuous infusion of magnesium sulfate significantly reduced the time to reach a core temperature of 35°C by 17 minutes. Wadhwa et al[20] also supported the use of magnesium sulfate, with evidence of a reduction in the shivering threshold of 0.3°C, to 36.3°C. However, this reduction is not significant enough to recommend magnesium sulfate as a sole agent during the induction of therapeutic hypothermia.

Nonpharmacological Methods

Nonpharmacological interventions[12-14,29,30] (Table 3) such as skin warming reduce the vasoconstriction and shivering thresholds because the thresholds are negatively and linearly related to skin temperature.[9] Skin counterwarming techniques are thought to be effective because mean skin temperature represents approximately 20% of the total regulatory input. Therefore, every 4°C increase in mean skin temperature results in a 1°C decrease in the shivering threshold.[9]

Air-Circulating Blanket

Badjatia et al[12] evaluated the effect of cutaneous counterwarming with an air-circulating blanket on energy expenditure in patients with brain injury who were undergoing therapeutic temperature modulation. The investigators found that core body temperature did not significantly change with removal of the air-circulating blanket (change, 0.04°C; SD, 0.06°C) and that use of the air-circulating blanket countered the metabolic impact of shivering during therapeutic temperature modulation. The findings of a significant reduction in shivering and metabolic variables of resting energy expenditure, oxygen consumption, and carbon dioxide production support the use of a surface counterwarming air-circulating blanket as an adjunct therapy for reducing shivering and metabolic demands during therapeutic hypothermia protocols.

Head Covering

Clevenger[30] examined the use of head covering on the incidence of shivering and rates of rewarming in cardiac surgical patients. Mean rewarming rates were significantly higher for the experimental group (0.013°C/min) than for the control

Table 3 Studies of nonpharmacological methods for reduction of shivering

Reference, year	Counterwarming method	Study design, cooling method, number of participants	Results/reduction in shivering threshold	Other outcomes/adverse affects
Badjatia et al,[12] 2009	Air-circulating blanket (Bair Hugger) at set temperature of 43°C	Prospective observational study Cold intravenous infusion or surface cooling (Arctic Sun) 50 patients receiving mechanical ventilation	No significant change in core body temperature with removal of counterwarming: 0.04°C (SD, 0.06°C) (P=.90) Significant change in all metabolic variables: resting energy expenditure, oxygen consumption, and carbon dioxide production with removal of the counterwarming device (P<.001)	Baseline shivering status increased 1 point on the BSAS in 55% of the patients with removal of counterwarming device Factors associated with changes in metabolic parameters included lower serum magnesium levels and moderate to severe shivering (BSAS score 2-3)
Doufas et al,[29] 2003	Arm warming via forced-air warming unit (Bair Hugger) Face warming via CPAP mask with 21 L/min air at 42°C, relative humidity 100%	Crossover design, single-blind study Intravenous infusion of cold (4°C) lactated Ringer solution and cool ambient room temperature of 22°C to maintain a mean skin temperature of 31°C 8 healthy men	0.2°C (SD, 0.3°C), to 36.5°C (SD, 0.3°C) 0.1°C (SD, 0.3°C), to 36.5°C (SD, 0.3°C) No significant difference in shivering thresholds between control group and arm- or face-warming groups (P=.34)	
Sweney et al,[13] 2001	Focal hand warming with forced-air hand muff (Bair Hugger) at 43°C (SD, 5°C)	Crossover design Circulating-water cooled mattress 8 healthy men	1.1°C (SD, 0.35°C), to 35.9°C (SD, 0.5°C) (P<.01)	Whole-body shiver level decreased from 6.3 (SD, 0.5) to 1.6 (SD, 1.9) (P<.01) Subjective comfort level increased from 1.8 (SD, 0.7) to 3 (SD, 0.5) (P<.01) A 63% reduction in electromyographic activity (P<.01)
Iaizzo et al,[14] 1999	Focal facial and airway warming via ventilation mask	Crossover design Circulating-water-cooled mattress and convective-air cooling coverlet 7 healthy men	1°C (SD, 0.32°C), to 36°C (SD, 0.34°C)	Decrease in subjective shiver index from 7 to 2.7 (SD, 1.5) (P<.01)
Clevenger,[30] 1994	Head covering with 2 terry cloth towels	Randomized prospective design Ambient room temperature of 21°C 40 patients after cardiac surgery	Mean rewarming rate significant for experimental group (0.013°C/min) vs control group (0.008°C/min) (P=.03)	No significant difference between groups in the incidence of shivering (P=.86) No significant difference in rewarming time or heat gain between the groups (P=.16 and P=.89, respectively)

Abbreviations: BSAS, Bedside Shivering Assessment Scale; CPAP, continuous positive airway pressure.

Table 4 Study of combination pharmacological and nonpharmacological methods for reduction of shivering

Reference, year	Drug/counterwarming method	Study design, cooling method, number of participants	Results/reduction in shivering threshold	Other outcomes/adverse affects
Kimberger et al,[15] 2007	Skin warming via forced-air warmer (Bair Hugger) at 43°C and circulating-water mattress at 41°C Meperidine, plasma concentration 0.9 µg/mL Skin warming via forced-air and warming mattress plus meperidine, plasma concentration 0.9 µg/mL	Randomized, crossover design Intravenous infusion of cold (4°C) lactated Ringer solution 8 healthy volunteers	0.6°C (SD, 0.5°C), to 34.9°C (SD, 0.5°C) (P=.01) 1.3°C (SD, 0.3°C), to 34.2°C (SD, 0.3°C) (P<.01) 1.7°C (SD, 0.3°C), to 33.8°C (SD, 0.2°C) (P<.01) Combination was additive (P=.59)	Combination produced only mild sedation and no toxic respiratory effects

group (0.008°C/min). However, rewarming time and heat gain did not differ significantly between the 2 groups. Limitations of the study were its small sample size (N=40), low clinical incidence of shivering, and use of a subjective shiver assessment.

Hand Warming

Sweney et al[13] examined whether hand warming could suppress shivering in unanesthetized men. In this study, use of focal hand warming significantly decreased the whole-body shiver index from 6.3 (SD, 0.5) to 1.6 (SD, 1.9). The participants' subjective comfort level also increased with use of focal hand warming, from 1.8 (SD, 0.7) to 3 (SD, 0.5). Focal hand warming also decreased electromyographic activity by 63% and reduced core temperature by 1.1°C (SD, 0.35°C), to 35.9°C (SD, 0.5°C).

Face Warming

Iaizzo et al[14] investigated the use of facial and airway heating in the reduction of the shivering threshold. The results indicated that the application of facial warming suppressed shivering and resulted in a significant reduction of core temperature by 1°C, to 36°C, with a significant decrease in the shiver index from 7 to 2.7 (SD, 1.5). Although the study showed the benefits of facial warming, application for use during a mild therapeutic hypothermia protocol may be limited when the degree of cooling must be substantially lower than 36°C.

Doufas et al[29] examined the use of arm warming or face warming on the reduction of the shivering threshold in volunteers cooled to a mean skin temperature of 31°C. Unlike the results of previous studies by Sweney et al[13] and Iaizzo et al,[14] the reduction in shivering threshold for either the arm-warming or the face-warming groups did not differ significantly from the reduction in the control group. The difference in the results of the 3 groups of investigators may be attributed to differences in the methods used. Doufas et al[29] quantified the shivering threshold and studied hypothermic volunteers, whereas Sweney et al[13] and Iaizzo et al[14] used a subjective shiver index to determine the shivering threshold of volunteers who were closer to a normothermic temperature.

Combination of Pharmacological and Nonpharmacological Methods

A combination of pharmacological and nonpharmacological methods can reduce shivering during therapeutic hypothermia (Table 4). Kimberger et al[15] investigated the combined effects of meperidine and skin warming on vasoconstriction and shivering thresholds during the induction of mild hypothermia. They found that skin warming reduced the shivering threshold by 0.6°C, to 34.9°C, whereas meperidine reduced the threshold by 1.3°C, to 34.2°C, and the combination of meperidine and skin warming additively reduced the shivering threshold by 1.7°C, to 33.8°C, while producing only mild sedation and no toxic respiratory effects.

Conclusions and Implications for Practice

Therapeutic hypothermia can significantly reduce mortality and improve neurological outcomes in comatose survivors of sudden cardiac arrest. However, establishment of the optimal therapeutic hypothermia protocol and management of

Table 5 Protocol for management of shivering during therapeutic hypothermia

Initiation of sedation/analgesia
• Sedation
◦ First choice: dexmedetomidine (Precedex): 1 µg/kg intravenously over 10 minutes, followed by 0.2-0.7 µg/kg per hour continuous intravenous infusion for maximum of 24 hours
◦ Second choice: midazolam (Versed): 0.02-0.1 mg/kg per hour (1-7 mg/h) intravenous infusion
• Analgesics
◦ First choice: fentanyl: 0.7-10 µg/kg per hour intravenous infusion
Shivering management
• First line: meperidine (Demerol): 25-50 mg intravenously every 4 hours as needed
• Application of arm/skin counterwarming via forced-air warming unit (Bair Hugger)
Refractory shivering
• Magnesium sulfate: 2-5 g infused over 5 hours
• Neuromuscular blockade with paralytic agent: vecuronium 0.1 mg/kg intravenous bolus, followed by intravenous infusion 1 µg/kg per minute (titrate) or pancuronium 0.01 mg/kg per hour to 0.1 mg/kg per hour infusion. Goal: Bispectral index value 40-60 or train-of-four 1 of 4

adverse effects, such as shivering, that counteract the benefits of therapeutic hypothermia, have yet to be determined.

Clinical trials have shown that several pharmacological and nonpharmacological methods are promising interventions to combat the effects of shivering during therapeutic hypothermia. Of all the pharmacological agents, meperidine appears to be the drug of choice for achieving the greatest reduction in the shivering threshold, with reported reductions ranging from 1.3°C to 6.1°C.

Because prolonged use of meperidine has adverse effects, such as respiratory depression and increased seizure risk, in a recent study, Lenhardt et al[18] examined novel combination therapies to achieve the same suppression of the shivering threshold. A combination of buspirone (0.7°C) and dexmedetomidine (2°C) additively reduced the shivering threshold by 2.5°C, to 34.1°C, with only minimal sedation. This unique drug combination achieved the greatest additive reduction in the shivering threshold. A close second was the combination of meperidine and buspirone, which synergistically reduced the shivering threshold by 2.0°C, to 33.4°C, an even lower temperature threshold for shivering.[22] Of note, buspirone is available only for oral administration and therefore is inappropriate for comatose patients. Nefopam and alfentanil additively reduced the shivering threshold by 1.8°C, to 34.5°C,[10] but nefopam is unavailable for use in the United States.

Research has also revealed that nonpharmacological methods that reduce shivering thresholds are most beneficial when used in combination with drug therapy. For example, Kimberger et al[15] found that a combination of meperidine and skin-warming techniques additively reduced the shivering threshold by approximately 1.7°C, to 33.8°C, with minimum sedation and no toxic respiratory effects.

Although the results of recent research on the management of shivering are promising, the studies do have limitations. The majority of the research was conducted in young healthy volunteers. Investigators also used a variety of techniques to induce therapeutic hypothermia and different methods to determine the shivering threshold. A randomized controlled clinical trial is needed of the most optimal pharmacological regimen in combination with skin counterwarming techniques in older patients with comorbid conditions who are receiving therapeutic hypothermia for sudden cardiac arrest.

By considering recent data on the combined use of pharmacological therapy and nonpharmacological methods for the management of shivering during therapeutic hypothermia, nurses will be better able to manage and prevent shivering in patients undergoing this therapy. Table 5 is a suggested protocol for the management of shivering based on current research on both pharmacological and nonpharmacological methods. This protocol should serve as a clinical guide and provide clinicians with evidence-based recommendations for the optimal management of shivering during the use of therapeutic hypothermia in patients after cardiac arrest.

Managing Mr P's Shivering

The challenges of managing shivering in a patient undergoing

therapeutic hypothermia are illustrated in the care of Mr P. Controlling Mr P's shivering during both the cooling and rewarming phases was difficult. Before the start of therapeutic hypothermia, midazolam and fentanyl infusions were started per our institution's protocol to achieve a score of -4 (deep sedation with no response to voice, but may see movement with physical stimulation) on the Richmond Agitation Sedation Scale and a pain goal of 0. During the induction phase, the goal was to reach a target temperature of 33°C as quickly as possible or at least within 4 hours from the time that the therapeutic hypothermia was initiated. Mr P's temperature before the start of therapeutic hypothermia was 34.9°C. Because his temperature was so close to the target temperature, we anticipated that we could reach the target cooling temperature within the expected time frame. About 30 minutes into the therapy, Mr P began to have moderate shivering, which continued despite increasing doses of the sedative and analgesic infusions. At the same time, counterwarming techniques were implemented by covering Mr P's hands and feet with socks, but this intervention had no effect. The next step was to administer meperidine. Mr P received 2 doses of meperidine per protocol without effect.

As a last option, Mr P was given intermittent boluses of the neuromuscular blocker vecuronium. Shivering was controlled, and we were able to reach and maintain the target cooling temperature.

After 24 hours of cooling at 32°C to 34°C, rewarming was begun at a rate of 0.25°C/h. The rewarming target temperature was set per our protocol at 36°C. We were again challenged with controlling Mr P's shivering. We had to continue using vecuronium intermittently throughout the rewarming phase. A total of 48 hours after admission, Mr P's condition became more stable, and he was weaned from the intra-aortic balloon pump.

After therapeutic hypothermia was completed, we began to wean him from the sedative and analgesic infusions. Mr P slowly began to respond to simple instructions and was eventually weaned from mechanical ventilation and extubated. Over time, he regained consciousness. He recognized his family but did not recall any of the events leading to his hospitalization. Ten days after admission, Mr P was discharged home with home health services, including physical, occupational, and speech therapy. We remain optimistic that he will continue to make progress toward regaining full function. CCN

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Financial Disclosures
None reported.

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