

Review

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Pathophysiology of accidental hypothermia

M.L. MALLET

From the Medical Assessment Unit, Royal United Hospital, Bath, UK

Summary

Accidental hypothermia is an uncommon problem that affects people of all ages, but particularly the elderly. This review briefly outlines the aetiological factors that may predispose to hypothermia, with particular reference to the effects of sepsis, although the specific situation of cold-water immersion is not addressed. A more detailed analysis of the pathophysiology of hypothermia then examines the cardiovascular, haematological, neurological,

respiratory, renal, metabolic, and gastrointestinal systems. Clinically relevant findings are highlighted and some associated management points are related to the physiological changes. Most of these changes are reversible on rewarming, and are resistant to pharmacological manipulation; some of the pathological effects are related more to the process of rewarming than to the hypothermia itself.

Introduction

Accidental hypothermia is defined as an unintentional fall in core temperature to $<35^{\circ}\text{C}$, and is classified into mild, moderate, and severe in different ways, mild usually being $33\text{--}35^{\circ}\text{C}$, $32\text{--}35^{\circ}\text{C}$, or $32.2\text{--}35^{\circ}\text{C}$, and severe usually being defined as $<28^{\circ}\text{C}$, $<27^{\circ}\text{C}$, or $<26.7^{\circ}\text{C}$. It is an uncommon cause of death: a study in Ireland found hypothermia to be responsible for 18.1 deaths per million¹ out of 53.6 cases per million population, and a smaller Glasgow study found a similar mortality equating to 22 per million,² out of 71 cases per million population. Official figures from death certificates give hypothermia as the cause of 300 deaths annually in the UK. Epidemiological studies, not surprisingly, have identified an at-risk group which is isolated, socially deprived, and ill;^{3,4} accidental hypothermia is also primarily a problem of older people, with 85% of one series being over the age of 60.⁵

Aetiology

Normal thermoregulation involves a dynamic balance between heat production and control of heat loss, with the aim of providing a constant core temperature. This is achieved in part by adjustment of central thermogenesis, and in part by maintaining a differential temperature gradient between the body core and the peripheries directly exposed to the environment; the amount of heat gained from or lost to the environment is closely and rapidly regulated in response to changing circumstances. Two types of cutaneous receptors are involved: cold and warm. Exposure to cold increases activity in the afferent fibres from the cold receptors, which stimulate the pre-optic nucleus of the anterior hypothalamus; direct reflex vasoconstriction reduces blood flow to the cooling skin, and colder blood also reaches temperature-sensitive neurons in the hypothalamus. The hypothalamus then initiates various responses, immediate responses via the

Address correspondence to Dr M.L. Mallet, Medical Assessment Unit, Royal United Hospital, Combe Park, Bath BA1 3NG. e-mail: mark.mallet@ruh-bath.swest.nhs.uk

autonomic nervous system, more delayed responses through the endocrine system, adaptive behavioural responses, extra-pyramidal skeletal muscle stimulation, and shivering. These responses aim either to increase heat production or to reduce heat loss.⁶

Older people are particularly susceptible to accidental hypothermia because thermoregulatory ability is progressively impaired with age. They may have a reduced ability to generate heat because of reduced lean body mass, impaired mobility, inadequate diet, and reduced shivering in response to cold.⁷ Sympathetically activated thermogenesis in brown adipose tissue is attenuated from the end of infancy. In addition, older people are susceptible to increased heat loss through a reduced ability to vasoconstrict appropriately, are less able to discriminate changes in temperature,⁸ may have abnormal adaptive behavioural responses, and may be prone to exposure to cold through falls or illness. Predisposing socio-economic factors may be particularly relevant to the elderly. Indeed, some elderly people suffer recurrent episodes of hypothermia,^{9,10} suggesting that they may have a particular predisposition to thermoregulatory failure that can be precipitated by a relatively minor insult.

In addition to this age-related impairment of adaptability to a fall in temperature, various pathological conditions may be implicated in the development of hypothermia. For example, central thermoregulatory ability can be impaired in such situations as stroke, CNS trauma or infection, tumours, or haemorrhage, and in uraemia, Parkinson's disease, multiple sclerosis and Wernicke's syndrome. Impaired control of peripheral vasculature through autonomic dysfunction can also play a part in diabetes,¹¹ infection and cardiac failure. Reduced heat production occurs in endocrinopathies such as hypothyroidism, hypoadrenalinism, and hypopituitarism, and hypoglycaemia alone can predispose to hypothermia,¹² particularly in the context of alcohol ingestion.¹³ Pancreatitis and diabetic ketoacidosis¹⁴ also need to be considered as precipitating causes of hypothermic episodes, even if they are not clinically apparent. Diabetes itself may also be a factor which increases the likelihood of accidental hypothermia,^{14,15} particularly in the context of malnutrition.¹⁶

Perhaps the most frequent precipitating factor in older people is sepsis, which in several series has been found in about 80% of elderly patients with hypothermia.¹⁷⁻¹⁹ In the 9–10% of patients in whom an infection results in hypothermia rather than fever, there is a significantly worse prognosis: mortality is approximately doubled, perhaps in part because of the higher rate of shock in these patients.²⁰ Sepsis may predispose to hypothermia

either by causing a failure of vasoconstriction, or by inducing an abnormal hypothalamic response. The mechanism for this remains unclear, but there is evidence of an increased cytokine response, with raised levels of tumour necrosis factor alpha (TNF- α) and interleukin-6, and elevated prostacyclin and thromboxane B2 metabolites in hypothermic septic patients.²¹ Animal work indicates that at lower ambient temperatures, injection of high doses of bacterial endotoxin in the form of lipopolysaccharide (LPS) induces a hypothermic response while lower doses result in pyrexia;²² it seems that LPS endotoxin can cause a lowering in the threshold temperature for activation of thermogenesis, and also has some behaviour-modifying effects.²³

Some pharmacological agents can cause central thermoregulatory failure (for example barbiturates, opioids, tricyclic antidepressants, and benzodiazepines), and phenothiazines can both impair central thermoregulation and also inhibit peripheral vasoconstriction in response to cold by their alpha-blocking activity.²⁴ Other alpha blockers such as prazosin have been reported to cause hypothermia,²⁵ and the elderly seem particularly susceptible to this effect of alpha blockade.²⁶ Lithium toxicity has been reported to lead to a reduction in core temperature,²⁷ and ethanol can lead to peripheral dilatation, impaired shivering, hypoglycaemia and environmental exposure to cold, as well as having a direct effect on the hypothalamus,²⁸ by which it lowers the thermoregulatory set point, resulting in a fall in core temperature.²⁹ Valproic acid has also been reported to cause hypothermia in a handful of cases, but the mechanism is unknown.³⁰

The end point of accidental hypothermia can, therefore, be considered as a failure of thermoregulatory control, which may have both underlying predisposing causes, including age, various pathologies both acute and chronic, and pharmacological agents, and also more immediate precipitating factors. These precipitating factors may vary between acute exposure to cold in an otherwise previously fit individual, through a more prolonged period in a less cold environment (so-called chronic hypothermia),³¹ to a relatively brief exposure to mild cold in the context of illness, often sepsis, or enforced inactivity such as after a fall. For a previously fit, younger victim of cold exposure, the outlook is generally good in the absence of apnoea or circulatory arrest; rewarming alone generally leads to full recovery. The more commonly encountered situation in clinical practice, however, is when an elderly person becomes hypothermic because of another condition, and the outcome is then generally determined by the nature of this underlying illness. Attention therefore

needs to be directed to finding and treating this precipitating condition—often sepsis—in parallel with measures to deal with the hypothermia.

Pathophysiology

Observational work since the early part of the last century, human and animal experiments, and monitoring of surgical patients undergoing induced hypothermia for cardiopulmonary bypass or neurosurgery, have provided much information about the physiological responses to cold. Whether the data from all these different situations can be extrapolated to that of accidental hypothermia, is not clear. The pathophysiological changes observed may be influenced by such things as underlying disease, hypovolaemia or drug ingestion, and will depend to some extent on the rate as well as depth of cooling,³² as there is some evidence that more severe problems with acid-base, electrolyte and fluid balance can occur in chronic hypothermia.³³ Apart from ischaemia-induced tissue infarcts, the changes induced by hypothermia are generally reversible on rewarming, and in many instances attempts to normalize physiological variables in this context are not only futile but dangerous.

Cardiovascular changes

In mild hypothermia, there is an initial tachycardia and peripheral vasoconstriction, and a consequent increase in cardiac output. The blood pressure increases slightly. These sympathetically driven changes can mostly be suppressed by drugs, however, with a proportional decrease in heart rate, blood pressure and cardiac output.²⁴ Ventricular ectopy is often suppressed by mild degrees of cold and reappears with rewarming. *In vitro* cooling of pig myocardium to 32 °C causes a prolongation of contraction, and an increase in contractile force by almost 40%.³⁴ As the temperature falls to a moderate degree of hypothermia, a progressive bradycardia develops consequent on decreased spontaneous depolarization of the pacemaker cells, and this is refractory to atropine. The resultant reduction in cardiac output may also be balanced by an increased systemic vascular resistance consequent on autonomic reflex response and catecholamine release. This elevated systemic resistance may be perpetuated by haemoconcentration, increased viscosity and local vasomotor responses.³⁵ Increased resistance in renal arteries has been found in animals while vasodilatation tends to occur in the splanchnic vasculature.³⁶

Repolarization abnormalities occur as evidenced by the appearance of a 'J' (Osborn) wave on the ECG, usually best seen in the lateral precordial leads; this tends to increase in amplitude with falling temperature, but is not otherwise affected by electrolyte disturbances.³⁷ J waves are not pathognomonic of hypothermia, but can also be seen in subarachnoid haemorrhage and other cerebral injuries, as well as in myocardial ischaemia. Increasingly broad QRS complexes develop, indicating slowing of myocardial conduction, in combination with ST elevation or depression and T-wave inversion; these ECG changes may be related to the increasing acidosis and ischaemia. At the cellular level, there is prolongation of the action potential duration, which is explained by delayed activation of the repolarizing potassium current, slowed inactivation of the sodium current, and delayed inactivation of the inward calcium current. The slowing of myocardial conduction is similarly attributable to reduced and delayed activation of the inward sodium current.³⁸ There is a prolongation of systole,³⁹ and conduction delay may be evidenced by an increased PR interval and second- or third-degree A-V block.⁴⁰ Delayed repolarization as reflected by QT prolongation may also be seen at lower temperatures. According to early observations, the QT prolongation may persist for hours or even days after rewarming,⁴¹ and atrioventricular block may develop days after normal temperature has been restored.⁴² Asystole 72 h after rewarming has also been reported.⁴³

The heart rate falls to 30–40 bpm at 28 °C; rates inconsistent with a patient's temperature should prompt a search for underlying pathology such as hypoglycaemia, hypovolaemia, or drug ingestion. At lower temperatures, the bradycardia may become extreme, with rates of about 10 bpm at 20 °C. Systemic vascular resistance falls as catecholamine release is blunted, and cardiac output decreases correspondingly. At temperatures less than about 24 °C, there is a high risk of asystole. Animal studies suggest that this threshold may be lowered in the presence of ethanol intoxication,⁴⁴ which may explain some observations of improved outcomes in this situation. Transvenous pacing may be difficult, owing to higher thresholds being necessary, and indeed hazardous in terms of the risk of precipitating ventricular fibrillation, but animal work confirms that transcutaneous pacing in hypothermia is effective and safe,⁴⁵ and is recommended by some.

It has been suggested that asystole is a primary manifestation of hypothermia, whereas ventricular fibrillation occurs secondary to rewarming, hypocapnia, alkalosis or physical manipulation.⁴⁶

Ischaemia, increased adrenergic activity and electrolyte disturbances certainly predispose to myocardial irritability, and in moderate hypothermia this frequently results in arrhythmias, commonly atrial fibrillation or flutter or nodal rhythms, but also multifocal ventricular extrasystoles and tachyarrhythmias. Ventricular fibrillation is more common below about 27 °C, and is particularly likely to develop if there is a sudden change in parameters such as physical movement, pO₂ or pCO₂, myocardial temperature, or changes in biochemical or acid-base status. It has been postulated that the development of a temperature gradient between the cooler endocardium and subendocardial conducting tissue and the relatively warmer myocardium facilitates conduction through the myocardium at the expense of normal neuromuscular transmission, which might explain why sudden changes in biochemistry or acid base status affect these tissues differently and predispose to the development of ventricular fibrillation.⁴⁷ An alternative explanation is that the small temperature differentials between myocardium and endocardium may cause dispersion of the action potential duration, refractory period and conduction speed, which are significantly lengthened in hypothermia, resulting in an increased vulnerability to arrhythmias.⁴⁸

The risk of precipitating ventricular fibrillation by tracheal intubation may have been overstated and relates to a lack of pre-oxygenation.⁴⁹ In severe hypothermia, ventricular fibrillation is usually extremely resistant to attempts at electrical cardioversion until rewarming has been achieved, although isolated case reports prove that there are exceptions to the rule.⁵⁰ Unless extra-corporeal circulation can be rapidly established, giving the best chance of recovery, prolonged cardiopulmonary resuscitation may be necessary until sufficient warming has occurred to allow defibrillation.⁵¹ In hypothermia, reduced chest wall elasticity and compliance of the heart and lungs makes chest compressions more difficult and probably less efficient, but survival of patients after up to 6½ h of cardiopulmonary resuscitation has been reported.⁴⁹ Bretylium is the only anti-arrhythmic agent of any use in this situation,^{52,53} and acts through increasing the refractory period and thus raising the ventricular arrhythmia threshold, without any apparent effect on conduction velocity or catecholamine levels.⁵⁴

Overall, there is no indication for prophylactic anti-arrhythmic treatment in the absence of malignant arrhythmias.⁵⁵ The administration of lidocaine is generally ineffective at temperatures less than about 30 °C, as indeed are procainamide, propranolol, diltiazem⁴⁸ and verapamil.⁵⁶ In general, pharmacological attempts to increase blood pressure

or heart rate are similarly problematic, although inotropes such as low-dose dopamine have been used in patients who are disproportionately hypotensive and who do not respond to volume replacement. This is not normally necessary, however, and indeed the utility of low-dose dopamine in general has provoked much recent debate. In moderate hypothermia, peripheral vasculature is already maximally vasoconstricted and administration of vasoconstrictors only predisposes to arrhythmias; indeed, the administration of epinephrine may precipitate ventricular fibrillation. Animal studies suggest that at around 29 °C the initial activation of the sympathetic system switches off, and there may be a role for catecholamine support below that temperature.⁵⁷ It should be emphasized that any medication should be administered intravenously: the intense peripheral vasoconstriction and consequent poor absorption means that intramuscular and subcutaneous injections should both be avoided.

Serum levels of HBD and creatine kinase are sometimes moderately elevated, but may not represent cold-induced ischaemic myocardial damage; the rise in total CK is independent of temperature, and is not accompanied by ECG changes or histological evidence of myocardial infarction at post-mortem,⁵⁸ although small degenerative foci are seen on microscopic examination of the myocardium in two-thirds of cases.⁵⁹ Studies with more specific markers of cardiac damage, such as troponins, would be helpful.

Haematology

The haematological changes that are associated with hypothermia are important, particularly the increase in blood viscosity, fibrinogen and haematocrit; these may underlie disorders in the function of many other organs. Changes in vascular permeability result in the loss of plasma to extravascular compartments, leading to haemoconcentration, and the accompanying hypovolaemia is compounded by a cold-induced diuresis. The haematocrit increases by about 2% for every 1 °C decline in temperature,⁶⁰ and a normal haematocrit in a moderately or severely hypothermic patient suggests pre-existing anaemia or blood loss. Hypothermia has also been reported to cause marrow suppression and progressive marrow failure,⁶¹ and to induce erythroid hypoplasia and sideroblastic anaemia.⁶²

Cold directly inhibits the enzymic reactions of both intrinsic and extrinsic pathways of the clotting cascade,⁶³ and hence a coagulopathy can develop. The prothrombin time and partial thromboplastin

time can be deceptively normal if measured at 37 °C, but can be significantly increased if measured at lower temperatures, even when clotting factor levels are known to be normal. Rewarming, rather than administration of exogenous clotting factors, is the appropriate management.⁶⁴ A disseminated intravascular coagulopathy has been reported on a number of occasions with no apparent cause other than the hypothermia;⁶⁵ this might be related to release of tissue thromboplastin from ischaemic tissue,⁶⁶ or the circulatory collapse itself may be the major factor.⁶⁷ Hypothermia may also impair both the endothelial synthesis of prostacyclin (PGI₂) and its inhibitory action on platelet aggregation, promoting platelet activation and thrombosis.⁶⁸ Thrombocytopaenia can also occur,^{69,70} this usually results from sequestration in the liver and spleen,⁹ but can be related to a disseminated intravascular coagulation, or marrow depression. In addition, platelet production of thromboxane B₂ is temperature-dependent, promoting a decline in platelet activity with falling temperature.⁷¹

Elevated cryofibrinogen levels may be found in hypothermia, which raise the blood viscosity,⁷² and they can do so in a dramatic way on exposure to further cold, impairing the microcirculation and, presumably, resulting in the widespread tissue micro-infarcts which are sometimes observed.⁷³ Excess cryofibrinogen occurs particularly with *E. coli* sepsis of the urinary tract, diabetes, folate deficiency and malignancy, all of which are more common in the elderly. Excessive purpura or bruising may suggest the presence of cryofibrinogenaemia, and is associated with an increased mortality. If antithrombotic prophylaxis is being considered for a hypothermic patient, it should be borne in mind that heparin (and dextran) can polymerize the cryofibrinogen in the presence of a cryofibrinogenaemia, and thus cause severe hyperviscosity;⁷³ indeed, despite the increased susceptibility to thromboembolism, there is no evidence at present to support the routine use of prophylactic heparin in accidental hypothermia.

Leukocyte depletion can occur in response to hypothermia,⁷⁴ and animal and *in vitro* studies suggest that neutrophil migration⁷⁵ and bacterial phagocytosis⁷⁶ are impaired, predisposing to infection, although this does not appear to have been demonstrated in man. In patients undergoing cardiopulmonary bypass, complement activation may be attenuated at lower temperatures.⁷⁷ The common finding of sepsis in elderly patients who present with hypothermia may therefore be a consequence as well as a predisposing cause of the failure of thermoregulation, and this underlines the need for routine antibiotic cover in these patients.

Neuromuscular effects

The central neurological effects of cold are often apparent clinically, with initial confusion and sometimes amnesia in the mild stages. As the temperature falls further, apathy, impaired judgement and paradoxical undressing may occur. Dysarthria, progressive depression of consciousness and ultimately coma develop, and consciousness is commonly lost below about 30 °C. There is a loss of cerebrovascular autoregulation at about 25 °C as well as a reduction in cerebral blood flow by 6–7% per 1 °C drop in temperature. However, in severe hypothermia there is a markedly reduced metabolic rate, and hence a considerably increased cerebral ischaemic tolerance; at temperatures less than 20 °C, ischaemic tolerance is ten times the normothermic.⁷⁸ The EEG becomes flat at below about 20 °C.

Shivering is initially increased in mild degrees of hypothermia, but then decreases as the temperature falls further; however the reported temperatures at which shivering is lost vary widely (24–35 °C), as in fact do the other neurological changes at a given depth of hypothermia.⁷⁹ Synovial fluid becomes more viscous at lower temperatures, and so in moderate hypothermia, stiffness of muscles and joints appears. Ataxia and loss of fine motor control are seen in the initial stages, followed by hyporeflexia, an extensor plantar response and pupillary sluggishness in moderate degrees of hypothermia; rigidity, pupillary dilatation and areflexia appear as the temperature falls below about 28 °C. In severe hypothermia, muscle and joint stiffness may simulate rigor mortis, although the stiffness may paradoxically lessen as the temperature falls below 27 °C.

Animal studies have helped to explain these changes by showing that peripheral nerve conduction is impaired in the cold, with a progressive reduction in conduction velocity as the temperature falls; this seems to be related to a reduced flux of potassium and chloride ions across the axon membrane.⁸⁰ The effect of this on autonomic circulatory control mechanisms may help to explain why marked postural hypotension is sometimes observed, and head-up or sitting positions are to be avoided in transferring victims out of their cold environments. The synaptic delay time is also prolonged as the neuromuscular junction cools,⁸¹ and muscle contraction is partially temperature-dependent, with a reduced rate of development of tension and maximal shortening velocity at lower temperatures, but little change in the maximum force obtained.⁸² With cutaneous temperatures as low as 12 °C, the pre-capillary sphincters cease to work, with a resultant

vasodilatation, and the increased blood flow that follows may then cause sufficient warming to restore their function and reinstate local vasoconstriction. This oscillation between dilatation and constriction is known as the 'Lewis Hunting Reaction' and occurs primarily on the finger tips, toes, ears and face.³²

Respiratory problems

In mild hypothermia, there is an initial tachypnoea, followed by a reduction in minute volume and reduced oxygen consumption; bronchospasm and bronchorrhoea occur. As the temperature falls to moderate levels of hypothermia, protective airway reflexes are reduced because of impairment of ciliary function, and this predisposes to aspiration and pneumonia. Significant reductions in oxygen consumption and carbon dioxide production occur, both falling by about 50% at 30 °C. Core temperature control is very dependent on pCO₂ level, which is detected by the carotid bodies and also more centrally, and these act on sources of thermogenesis and thermolysis.⁸³ A direct cooling effect depresses ventilatory drive at the respiratory centres, and at temperatures below 34 °C sensitivity to pCO₂ stimulation is attenuated, although the hypoxic drive is maintained to deeper levels of hypothermia. Physiological and anatomical respiratory dead space are increased through bronchial dilation, but alveolar dead space is unchanged.²⁴ Local gas exchange is not affected by hypothermia, but there is an increase in pulmonary vascular resistance and a degree of ventilation-perfusion mismatch in the lungs. In severe hypothermia, progressive hypoventilation and apnoea develop, and (more rarely) pulmonary oedema.

There is initially a left shift of the oxyhaemoglobin (Hb-O₂) dissociation curve in response to falling temperature, which results in impaired oxygen delivery and tissue hypoxia, but this is balanced to some degree by the resultant lactic acidosis and by other factors contributing to an overall acidosis, both respiratory (reduced carbon dioxide excretion) and metabolic. Shivering may greatly increase lactate production, and its clearance by the liver is impaired; frequently the metabolic acidosis gets worse during rewarming as the products of anaerobic metabolism are returned to the circulation, and this can contribute to the increased risk of arrhythmias. In severe hypothermia, the acidosis is frequently profound, so that there is an overall right-shift to the Hb-O₂ dissociation curve. The significance of impaired oxygen delivery to the tissues is reduced because of the decline in oxygen demand at lower temperatures.

Management of acid-base status during hypothermia has been controversial. Blood gases are normally warmed to 37 °C for analysis, which results in higher oxygen and carbon dioxide levels and lower pH values than the hypothermic patient's true state, while the presence of large temperature gradients in the body make accurate calculation of the corrected values difficult. In practice, some suggest that this calculation is unnecessary, and attempts should be made to maintain the temperature-*uncorrected* pH around 7.40, as this helps to avoid over-enthusiastic use of bicarbonate or hyperventilation. These may depress cardiac output further, and increase the predisposition to ventricular fibrillation; also transport of bicarbonate across hypothermic cell membranes is slow, and severe metabolic alkalosis may result during rewarming.⁸⁴

Renal and metabolic

In mild hypothermia, there is a cold-induced diuresis, which occurs before any fall in body temperature. This is initially due to an increase in renal blood flow consequent on vasoconstriction, then with falling temperature, a loss of distal tubular ability to reabsorb water and a resistance to the action of vasopressin (ADH). The cold-induced diuresis is accompanied by an increase in urinary electrolyte excretion, probably as a result of reduced tubular sodium reabsorption.⁸⁵ In moderate hypothermia, the glomerular filtration rate falls as cardiac output and hence renal blood flow fall, the last of these being reduced by half at 27–30 °C. There is also a further reduction in tubular function, and renal clearance of glucose is reduced. At lower temperatures still, tubular capacity for H⁺ ion secretion is reduced, and hence there is a renal contribution to the acidosis. Clinically, acute renal failure is seen in over 40% of patients with accidental hypothermia who require admission to an intensive care unit.¹⁹ Biopsies have demonstrated ischaemic damage to the kidneys, which is thought to occur in the rewarming phase, following a period of relative protection at lower temperatures. This 'pre-renal' failure, essentially consequent on the fall in renal blood flow, may therefore be preventable to some extent by careful volume replacement.⁸⁶

Total body metabolism reduces with increasing hypothermia, as measured by a fall in oxygen consumption, which is about 6% for every degree Celsius fall in temperature.²⁴ The basal metabolic rate is therefore reduced by 50% at 28 °C. In animal studies, vasopressin and oxytocin secretion is reduced,

but the associated reduction in ACTH secretion is not reflected by the plasma cortisol levels, which are usually raised; this is likely to be due to reduced hepatic clearance.⁸⁷ Pituitary, adrenal and thyroid function is thought to be normal, although a depressed cortisol response to ACTH stimulation has been found by some.⁸⁸ Plasma concentrations of TSH and thyroxine are normal,⁸⁹ but should be measured to exclude hypothyroidism as an underlying cause. If a patient is resistant to attempts at rewarming, administration of hydrocortisone with or without levothyroxine should be considered, in case occult hypothyroidism, hypopituitarism or previous chronic steroid use are contributory factors. Routine administration of steroids is not beneficial and is not recommended.

If the hypothermia has developed rapidly, many different processes may contribute to hyperglycaemia, which can contribute an osmotic component to the diuresis. Insulin release is inhibited by increased corticosteroid levels, as well as by a direct cooling effect on the islets of Langerhans;⁹⁰ in addition, peripheral uptake of insulin at the tissues is impaired. Sympathetic activity is increased, with raised plasma norepinephrine and free fatty acid levels,⁹¹ and the catecholamine-induced glycogenolysis and gluconeogenesis contribute to the hyperglycaemia. The glucagon level is increased, and plasma cortisol levels correlate with lactate and glycerol levels, implying active stimulation of glycogenolysis and lipolysis.⁹² In cases where hypothermia has developed more slowly or is long-lasting, glycogen stores may be depleted, and then it is likely that hypoglycaemia will develop. Shivering may also deplete glycogen stores and in the longer term contribute to hypoglycaemia. With rewarming, the factors leading to a raised plasma glucose correct, and so moderate degrees of hyperglycaemia should be tolerated rather than be treated, in order to avoid profound hypoglycaemia on rewarming. Exogenous insulin has little effect in the hypothermic state, and high doses would be needed for any apparently beneficial effect. If hyperglycaemia persists during the process of rewarming, diabetic ketoacidosis and pancreatitis need to be considered, and insulin therapy instituted once the temperature has returned to >30 °C.

Hypokalaemia results from a shift of extracellular potassium into the cells,⁹³ due to changes in both membrane permeability and the function of the sodium-potassium pump. Hyperkalaemia, on the other hand, is a marker of acidosis and cell death and is therefore a sign of poor prognosis. The ECG is not helpful here, as the potassium-induced changes in the ECG can be reduced in hypothermia, and lower temperatures enhance the

cardiac toxicity of hyperkalaemia. Plasma sodium, calcium, magnesium and chloride concentrations do not change significantly above about 25 °C, but there are reports of severe hypophosphataemia on rewarming from profound hypothermia.^{94,95} This may be more common than is appreciated, because serial phosphate measurements are not routinely made, and moreover might be contributing significantly to the morbidity and mortality associated with rewarming. Further work in this area is needed.

Gastrointestinal effects

Intestinal motility decreases below about 34 °C, resulting in an ileus when the temperature falls below 28 °C, and therefore a nasogastric tube should be placed to reduce the chance of aspiration. Furthermore, the absorption of medication given orally or by nasogastric tube will be impaired in this situation, and this route should therefore be avoided. Punctate haemorrhages may occur throughout the gastrointestinal tract, and autopsy studies have found gastric erosions and submucosal haemorrhages to be common but not clinically significant.⁶ The shallow gastric ulcers are known as Wischnevsky's ulcers and are seen in the majority of cases at post-mortem examination. A characteristic linear pattern is seen, said to be consistent with acute cold stress.⁹⁶ Cystic dilatation of the capillaries is found on histological examination, presumed to be due to reperfusion after functional collapse of the microcirculation in the gastric mucosa.⁹⁷ Animal work has shown that hypothermia increases gastric acid production and reduces duodenal bicarbonate secretion, predisposing to this mucosal damage in both the stomach and the duodenum.⁹⁸

Hepatic impairment can develop, probably consequent on the reduced cardiac output, and the decreased metabolic clearance of lactic acid contributes to the acidosis. It follows that if warmed intravenous fluids are given, these should not include Hartmann's solution, since the liver cannot handle the added lactate efficiently.⁹⁹ The liver's functions of detoxification and conjugation are also depressed, affecting the half-life of many drugs, and prolonging the effects of ethanol. This may be particularly relevant in the situation of an overdose, where the resultant hypothermia perpetuates the effects of the drug ingested.

Pancreatitis frequently occurs as a consequence of hypothermia, being found at autopsy in 20–30% of cases,¹⁰⁰ and a mildly elevated serum amylase without clinical evidence of pancreatitis is even

more common, being present in 50% of patients in one series.¹⁰¹ The reason for this is not well understood, but is thought to result from thrombosis in the microcirculation, and resulting ischaemia and perilobular necrosis in the pancreas; this may be a similar underlying process to that which causes micro-infarcts in the gut, liver, brain, myocardium, and many other organs.¹⁰² Portal vein thrombosis has also been reported in conjunction with haemorrhagic pancreatitis.¹⁰³ Animal studies have demonstrated impaired pancreatic exocrine function and increased serum amylase levels as a result of cooling the pancreas for a few hours.¹⁰⁴ Other enzymes associated with cellular damage are often mildly elevated, such as AST, ALT and bilirubin.

Clinical presentation

The patient with mild hypothermia might present with vigorous shivering, a diuresis, cold white skin, and a tachycardia. With a moderate degree of hypothermia, one might see amnesia, apathy, and a loss of fine motor skills, paradoxical undressing, and reduced shivering. Speech might be slurred, and bradycardia and arrhythmias may be hard to detect peripherally. Joints become stiff and there is hyporeflexia. In the severe case it would be common to find loss of consciousness, extreme bradycardia and slow respiration or apnoea, hypotension and impalpable peripheral pulses, along with cold oedematous skin, areflexia, and fixed dilated pupils, which are not in this situation an indication of brain stem death. It must be emphasized, however, that the clinical picture does not in general correlate well with the degree of hypothermia, and there are many reports of situations at variance with this broad picture, and at least one instance of an elderly lady maintaining consciousness (albeit confused) at 24.3 °C core temperature.¹⁰⁵

Conclusion

Many factors predispose to accidental hypothermia, including socio-economic, environmental, pharmacological, pathological, and the normal ageing process. Hypothermia has profound and widespread physiological effects which can result in diverse pathology; many of these changes are reversible on rewarming. Attempts to normalize physiological or biochemical variables may be misplaced as well as futile, and delayed metabolism and excretion of many drugs could result in overtreatment as the temperature is returned to normal. Full recovery is well documented from

profound levels of hypothermia and the associated markedly abnormal physiological states, but arrhythmias and sepsis contribute to an appreciable mortality. In the elderly in particular, underlying predisposing or precipitating factors usually determine the outcome.

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