Induced and Accidental Hypothermia

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ABSTRACT

Objective: *To review human thermoregulation and the pathophysiology and management of induced and accidental hypothermia.*

Data sources: *A review of studies reported over ten years from 1990 to 2000 and identified through a MEDLINE search of the English-language literature on thermoregulation and induced and accidental hypothermia.*

Summary of review: *Hypothermia is defined as a core temperature less than 35°C, and may be therapeutic (i.e. induced for clinical benefit) or accidental. Hypothermia induced prior to cardiovascular or neurosurgical procedures (i.e. therapeutic hypothermia) allows for a greater hypotensive operative period with less risk of cerebral or cardiac ischaemic injury. Hypothermia induced following tissue injury (e.g. closed head injury, cerebrovascular accident, adult respiratory distress syndrome) has also been used to reduce ischaemic tissue injury, although significant clinical benefits have not yet been demonstrated.*

Inadvertent hypothermia (i.e. accidental hypothermia) is classed as mild from 33°C - 35°C, moderate from 30°C - 33°C and severe if less than 30°C. Treatment includes surface and core warming methods, all of which have a valid basis from experimental studies. However, no prospective, randomised controlled clinical trials exist that have compared the various rewarming methods. Currently, passive rewarming methods (e.g. reflective metalloplastic sheets, blankets) are recommended for patients with mild hypothermia (≥ 33°C), active surface rewarming (e.g. heated blankets, hot air circulators) for moderate hypothermia (≥ 30°C), active core rewarming (e.g. heated haemodialysis, haemodiafiltration or peritoneal dialysis) for severe hypothermia (< 30°C), and heated cardiopulmonary bypass for severe hypothermia with cardiopulmonary arrest.

Conclusions: *Operative* h*ypothermia reduces ischaemic injury during cardiac and neurosurgical procedures. Hypothermia induced following tissue injury has not yet been shown to be of benefit. Management of accidental hypothermia requires passive and active warming methods, the indication of each depending on the availability of the method and severity of hypothermia.* (**Critical Care and Resuscitation 2000; 2: 22-29**)

Key Words: Hypothermia, thermoregulation, active rewarming, passive rewarming, hypothermic cardiac arrest

Normal body function depends upon a relatively constant body temperature, which is determined by the balance between heat production and heat loss. The core temperature (e.g. rectal, oesophageal, bladder or intravascular temperature) is normally 0.5°C higher than the oral temperature and undergoes a circadian fluctuation of ± 0.6°C with the temperature lowest at 6 a.m. and highest at 8 p.m. In females there is a monthly cycle in which the temperature rises at ovulation by 0.5°C and falls to normal at the onset of menstruation. The normal adult core temperature ranges from 36°C to 38°C, and during exercise may increase up to 40°C.[1-4]

Thermoregulation about a set point of 37°C is normally carried out by two hypothalamic temperature

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regulating centres (Figure 1). The posterior hypothalamic heat maintenance centre is stimulated by the cortex when the sensation of 'cold' is registered, activating mechanisms to increase heat production and reduce heat loss (Table 1). Lesions of the posterior hypothalamus may cause the patient to become a poikilotherm, often with a reduced body temperature.

The anterior hypothalamic heat loss centre is temperature sensitive and is stimulated by an increase in circulating blood temperature above the 'set point', activating mechanisms to increase heat loss and decrease heat production (Table 1). Lesions of the anterior hypothalamus may cause the patient's temperature to rise up to 43°C.

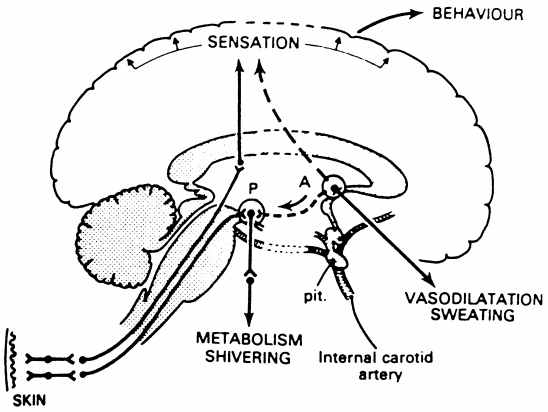

Figure 1. A sagittal section of the brain showing the pituitary (pit.) and internal carotid artery supplying the hypothalamus. The anterior hypothalamic heat loss centre (A) and posterior hypothalamic heat maintenance centre (P), are also shown along with neural connections believed to be involved in thermoregulation.

Table 1. Temperature regulating mechanisms

Mechanisms activated when feeling cold
- Increase in heat production
  shivering, increased muscular activity, hunger
  increased TSH, noradrenaline, adrenaline secretion
- Decrease in heat loss
  cutaneous vasoconstriction, piloerection
  behaviour modification
  (e.g. putting on clothing, building a fire)

Mechanisms activated when feeling hot
- Increase in heat loss
  cutaneous vasodilation, sweating
  behaviour modification
  (e.g. taking off clothing, standing in shade)
- Decrease in heat production
  decreased activity, anorexia
  decreased TSH, noradrenaline, adrenaline secretion

A fever is a regulated rise in core body temperature above 38°C, due to the increase in the hypothalamic 'set point'.[3,5-7] The temperature rarely exceeds 41°C (unless the thermoregulatory mechanisms are compromised),[7,8] contrasting with heatstroke and malignant hyperthermia where temperatures are always greater than 41°C. During a fever the normal diurnal temperature variation continues with the temperature tending to 'spike' in the evening and fall in the morning. While hyperthermia (i.e. temperature > 41°C) may cause seizures, cerebral oedema, hepatic failure and disseminated intravascular coagulation,[9-12] the beneficial effects of a fever (i.e. 38°C - 41°C) during an infection are to provide, an adverse affect on the replication of microorganisms, an increase in the generation of cytolytic T-cells, B-cell activity and immunoglobulin production, an increase in the microorganism's requirement of iron for growth, and a decrease in the serum iron concentration.[6,13,14]

HYPOTHERMIA

Hypothermia is defined as a core temperature of 35°C or less.[15] It is either induced (i.e. therapeutic) or accidental.

Induced (therapeutic) hypothermia

Hypothermia has been used both before and after the onset of tissue injury.

Before tissue injury: By reducing tissue consumption for oxygen, perioperative hypothermia reduces significantly the incidence of cerebral[16] or spinal cord[17] damage during cardiovascular and neurosurgical procedures. The basal metabolic rate falls by 7% - 8% per degree Centigrade, to reach 85% - 75% of normal at 35°C - 33°C, 65% - 75% of normal at 30°C - 33°C and 55% - 65% of normal at 28°C.[15] At 18°C the EEG is isoelectric,[18] and cerebral oxygen requirement is reduced by 45% – 50%. The reduction in temperature affects both carbon dioxide production and oxygen consumption similarly, thus the respiratory quotient remains constant.[19]

After tissue injury: Hypothermia has been used following cerebral trauma, focal or global anoxic brain injury, cerebral oedema, acute respiratory distress syndrome and carbon monoxide poisoning, showing some benefits in the experimental model and in some clinical studies.[20,21]

The most common use for hypothermia, however, is following cerebral trauma. One randomised controlled study in patients with severe closed head injury demonstrated that hypothermia (32°C - 33°C) for 24 hours (within 10 hours of injury) significantly improved the outcome at 3 - 6 months in patients with an admission Glasgow coma score (GCS) of 5-7 (but not with a GCS of 3-4), although the improvement was not

significant at 12 months.[22] However, the therapeutic window for the beneficial effect of hypothermia following cerebral injury may be very narrow with one study concluding that mild hypothermia should be applied within the first 30 minutes after the onset of ischemia.[23]

Hypothermia has also been used to manage resistant intracranial hypertension, with one randomised controlled study of 33 patients with severe head injury and resistant intracranial hypertension, documenting a significant reduction in intracranial pressure (ICP) and reduction in mortality with hypothermia (e.g. 34°C for 48 hr).[24] The reduction in ICP was caused by a reduction in cerebral oxygen requirement as the cerebral blood flow and arterio-jugular venous oxygen differen-ce was also reduced.[24] In a later study, this group could not confirm any advantage with hypothermia in head injured patients with normal ICP (i.e. those in whom the ICP could be maintained below 20 mmHg by conventional treatment).[25]

However, hypothermia has been associated with adverse effects, including an increase in wound infection following surgery[26] (which may be due to peripheral vasoconstriction, shift in the oxygen-haemoglobin dissociation curve to the left,[27] and an impairment of granulocyte chemotaxis, phagocytosis[28] and oxygen dependent microbial killing[29]), an increase in blood loss during surgery[30] (which may be due to an alteration in coagulation[31] and platelet function[32]) and an increase in multisystem failure (which may be due to an elevation in plasma levels of IL-6 and IL-8).[33] Also patients who develop accidental mild hypothermia following major surgery,[34,35] massive transfusion,[36] continuous renal replacement therapy,[37] burns,[38] multisystem trauma,[39-42] or sepsis[43,44] have an increased morbidity and mortality when compared with normothermic patients.

Currently, there are no large prospective randomised controlled clinical studies that have shown a significant reduction in morbidity or mortality when therapeutic hypothermia has been initiated after the onset of any clinical disorder.[45]

Accidental hypothermia

Accidental hypothermia often occurs in the elderly in whom circulatory adjustments, shivering and voluntary muscular activity are less effective in reducing the effect of cooling, or in infants in whom body surface area is large in comparison to their weight, increasing their capacity to lose heat.[46] It may also occur in normal individuals with excess or prolonged exposure to a cold environment (e.g. mountain climbers, swimmers, long distance runners).[47] Conditions that predispose to accidental hypothermia are listed in Table 2.

Table 2. Predisposing causes of hypothermia

Reduction in heat production
Endocrine disorders
myxoedema, Addison's disease, hypopituitarism, diabetic ketoacidosis, hypoglycaemia, lactic acidosis
Severe infection
Septicaemia, pneumonia, peritonitis pyelonephritis, meningitis
Malnutrition
Wernicke's encephalopathy
Uraemia
Cirrhosis
Pancreatitis
Increased heat loss
Cardiovascular accident
Major surgery
Burns, exfoliative dermatitis
Trauma
Massive transfusion
Renal replacement therapy, dialysis
Drugs
ethanol, opiates, barbiturates, benzodiazepines phenothiazines, tricyclics

Clinical features. As the standard mercury glass thermometer reads from 35°C to 42°C, hypothermia may be missed unless a thermometer which can record accurately down to 20°C is used. Hypothermia is often divided into:[48]

1. *Mild hypothermia* (i.e. core temperatures 33°C - 35°C). In normal individuals shivering usually occurs when the core temperature is reduced by 0.7°C (increasing the metabolic rate by up to 5 times). When the temperature is reduced to 35°C the patient usually shivers uncontrollably. The reduction in temperature also produces dermal vasoconstriction, tachycardia, elevation of the cardiac output, elevation of plasma catecholamine levels, a 'cold' diuresis and hyper-glycaemia. If glycogen stores are depleted, hypo-glycaemia may occur which inhibits shivering. The plasma levels of thyrotropin releasing hormone (TRH), triiodothyronine (T_3), L-thyroxine (T_4), growth hormone, thyroid-stimulating hormone (TSH) and adrenocorticotropic hormone (ACTH) stimulation tests are normal, suggesting normal pituitary, adrenal and thyroid function during mild hypothermia.[49]
2. *Moderate hypothermia* (i.e. core temperatures 30°C - 33°C). At temperatures below 33°C, shivering

gradually decreases, muscle and joints become stiff and there is a delayed relaxation phase of the stretch reflexes. The patient becomes lethargic, drowsy and often falls asleep. Unconsciousness rarely occurs at temperatures above 28°C, so another cause of coma should be sought if coma exists at levels above this temperature.[50] The pulse, blood pressure and respiratory rate are usually depressed.

3. *Severe hypothermia* (i.e. core temperatures below 30°C). At a temperature below 30°C, the body loses its ability to spontaneously return to a normal temperature (i.e. the patient becomes poikilothermic); thus active rewarming must be performed. At a temperature below 28°C, the patient is unconscious, areflexic with fixed and dilated pupils, and life may be difficult to detect. Bradycardia and atrial fibrillation occur at temperatures below 30°C and ventricular fibrillation (VF) may occur at temperatures below 28°C. At 20°C asystole is more common than VF. Respiratory frequency maybe reduced to 1 - 2 breaths/min. Bronchorrhoea is common (probably due to deficient ciliary function), whereas pulmonary oedema is rare. Circulatory arrests for 10 min at 30°C, 25 min at 25°C, 45 min at 20°C and 60 min at 16°C are often quoted as being the limits at which cerebral function may return to normal, although case studies indicate that these limits can be extended.[48,51] The lowest temperature recorded in a person who has subsequently survived is 16.4°C,[52] although under controlled hypothermic conditions for surgical procedures, temperatures down to 10°C are used, and temperatures as low as 6°C have been recorded.[48]

Investigations. Investigations that are commonly performed in a patient with accidental hypothermia include:

Biochemical and haematological tests: the haematocrit rises with cooling, due to a loss of plasma into the interstitial compartment; granulocytopenia and thrombocytopenia also occur due to splenic sequestration. Hypokalaemia (due to an intracellular redistribution of potassium from the extracellular compartment[53,54] caused largely by a decreased cell wall potassium permeability), hyperglycaemia, hypoglycaemia, moderate elevation of liver enzymes and hypercalcaemia may also be found.

Arterial blood gases: arterial blood PCO_2 and pH alter with changes in the patient's temperature, due to the change in solubility of a gas in a liquid. With hypothermia, the partial pressure of dissolved gases decrease as the temperature drops. With the decrease in $PaCO_2$, the pH rises. While the pH increases with falling temperature, so does the neutral point of water.[55] Because the neutral point specifies the state of ionisation of enzymatic and other proteins, the biologically normal pH (i.e. 7.40) should be higher than 7.4 at temperatures below 37°C. This is taken into account during treatment by maintaining the 'uncorrected' arterial PCO_2 and pH (i.e. values measured at 37°C) at 40 mmHg and 7.40, respectively[56,57] (known as the ectothermic strategy[58]).

With hypothermia, a respiratory alkalosis usually occurs first, followed by a mixed respiratory and lactic acidosis.

Microbiological tests: Blood cultures are performed as septicaemia is a common cause of hypothermia, particularly in the cirrhotic patient. Depending on the clinical circumstance, urine, sputum, cerebrospinal fluid and ascitic fluid may also be taken for culture.

ECG: The ECG changes associated with hypothermia include shivering artefact, bradycardia (with heart rates of 10/min at 20°C, falling to 3 - 4/min at 10°C if the circulation remains intact),[59] AV block (first, second or third degree), atrial fibrillation (which only occurs at temperatures below 30°C) and, at temperatures below 28°C, multifocal ventricular ectopics and ventricular fibrillation. The QRS complex appears widened due to J waves or Osborn waves[60] (which are prominent in the mid and lateral precordial leads and are due to the delayed depolarisation of the inferior surface of the heart occurring at temperatures below 31°C.[61] Figure 2), and the QT_c segment is prolonged.[48,62] At temperatures between 21°C and 24°C there is a high risk of VF, whereas at temperatures below 20°C asystole is more common than VF.[48] Reversal of the ECG changes may be delayed and ECG changes can persist for days after rewarming.[63]

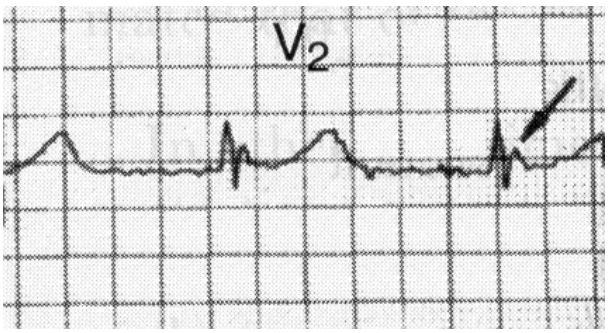

Figure 2. Precordial V2 lead in a hypothermic patient (29°C) demonstrating characteristic Osborn waves (arrow) as well as bradycardia and prolonged QTc interval (Modified from Patel A, et al. N Engl J Med 1994;330:680)

Treatment. Therapy for accidental hypothermia includes:

1. *Resuscitation*: the main hazard of rapid rewarming is hypotension due to dilation of the peripheral vessels and

hypovolaemia (some of which is caused by cold diuresis). Core temperature, ECG, cardiac pressures (using a central venous catheter with mild hypothermia, or right heart catheter with moderate to severe hypothermia) and urine output are monitored. If the patient is unconscious the airway needs to be protected from aspiration using an endotracheal tube,[64] and intubation with mechanical ventilation will be required for patients with respiratory failure. Arterial blood gases, plasma electrolytes and glucose, liver function tests, and blood cultures, should also be monitored.

Intravenous fluids, glucose, and low dose catecholamine infusions may be required. Hypokalaemia should be monitored and potassium supplements should not be given unless it remains after the temperature is increased to > 35°C, as potassium replacement has been associated with lethal rebound hyperkalaemia on rewarming.[65]

2. *Rewarming*: this may be either passive or active.

Passive rewarming. Passive rewarming means that the patient is rewarmed by endogenous heat production. If shivering does not occur then passive rewarming (e.g. using blankets and thin reflective metalloplastic sheets) is slow, with the core temperature usually rising by 0.5 - 1°C/hr.[66] Shivering may double this rewarming rate. These techniques are usually adequate for patients with mild hypothermia (i.e. ≥ 33°C).

Active rewarming. Active rewarming means that the patient is rewarmed by an external energy supplement and should be used if the core temperature is < 33°C or the patient is hypotensive or in respiratory failure.[67] Active rewarming techniques may consist of:

a) *Surface rewarming*, for example heated blankets, hot air circulators, radiant heat cradles or a warm bath. While 'rewarming shock' has been reported when active surface rewarming methods have been used (due to the effects of peripheral vasodilation[15]), if external temperatures are no greater than 40°C, this effect is avoided.[68] Surface rewarming techniques are usually used for moderate hypothermia (i.e. ≥ 30°C).
b) *Core rewarming*, (considered for severe hypothermia, i.e., core temperatures below 30°C)[69] for example,
   - humidified and warm air inhalation (warmed to 42°C) is a useful adjunct to other methods of rewarming.[70]
   - infusing warm intravenous solutions. Solutions are warmed only to 41°C as haemolysis may occur if solutions with temperatures greater than 42°C are used[71,72] (although solutions with temperatures up to 65°C have been recommended if administered via a central venous access[73]). This is also an adjunct to other methods of rewarming, as it requires from 3-4 litres of preheated solution to increase the temperature of an adult by 1°C.
   - lavage body cavities with warm fluid. While gastric, mediastinal or pleural cavity lavage have been used in isolated reports of hypothermia,[48] peritoneal dialysis (e.g. warming the dialysate fluid to 44°C with rapid instillation and immediate removal) has been recommended as the method of choice if body cavity lavage is to be performed[74] as the resultant rewarming from 4 - 6°C/hr is as rapid as extracorporeal circulation techniques.[48,51]
   - extracorporeal shunt rewarming. Continuous arteriovenous or venovenous diafiltration,[75] or haemodialysis (with blood flow rates of 300 - 500 mL/min and dialysis fluids warmed to 42°C and with flow rates of 300 mL/min),[76,77] have become the methods of choice for active rewarming in the non-cardiopulmonary arrest, severely hypothermic patient.
   - cardiopulmonary bypass[78] (using a heparin coated bypass system and femoral access). If available, this is the method of choice in the hypothermic cardiopulmonary arrest patient, as it provides rapid rewarming (e.g. up to 8.8°C/hr) as well as oxygenation and perfusion of vital organs. Haemodialysis may also be used in the cardiac arrest patient to correct electrolyte abnormalities and remove toxins.

If active rewarming is performed, then it should be used until the temperature reaches 33°C, thereafter rewarming at 1°C/hr with passive rewarming techniques should be used.

3. *Antibiotics*: intravenous broad spectrum antibiotics until the results of the blood culture are known, may be used particularly in the debilitated patient.

4. *Corticosteroids:* there are no benefits from routine use of corticosteroids or thyroxine in patients with hypothermia.[48]

5. *Antiarrhythmics*: malignant cardiac arrhythmias are not a feature of rewarming during treatment of hypothermia, thus prophylactic antiarrhythmic drugs are not indicated.[66]

Treatment of hypothermic cardiac arrest. Death from hypothermia is often due to cardiac arrest, because there is a high risk of ventricular fibrillation at temperatures below 28°C. However, as defibrillation has little effect at these temperatures,[79] it is believed that if

cardiopulmonary bypass is not available cardio-pulmonary resuscitation (CPR), at half the normal rate, with 100% oxygen and reduced ventilation, should be performed in association with core rewarming methods[51] until the temperature has increased to 30°C, when defibrillation may then prove to be effective.[51] However, as hypercapnia and metabolic acidosis have been reported during CPR for hypothermic cardiac arrest using normal compression and ventilation rates,[80] an alteration in normal CPR may not be necessary.

There are reports of resuscitation with a return to normal neurological status with rectal temperatures as low as 14.4°C in children,[81] and 13.7°C in young adults,[80] despite cardiac arrests of up to 4.75 hr duration.[52] Therefore, it is recommended that the patient should not be certified dead until the patient is warmed to at least 35°C.[47]

In an attempt to predict hypothermic cardiac arrest patients who are likely to be successfully resuscitated, one study found that a plasma potassium of greater than 10 mmol/L (taken immediately on admission) was a reliable index of irreversibility;[82] a finding that was confirmed by a later multicentre study.[83] However, in another multicentre prospective study of 428 hypothermic patients, 267 of whom had a measured potassium, no patient, irrespective of outcome, had a serum potassium > 10 mmol/L (although, a higher potassium level of 4.60 $\pm$ 1.57 mmol/L was noted in the 52 nonsurvivors compared with 4.10 $\pm$ 0.80 mmol/L in the 215 survivors[84]).

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