Pathophysiology, management and complications of hypothermia

Hypothermia, either accidental or therapeutic, is when the body's core temperature is less than 35.0°C. This article examines the pathophysiology, clinical features and management of both intentional and unintentional hypothermia with a focus on the current literature regarding treatment protocols.

Hypothermia is when the body's core temperature is below <35.0°C (Aslam et al, 2006). This cooling can occur either unintentionally (by accident) or intentionally (for therapeutic reasons).

Accidental hypothermia is a disease state that affects a wide variety of patient populations. Early recognition by emergency medical personnel along with aggressive management of complications is vital to decrease the morbidity and mortality of the patient. In this instance, hypothermia develops when the body's ability to generate and conserve heat is overwhelmed by environmental exposure. Often seen as a disease of winter, it can occur in nearly any climate or weather condition and is often complicated by metabolic conditions, medications, use of illegal drugs or alcohol, and trauma (Hermann and Weingart, 2003). Therapeutic hypothermia has been promoted in order to preserve neurological function in cardiac arrest, traumatic brain injury and cerebrovascular attack patients (Polderman, 2011). Therapeutic hypothermia is the only intervention shown to improve neurological outcomes after cardiac arrest. This review examines the pathophysiology, clinical features and management of both unintentional and intentional hypothermia, with a focus on the current literature regarding treatment protocols.

Pathophysiology

Stages of hypothermia

Hypothermia is subdivided into four different stages (Gardner, 2009). The body responds to mild hypothermia (32–35°C) with primitive physiological responses to preserve heat (e.g. shivering, vasoconstriction, cold diuresis) and is characterized by mild states of confusion, hepatic dysfunction and hyperglycaemia (Aslam et al, 2006). The transition to moderate hypothermia (28–32°C) is marked by violent shivering and severe confusion with disorientation, delirium and memory loss. Severe hypothermia (20–28°C) and profound hypothermia (less than 20°C) are defined by cardiac dysrhythmias, shallow breathing and a progressive decline in consciousness leading to death (MacCaughelty et al, 1995).

Development of hypothermia is hastened by any reduction in blood circulation, medications, substances or severe dehydration (McCullough and Arora, 2004), increased heat lost (burns or an infant's higher surface-to-body mass ratio), or decreased thermoregulation (hypothyroidism, hypoadrenalism or hypoglycaemia) (Gardner, 2009). The stages of hypothermia and the body's reactions are further delineated in *Table 1*.

Mechanisms of heat transfer

The four mechanisms of heat transfer are detailed in *Table 2*. In general, higher temperature gradients and denser heat transfer mediums result in higher rates of heat transfer. For example, water immersion will lead to 25 times greater heat loss than in air (Gardner, 2009). Stone floors have 100 times the heat transfer rate compared to air, leading to a high rate of post-fall hypothermia in the elderly (Hermann and Weingart, 2003).

Systemic changes

The cardiovascular system responds to heat loss initially with tachycardia, progressing to bradycardia as the temperature declines (Wong, 1983). Reflex vasoconstriction of the peripheral blood vessels shunts blood flow from the cooling skin towards deeper tissues, leading to a 600% increase in insulating capacity (Hermann and Weingart, 2003). Shivering greatly raises the basal metabolic rate (200–500%; MacCaughelty et al, 1995). Behaviour changes are manifested by adding clothing for layering and seeking warm shelter (Gardner, 2009).

As the patient becomes more hypothermic, there is depression in P wave amplitude with PR, QRS and QTc prolongation, as well as progressive T-wave changes that mimic ischaemia (Wilkey, 2004). When internal temperature reaches 32.2°C there is an elevation at the junction of the QRS and ST segments resulting in Osborne or J-waves, which are relatively uncommon (Wong, 1983). These changes are best seen in leads II and V6 (Aslam et al, 2006), similar to what is shown in *Figure 1*

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(Mareedu et al, 2008). This feature can also be seen in patients with subarachnoid haemorrhage, hypercalcaemia, or can be a normal variant (Hermann and Weingart, 2003). Atrial fibrillation occurs in 50–68% of patients with core temperatures below 32.2°C, progressing to defibrillation-resistant ventricular fibrillation at temperatures below 28°C (Aslam et al, 2006).

At a body temperature of 28°C there is decreased spontaneous depolarization and conduction, slowing the heart rate to ~50% normal (Aslam et al, 2006). A concomitant decrease in stroke volume, ventricular wall compliance, and a drastic increase in vascular resistance secondary to peripheral vasoconstriction (310% of baseline at 20°C) results in a progressive decline in cardiac output that is refractory to atropine (Aslam et al, 2006). The patient begins to experience a state of drowsiness accompanied by exhaustion, slurred speech and poor coordination as temperature declines into hypothermic ranges. There is decreased peripheral nerve conduction, blunted deep tendon reflexes and increasing muscle tone (MacCaughelty et al, 1995). This global neurological slowing can be visualized on an electroencephalogram (Ulrich and Rathlev, 2004).

Table 1. Stages of hypothermia

Stage	Body temperature	Clinical changes	
Mild	32.2–35°C (90–95°F)	Sympathetic nervous system excitation	Hypertension
			Shivering
			Tachycardia
			Tachypnoea
			Vasoconstriction
		Pathological changes occurring with fatigue	Cold diuresis
			Confusion
			Hepatic dysfunction
			Hyperglycaemia
			Apathy
			Ataxia
Moderate	28–32.2°C (82.4–90°F)	Shivering becomes violent and eventually extinct	
		Disorientation, memory loss	
		Drowsiness leading to exhaustion	
		Fumbling hands and poor coordination	
		Slurred speech	
		Numbness	
		Atrial dysrhythmias	
		Bradycardia and bradypnoea	
		Miosis	
		Decreased gag reflex	
		Hyporeflexia	
		Hypotension	
		Development of a J-wave	
Severe	<28°C (<82.4°F)	Ventricular dysrhythmias or asystole	
		Eventual depressed cardiac conductivity	
		Weakening of the pulse	
		Progressive decline in consciousness	
		Apnoea	
		Coma	
		Oliguria	
		Pulmonary oedema	
		Non-reactive pupils	

Increased vascular permeability leads to third spacing of fluids and a 2% increase in the haematocrit for every 1°C drop in core temperature (Hermann and Weingart, 2003). Hypothermia is a coagulopathic state. Increasing blood viscosity, platelet dysfunction and inhibition of the clotting cascade leads to microinfarctions in end organs (Mallett, 2002).

Early tachypnoea progresses to a gradual slowing of the respiratory rate with cessation of spontaneous respiration at 24°C (Wong, 1983). Cellular metabolism is reduced so that at 30°C there is a 50% reduction in both oxygen consumption and carbon dioxide production. Additionally, at temperatures <34°C there is a decreased ventilatory drive and increased response to partial pressure of carbon dioxide (pCO_2) (MacCaughelty et al, 1995). Impaired protective airway mechanisms (decreased ciliary motility, bronchorrhoea and thickening of secretions) favour the development of pneumonia and non-cardiogenic pulmonary oedema.

As temperature declines the kidneys can no longer concentrate urine as a result of tubular dysfunction, renal arterial vasoconstriction, inhibition of antidiuretic hormone and retention of metabolites. This cold-induced diuresis leads to acute renal failure complicated by hyperglycaemia, metabolic acidosis and decreased clearance of toxic ingestions (Ulrich and Rathlev, 2004; Gardner, 2009).

Unintentional (accidental) hypothermia

General approach to initial presentation

Identification of potentially hypothermic individuals, based upon a high index of suspicion, is the key initial step. When a patient presents with suspected hypothermia, one should place a temperature probe to determine the patient's core body temperature. The sites that best match the temperature of the CNS are the oesophagus, nasopharynx, and a pulmonary artery (via catheter), as bladder, rectal, oral and tympanic temperatures may differ by 1°C and are slow to change (Clifton et al, 2010). There must be an immediate evaluation for comorbid conditions, such as signs of trauma, hypothyroidism, hypopituitarism, adrenal insufficiency or neurological disease (Wilkey, 2004). Finger stick glucose is vital as hyperglycaemia and hypothermia can induce each other

and are frequently found in the same patient. Sedative-hypnotics, antipsychotics, thyroid replacement, beta-blockers, insulin and oral hypoglycaemic agents predispose patients to hypothermia (McCullough and Arora, 2004).

Bradycardia can be adequate for perfusion considering the decreased metabolic needs of the hypothermic patient as a result of decreased metabolic rate and low cardiac output needs (Wong, 1983). Neurologically, patients demonstrate decreased cognitive function, increased muscle tone and ataxia (Hermann and Weingart, 2003). Decreased blood flow to the abdomen leads to distension and rigidity and overlying skin will show gradual changes from pallor to cyanosis and eventual necrosis as vasoconstriction increases (MacCaughelty et al, 1995).

Patients can have a combined metabolic and respiratory acidosis because of a high lactate level and a decreased ventilation (Gardner, 2009). However, there are no data supporting induction for airway management, including intubation, until hypothermia resolves (Mallett, 2002). Importantly, intubated patients can be easily hyperventilated, which can exacerbate myocardial irritability (Aslam et al, 2006). Hypothermic patients who do not have a clear airway must be thoroughly evaluated for secretions. Vasoconstriction limits the accuracy of pulse oximetry, so one must have a high index of suspicion for hypoxia (Hermann and Weingart, 2003).

Treatment and complications

Rewarming strategies

Classically there are three methods of rewarming. Each method gives a different rate of rewarming, but this does not correlate to rates of morbidity or mortality (McCullough and Arora, 2004). A basic algorithm for the treatment of severe hypothermia can be seen in *Figure 2* (Headdon et al, 2009).

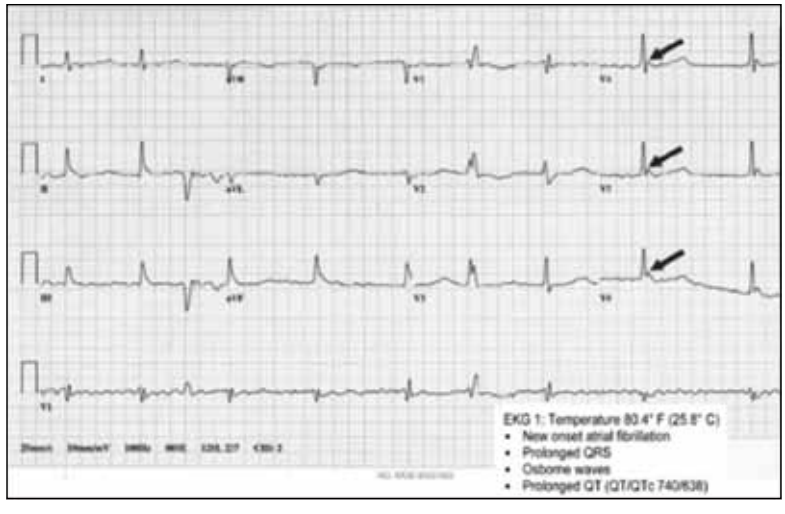
Passive rewarming is used for mildly hypothermic, young and otherwise healthy patients with an intact shivering response (Ulrich and Rathlev, 2004). The patient is stripped of all clothing and wrapped in cotton blankets to keep an insulating layer around the patient. This method is ineffective when core temperature drops below the shivering threshold of 28–30°C but can lead to a rewarming rate of 0.2–0.85°C/hour and reduces heat loss by 50% (Hermann and Weingart, 2003). Administration of an energy substrate in the form of food or intravenous dextrose is often required to maintain the increased metabolic needs and ensuing hypoglycaemia, so close monitoring is required.

Active external rewarming is used for mild to moderate hypothermia or for individuals with significant comorbidities. This non-invasive method uses forced air rewarming and/or resistive heating methods, such as electric blankets, to achieve conductive heat transfer from skin into the underlying tissue as well as convection of warmed peripheral blood into the core (MacCaughelty et al, 1995). Active rewarming is the cornerstone of most treatment regimens as it is quicker than passive rewarming and can be combined with airway rewarming for maximum effect of approximately 0.9–3.3°C/hour (Hermann and Weingart, 2003). Owing to the larger ratio of surface to body mass this method is very efficient in children and infants (Gardner, 2009).

Table 2. Mechanisms of heat transfer

Radiation	Transfer of thermal energy through space by electromagnetic waves
	Proportional to the difference between the ambient and surface temperatures to the fourth power
	Dependant on the exposed surface area
	Normally lose approximately 60% of heat via this mechanism
Conduction	Heat transfer between two objects in direct physical contact
	Most occurs in immersion, as water conducts heat away from the body 25x faster than air
	Granite floors are 4x the conductivity of water, thus there is a high post-fall rate of hypothermia for the elderly
	Wet clothes increase conductive heat loss 5x
Evaporation	Heat loss resulting from converting water from a liquid to a gas
	Occurs via insensible perspiration (70% humidity at the body surface) and respiration (water vapour during exhalation)
	Lowers the body by 0.6 kcal/g or about 15% of the daily dietary intake
	Can lead to volume loss and dehydration by insensible losses
Convection	Heat transfer facilitated by movement of air or liquid across an object
	Rate of heat loss depends on the temperature gradient, density and velocity of the moving substance
	In combination with evaporation (wet clothes on a windy day) leads to extreme heat loss
	Wind chill is a combination of wind velocity (squared) and temperature

Figure 1. Electrocardiogram with many of the classic findings in hypothermia, including Osborne waves. From Mareedu et al (2008).



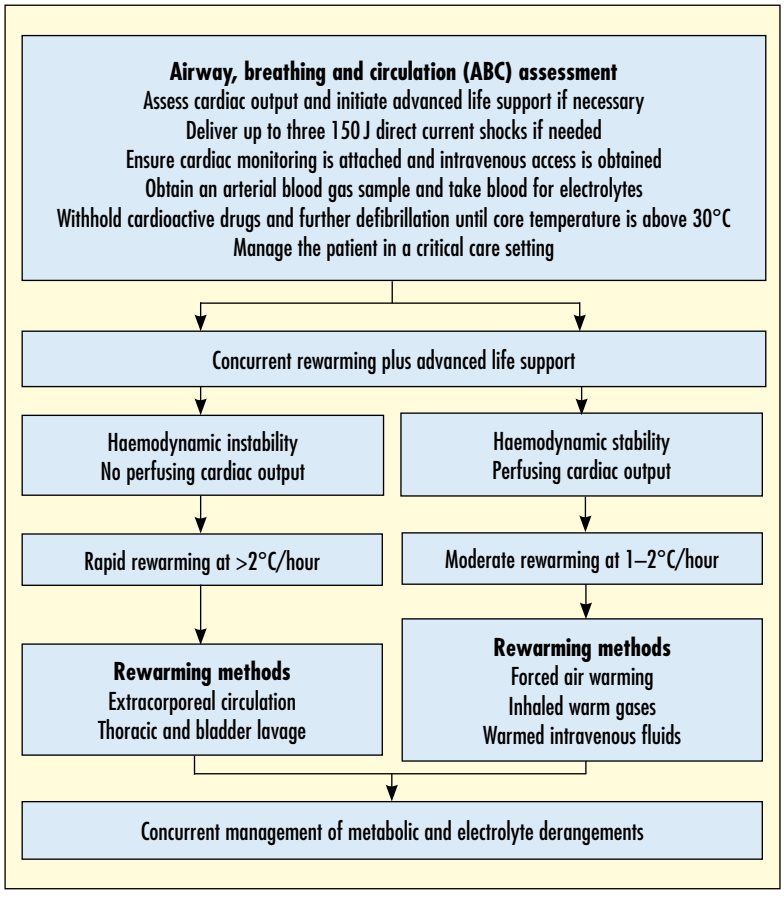


Figure 2. Severe hypothermia management algorithm. From Headdon et al (2009).

Active core rewarming is used only for severe hypothermia (<30°C). While it features the fastest return to normothermia, it is riskier because it is invasive (McCullough and Arora, 2004). Core organs are responsible for 50% of the heat production in basal metabolism at normothermia, and an even higher amount in hypothermia, therefore concentrating on heating the most metabolically active tissues leads to very effective rewarming techniques (Wilkey, 2004). Methods for active rewarming are noted in *Table 3*.

Complications

Afterdrop occurs when the core temperature continues to decline even with rewarming (Hermann and Weingart, 2003). The return of cooled blood from the periphery via vasodilation leads to a drop in the core temperature, coupled with a conductive heat gradient with the cool periphery transferring heat from a warm core. This gradient does not reverse immediately, even during active external rewarming, and there is continual heat transfer from the core to the periphery until equilibrated.

Cardiovascular shock can occur with active rewarming and is referred to as rewarming shock (Mallett, 2002). With external rewarming there is an increased metabolic tissue rate and vasodilation of the periphery that demands increased cardiac output from a cooled heart. If the heart cannot meet these metabolic needs a shock state results and standard shock treatment with cardiovascular assistance is required.

Prognosis

The final outcome of the hypothermia patient depends on the cause and degree of the hypothermia, comorbid conditions and prehospital treatments. Generally, individuals with no significant underlying cardiopulmonary conditions have a better prognosis. Patients presenting with moderate hypothermia have 12% inpatient mortality, increasing to 40% with severe hypothermia and 50% when there is concomitant cardiopulmonary or neurological disease (Hermann and Weingart, 2003). A low threshold for admission must be maintained, especially in the extremes of age. All patients who have had a loss of consciousness, required invasive rewarming and/or have haemodynamic instability must be admitted to an intensive care setting in order to evaluate for secondary causes of hypothermia such as sepsis (Gardner, 2009). All patients with frostbite also require admission or close outpatient follow up as the injury can often worsen 12–24 hours after the initial insult with lines of injury taking days or weeks to develop (Ulrich and Rathlev, 2004). Admitted patients will require daily hydrothera-

Table 3. Rewarming methods

	Method	Ideal patient population	Initial core temperature range	Rewarming rate
Passive	Expose and dry patient, then wrap in warm, dry blankets	Otherwise healthy young patients	Mild hypothermia (32–35°C)	0.2–0.85°C/hour
Active external	Expose and dry patient, then use forced air heating or heating blankets	Most efficient in infants, children	Mild–moderate (35–28°C)	0.9–3.3°C/hour
Airway rewarming	Warm air (max 46°C) during intubation	Multiple comorbid individuals	Severe hypothermia (<30°C)	0.05–0.5°C/hour
Gastrointestinal irrigation	Stomach lavage with boluses of warm fluid (250 ml at 40°C) via nasogastric tube	Individuals with multiple comorbidities	Severe hypothermia (<30°C)	1.5°C/hour
Cardiopulmonary bypass	Bypass, dialysis	Patients with cardiac arrest	Severe hypothermia (<30°C)	>9°C/hour

py, limb elevation, non-steroidal anti-inflammatory drugs and aloe vera application. A low threshold is required for operative debridement, escharotomy or other operative techniques to reduce complications (Petrone et al, 2003).

Patients with mild hypothermia who are adequately rewarmed in the emergency department and have few comorbidities can be safely discharged (McCullough and Arora, 2004). However, the source of the hypothermia must be addressed adequately. Homeless individuals will require provisions of well-fitting clothing and a social work evaluation for shelter placement. Those living alone, especially the elderly, often require an evaluation of the home environment concerning adequate access to heat and food. Intoxicated individuals may need a referral to a detoxification centre. Regardless of the cause, all individuals discharged must be seen by a primary care physician for evaluation of complications in 3–5 days (Hermann and Weingart, 2003).

Associated conditions

There are a number of conditions associated with unintentional hypothermia, including frostnip (ice crystal deposition in the dermis), frostbite (frozen skin surfaces), trench foot (tissue necrosis without freezing), and chilblains or pernio (repeatedly partially frozen and thawed epidermis). These conditions, and their treatments, are further delineated in *Table 4*.

Intentional (therapeutic) hypothermia

Intentional hypothermia theory

Therapeutic hypothermia is the only intervention shown to improve neurological outcomes after cardiac arrest (Hachimi-Idrissi et al, 2001; Bernard et al, 2002; Holzer and the Hypothermia After Cardiac Arrest Group, 2002). Hypothermia enhances the survival of reversibly ischaemic brain cells by suppressing a number of temperature-dependent biochemical processes.

Ischaemia enhances calcium influx into cells and activates numerous enzymes (caspases and kinases), leading to cell death (Clifton et al, 2010; Polderman, 2011). Lysing cells release still more of these chemical messengers, contributing to an overall toxic level of excitatory transmitters. All of these processes are mitigated by hypothermia (Polderman, 2011). As a patient's temperature falls, his/her cellular metabolic demand decreases, allowing marginally ischaemic cells to survive long enough for the body to begin to heal itself.

Current indications

The initial studies in hypothermia examined patients with witnessed collapse, resuscitation was initiated within 5–15 minutes, and the patient had a presenting rhythm of ventricular fibrillation or ventricular tachycardia (Hachimi-Idrissi et al, 2001; Bernard et al, 2002; Holzer and the Hypothermia After Cardiac Arrest Group, 2002). Current guidelines state that cooling should be initiated in unresponsive patients after return of spontaneous circulation from ventricular fibrillation- or ventricular tachycardia-related cardiac arrest (Clifton et al, 2010). While the evidence supporting the use of therapeutic hypothermia in patients with other causes of cardiac arrest (e.g. pulseless electrical activity, asystole) is still being developed (Garrett et al, 2011; Testori et al, 2011), it seems reasonable to cool these patients as well (Clifton et al, 2010). Contraindications to therapeutic hypothermia are multiple organ failure, sepsis or a pre-existing coagulopathy.

After return of spontaneous circulation, the clinician should treat the patient's hypotension and optimize his/her ventilation and oxygenation. Clinicians should search for and treat the cause of the patient's presentation. The most common cause of cardiac arrest is underlying cardiac disease, and both percutaneous coronary intervention and thrombolysis are safe for patients undergoing therapeutic hypothermia (Wolfrum et al, 2008; Schefold et al, 2009). Catheterization is independently associated with good outcomes (Reynolds et al, 2009).

Table 4. Hypothermia-related conditions

	Exposure	Damage	Signs	Symptoms	Treatment*
Frostnip	Freezing and damp, over hours to days	Only dermis frozen	Pale, numb, stiff tissue; commonly nose, ears, fingers, toes	Sensation of cold, then burning, and finally numbness	Immersion and movement of the affected area in warm water (37–41°C) for 15–30 minutes
Frostbite	Freezing and damp, over hours to days	Dermis frozen and deeper structures	Pale, numb, stiff tissue; commonly nose, ears, fingers, toes	Sensation of cold, then burning, and finally numbness	Immersion and movement of the affected area in warm water (37–41°C) for 15–30 minutes
Trench foot	Cold water for hours to days	Tissue necrosis without freezing	Pale skin that sloughs off	Sensation of cold, then burning, and finally numbness	Immersion and movement of the affected area in warm water (37–41°C) for 15–30 minutes
Chilblains	Chronic cold, dry, wind over weeks	Epidermis repeatedly partially frozen and thawed	Erythematous, scaly ulcers; usually on exposed skin	Ulcers are painful and pruritic	Calcium-channel blockers provide pain relief and decrease recurrence

*All conditions are treated by removal of the patient from the cold environment with consideration of tetanus prophylaxis and antibiotics

Table 5. Cooling methods

Technique	Method	Benefits	Drawbacks
Ice	Bags of ice applied to groin, axilla, chest	Cheap, effective	Easily over-cools patient, requires intensive nurse monitoring
Cooling helmets and blankets	Device applied to patient's head or chest	Automated, effective, high degree of temperature control	Expensive
Cold infusions	30 ml/kg bolus of 4°C normal saline or Ringer's lactate	Cheap, effective, available on-scene	Ineffective as stand-alone therapy

Cooling and warming

Strategies

Therapeutic hypothermia should be instituted to a core temperature between 32 and 34°C as soon as possible after return of spontaneous circulation for at least 12–24 hours (Clifton et al, 2010). This range is above the point where there is an increased risk for cardiovascular arrhythmias (<28°C), but below the temperature where shivering occurs (>34°C). Patients should be closely monitored to ensure that their temperature does not fluctuate more than 0.5°C. Patients should not be warmed faster than 0.2–0.5°C/hour to preserve the benefit of hypothermia, and the warming process is much the same as for accidental hypothermia.

Methods

There are a number of methods of cooling patients (*Table 5*). Unless contraindicated, an appropriate initial step in resuscitating patients in cardiac arrest is to infuse a bolus of 30 ml/kg of 4°C saline or Ringer's (Garrett et al, 2011). There is some evidence showing that initial infusion of at least 200 ml of cooled normal saline helps regain return of spontaneous circulation in the prehospital setting, regardless of presenting rhythm (Garrett et al, 2011). Ice bags, while cheap and convenient, require intensive monitoring and may lead to overcooling (Merchant, 2006). If a mechanical or automated method of cooling is deployed, current recommendations support the use of two continuous temperature measures.

Complications

In the original Hypothermia After Cardiac Arrest study (Holzer and the Hypothermia After Cardiac Arrest Group, 2002), the most common complications were arrhythmia, bleeding, pneumonia and sepsis. The incidence of the latter two increased in the hypothermia arm (from 29% to 37%, and from 7% to 13% respectively). Hyperglycaemia was also common, and should be treated to a level of permissive hyperglycaemia (<180 mg/dl) to avoid hypoglycaemia. Clinicians should anticipate and treat electrolyte abnormalities that result from the fluid shifts and diuresis that occur during cooling and warming.

Future indications and areas of development

The data are still being developed for indications outside of comatose patients with return of spontaneous circulation after a witnessed ventricular fibrillation-cardiac arrest. Two recent studies (Mooney et al, 2011; Testori et al, 2011) have shown that survivors of out-of-hospital arrest with a non-shockable rhythm who underwent therapeutic hypothermia had improved neurological outcomes.

Therapeutic hypothermia for newborns who have suffered anoxic injury may be protective, reducing both death and disability (Jacobs et al, 2007). Another area of active interest is the use of hypothermia for traumatic brain injury, but most trials have been small and of varying methodologies and quality (Sydenham et al, 2009). The largest and most definitive trial was recently halted for futility (Harshman et al, 2011). Hypothermia has been shown to be relatively safe for patients with acute ischaemic stroke (the greatest risk is of infection), but it has not yet been determined whether there is a benefit (Den Hertog et al, 2009).

KEY POINTS

- Use the least invasive rewarming technique possible for unintentional hypothermia, but have a low threshold to increase aggressiveness.
- Consistently follow the blood glucose level as hypoglycaemia can worsen hypothermia and correction is an important adjunct to rewarming the patient.
- Thoroughly question all witnesses as often there is a secondary head trauma associated with hypothermic cases.
- A change in behaviour is the first manifestation of hypothermia, followed by decreased fine motor skills, dysarthria and a decrease in gross motor skills. A mnemonic for this is: mumbles, grumbles, fumbles, stumbles, tumbles.
- Because cardiac arrest is commonly caused by myocardial infarction, initiate therapeutic hypothermia after return of spontaneous circulation and then arrange for emergent cardiac catheterization for the patient.
- In addition to ventricular fibrillation or ventricular tachycardia arrest, consider therapeutic hypothermia in patients with pulseless electrical activity and asystole or unwitnessed arrest.
- Consider a cold saline bolus (30 ml/kg of 4°C normal saline or Ringer's lactate) as the initial resuscitative fluid in cardiac arrest, especially in the prehospital setting.
- There is not yet enough evidence to recommend therapeutic hypothermia for traumatic brain injury or ischaemic stroke.

Conclusions

Hypothermia is when the body's core temperature is below <35.0°C. This cooling can occur either unintentionally (by accident) or intentionally (for therapeutic

reasons). Unintentional hypothermia needs to quickly recognized and appropriately treated, as mortality in moderate to severe hypothermia is significant. Intentional hypothermia is rapidly becoming an important component of post cardiac arrest treatment and should be implemented in accident and emergency departments. **BJHM**

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