Part X: Trauma

Chapter 74: Thermal Syndromes

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An abnormal body temperature is a common finding in Intensive Care patients, and accurate monitoring with attention to thermal environment is routine practice. From a therapeutic viewpoint, the conditions of greatest interest are hypotheramia, heat stress, malignant hyperthermia, and the neuroleptic malignant syndrome.

Regulation of Body Temperature

Temperature varies throughout the body, but a suitable model is the "Core and Shell" hypothesis. In health, the core or central temperature, is normally kept within the range 36.0-37.5°C, by a balance between heat production and loss. Heat is produced from obligatory metabolism, assimilation of food, and muscle activity. It is dissipated by radiation, conduction, convection, and evaporation of sweat and respiratory water. The interplay of heat production and loss is regulated by a complex, highly sensitive feedback system based on sensing afferents, central integration with set-point, and reflex efferents.

Sensory Systems

Cutaneous thermoreceptors, abundant on exposed areas of the body, are the most sensitive to detect a change in environmental temperature. There are 2 types of receptors: cold-sensitive and warm-sensitive receptors. The cold receptors are stimulated by temperatures below 24°, whereas the warm receptors are stimulated by temperatures above 44°. Deep thermoreceptors in the spinal cord and intra-abdominal viscera are found in animals and probably in man. Information from the peripheral receptors is relayed via the lateral spinothalamic tract, the reticular system of the medulla, and the thalamus to the anterior hypothalamus. Warm and cold receptors which can respond directly to the blood temperature bathing themm, are located within the anterior hypothalamus itself. Whether central or peripheral input plays the dominant role has been a matter of continuing debate. However, it is now believed from experiments that an interaction occurs between the cutaneous and the central regulating systems.

Central Integration

The anterior and posterior hypothalamus together make up the temperature regulating centre. The centre sets a reference temperature which is influenced by diurnal rhythm, age, exercise, hormones, neurotransmitters, pyrogens, and drugs. When a difference occurs between the body temperature and set-point, the posterior hypothalamus initiates the appropriate thermoregulatory response. The effector responses, which are controlled either neurally or hormonally, act either to conerve or to generate heat accordingly.

Effector Systems

1. *Higher cortical centres* - These are sensitive to signals from the hypothalamus, and can alter behaviour to conserve or to lose heat, such as posture, activity, appetite and clothing.

2. *Shivering thermogenesis* - This is a centrally mediated neural response which consists of involuntary rhythmic contractions of skeletal muscle. Shivering, although independent of sympathetic nervous system, is facilitated by catecholamines.

3. *Non-shivering thermogenesis (NST)* - This refers to an increase in combustion of fatty acids and glucose, both exothermic reactions. In adults, the most active metabolic areas are the liver and skeletal muscles. In the neonate, the highly vascular and richly innervated brown fat is the potent source for NST. The non-shivering thermogenesis is mediated by sympatho-adrenal (rapid response) and thyroid (slow response) function. On acute exposure to cold, noradrenaline is secreted from the peripheral nerve terminals to stimulate calorigenesis in fat and muscle cells. Adrenaline and thyroxine are important in long term cold adaptation, but play a minor role in the initial response to cold stress.

4. *Sweating* - Increase in eccrine sweat secretion is produced by direct or reflex stimulation of the centres of the spinal cord, medulla, hypothalamus or cerebral cortex. Shivering and sweating provide fairly coarse control of heat balance.

5. *Cutaneous blood flow* - This allows fine control of heat balance. These reflex changes in cutaneous blood flow are mediated by the sympathetic nervous system and occurs within seconds.

Abnormal body temperature may occur when the system is over-stressed (as in cold immersion or malignant hyperthermia), or as a result of failure of the thermoregulatory mechanism. The latter may be due to defective central regulation (eg, caused by pyrogens or head injury), or to depression of sensory and effector mechanisms, as occurs in anaesthesia, drug overdose or hypothyroidism.

Measurement of Body Temperature

The most useful instruments are the mercury thermometer (including the low reading type) and the thermistor. Sites for temperature monitoring are the mouth, nasopharynx, aural canal, oesophagus, rectum, and axilla. Rectal temperature is traditionally used to indicate the core temperature despite several disadvantages. It can be affected by heat-producing organisms in the bowel, cool blood returning from the legs, and insulation effect of faeces. Oesophageal probe should be positioned accurately in the lower end of the oesophagus, and it is the best single monitor of core temperature for hypothermic patients. Nasopharyngeal measurements can be affected by leakage of air around the endotracheal tube cuff. Axillary reading is the best monitor of muscle temperature, and therefore, the most sensitive in malignant hyperthermia. However, it is a poor measure of core temperature. Aural canal probe is traumatic and can be rendered inaccurate by cerumen. Skin temperature in correlation with core temperature is used clinically to assess tissue perfusion. Monitoring of readings from 4 or more sites to determine mean skin temperature is generally used in research.

Hypothermia

Hypothermia is defined by a core temperature below 35°C, requiring emergency and intensive management. It is frequently underdiagnosed and has a high mortality.

Classification

Many classifications of hypothermia have been proposed. The practical ones are based on either aetiology or severity of the hypothermia as determined by body temperature measurements. Clinically, hypothermia is classified according to the core body temperature.

1. *Mild hypothermia* - 32-35°C

2. *Moderate hypothermia* - 28-32°C

3. *Severe hypothermia* - below 28°C.

Aetiologically, hypothermia can be divided into:

1. *Induced hypothermia* - The body temperature has been lowered deliberately as part of a therapeutic regimen.

2. *Accidental hypothermia* - This occurs without deliberate intention, and it is useful to further differenitate into:

(a) *Primary* accidental hypothermia, in which the body possesses normal thermoregulation, but the exposure to cold is overwhelming (eg, from immersion or exposure).

(b) *Secondary* accidental hypothermia in which mild to moderate cold exposure leads to hypothermia because of abnormal thermogenesis. This division is helpful in the assessment and management.

Causes

There are numerous causes for hypothermia (Table 1). It is more common in the elderly and infants, where thermal liability and poor thermoregulation contribute to increased vulnerability to cold. Many underlying diseases and drugs predispose them to hypothermia, and increase mortality.

Pathophysiology

As body temperature decreases, the following changes occur:

1. *Cardiovascular System* - Sympathetic activity is initially stimulated with elevated plasma levels of noradrenaline and free fatty acids. There is peripheral vasoconstriction, tachycardia, and increased cardiac output in mild hypothermia. However, a progressive fall in heart rate, cardiac output and blood pressure then follows as hypothermia progresses. This

reduces tissue perfusion, ECG changes include bradycardia, prolongation of all phases of the cardiac cycle, conduction abnormalities, T-wave investion, and the occurrence of "J" ofr "Osborn" wave, an extra deflection at the QRS-ST junction. Supraventricular arrhythmias, in particular atrial fibrillation (AF) are common below 30°C and ventricular fibrillation (VF) may occur below 28°C. This form of VF has been reported to be refractory to electrical or pharmacologic cardioversion, unless core temperature is brought above 28°C. Fibrillation can occur earlier, in the presence of diseased or ischaemic myocardium, or with stimuli such as insertion of central venous line or endotracheal intubation.

Table 1. *Causes and Predisposing Conditions of Hypothermia*

Accidental	Immersion
	Environmental exposure
	Immobility
	Poor living conditions
Drug induced	Anaesthetic agents (prolonged anaesthesia)
	Phenothiazines
	Barbiturates
	Antidepressants
	Phenformin
	Ethanol
Infections	Pneumonia
	Sepsis
Nutrition	Protein-calorie deficiency/malnutrition
Cardiovascular	Cerebrovascular accidents
System	Head injury
	Cerebral neoplasm
	Progressive mental deterioration
Renal	Uraemia
Endocrine	Hypopituitarism
	Myxoedema
	Hypoglycaemia
	Diabetic ketosis
	Hypoadrenalism.

Cardiac creatinine phosphokinase and lactate dehydrogenase levels are frequently elevated. This may be due to leakage from cells with impaired membrane integrity or microinfarction. Unnecessary manipulation should be avoided in these patients, because of the potential for cardiac arrhythmias. Cardiac ischaemia together with acidosis may partly be responsible for the ECG changes, arrhythmias and enzymatic changes.

There is an increased haematocrit caused by dehydration, and blood viscosity is increased significantly from cooling of blood per se and peripheral fluid sequestration.

2. *Respiratory System* - Following initial reflex stimulation from which tetany may result, ventilation is progressively depressed and ceases at 24°C. Hypoventilation results from a reduction in respiratory rate and minute ventilation volume. There is an impairment in hypoxic pulmonary vasoconstriction, and decreased gaseous diffusion capacity. Impaired cough reflex associated with hypothermia, together with diminished consciousness and dehydration, render the aged more susceptible to pulmonary infections and to aspiration.

The solubility of respiratory gases (including anaesthetic agents) in plasma increases with hypothermia. The oxygen-haemoglobin dissociation curve is shifted to the left, primarily due to increased affinity of haemoglobin for oxygen. Blood gas analysis measured at a temperature of 37°C are traditionally corrected by factors from normogram or formulae, or automatically corrected by modern blood gas analysers.

3. *Metabolic System* - Grave acidosis develops in the severely hypothermic patient which eventually shifts the oxygen-haemoglobin curve to the right. The acidosis contains both a respiratory and a metabolic component. CO_2 retention is due to inadequate ventilation, and the metabolic component is caused by reduced tissue perfusion with accumulation of lactate and other acid metabolites. A renal component due to a reduced tubular H+ ion secretory capacity, contributes to the acidosis in long standing hypothermia. Measurements of pH made at 37°C should be corrected by addition of 0.0147 pH unit for each degree *below* this temperature. It has, however, been suggested that correction offers no practical management benefits.

Metabolic rate is raised during the shivering phase. However, it eventually falls and the basal metabolic rate (BMR) declines at a rate of 5-7% per °C. Hyperglycaemia is a common feature. This is thought to be due to decreased insulin release and impaired peripheral utilization of glucose, or related to mild pancreatitis. Insulin administration has little effect and the condition reverts on rewarming. However, in long standing hypothermia, the glycogen stores may be exhausted and hypoglycaemia will ensue. Liver function is depressed, affecting most enzymatic and detoxifying processes. Plasma cortisol levels are usually elevated despite a reduced ACTH secretion. This is probably due to a reduced hepatic hormone clearance rate.

4. *Renal System* - The decrease in renal perfusion reduces the glomerular filtration rate (GFR) and clearance of multiple drugs. Cold-induced diuresis is secondary to the volume load imposed on capacitance vessels by peripheral vasoconstriction, and also results from a depression of tubular reabsorptive function despite a diminished GFR. Glycosuria may add an osmotic contribution to the polyuria. Serum potassium concentration is variable. Hypokalaemia has been observed in hypothermic patients which is in contrast to the expected hyperkalaemia from a concomitant metabolic acidosis.

5. *Neurological System* - There is generalized cerebral depression. Loss of consciousness and pupillary dilation supervene at 30°C. Cerebral blood flow is reduced at a rate of 7% per °C drop. There is a corresponding reduction in cerebral metabolic rate so that

demand does not outstrip supply. Shivering is gradually replaced by muscular rigidity at 33°C and a rigor mortis like appearance develops at 24°C.

6. *Gastrointestinal System* - Intestinal motility decreases below 34°C, with ileus occurring frequently.

Diagnosis

The diagnosis of hypothermia rests upon reliable temperature measurement. It may be difficult to differentiate from death especially in the immersion victim. Death should not be assumed until resuscitation attempts have failed in an adequately rewarmed patient. (See Chapter 72, Near-Drowning.) Investigations are indicated to monitor progress, clarify and underlying cause and detect complications. Useful tests include a full blood count, serum electrolytes, urea, creatinine, glucose and amylase, blood gases and pH, liver function studies, blood culture, drug and alcohol screen, chest X-ray; ECG, and thyroid function tests.

Management

1. General Measures

The hypothermic patient should be managed with careful monitoring of temperature, vital signs and fluid balance. Excessive handling may precipitate VF. Antiarrhythmic drugs and electrical deribrillation are ineffective at low temperatures. Adequate intravenous access and a patent airway are essential. Optimal oxygenation, if necessary by controlled ventilation, should be ensured. Hypoglycaemia should be corrected. All intravenous fluids must be prewarmed. Bradycardia may require the use of atropine and/or isoprenaline. If these drugs fail, cardiac pacing may be necessary until rewarming methods have stabilized the cardiovascular system. Bicarbonate may be required to correct acidosis. Electrolyte imbalances should be corrected with care. Intravenous corticosteroids are no longer used as part of initial treatment. Infection which usually involves the lower respiratory or urinary tracts, requires broad-spectrum, bactericidal antibiotics (after appropriate cultures).

2. Specific Treatment

The mainstay of treatment is rewarming. Various methods of rewarming have been employed (Table 2). The choice is best based on the cause and degree of hypothermia.

(a) *Passive External Rewarming (PER)* - This method is recommended for the elderly and for those with mild hypothermia. The patient is placed in a warm room covered with warm blankets and allowed to warm at his/her own pace. Rewarming is gradual at 0.5°C/h.

(b) *Active External Rewarming (AER)* - This method has been used successfully in young patients with accidental or environmentally induced hypothermia. The limbs should be excluded during immersion in hot water (40-45°C) to reduce the after drop in core temperature, and to protect against "rewarming shock" secondary to peripheral vasodilation. Other techniques include the use of electric blanket or hot water bottles. Hypotension, decreased coronary perfusion, and a shunting of cool blood to the myocardium leading to

arrhythmia, are potential hazards. These may be too dangerous for elderly patients especially those with fragile cardiovascular systems.

(c) *Active Core Rewarming (ACR)* - This method may be used for moderate to severe hypothermia, and may have advantages over other methods. It produces a preferential warming of the myocardium, leading to an increase in cardiac output, less cardiac irritability, and a rapid return to a near normal core temperature. The necessary equipment for ACR is usually sophisticated and may not be readily available. Recently, an oesophageal thermal tube has been developed. This is a non-invasive closed system using a disposable thermal tube (with water at 42°C at a flow rate of 3 L/h) in the oesophagus. The rewarming rate is approximately 1.5°C/h. It is a simple method, suitable even in the field situation, but the patient has to be intubated. It is now officially recommended as the treatment of choice for severe accidental hypothermia in Denmark.

Table 2. *Rewarming Methods*

Passive
- Warm environment (> 25°C)
- Insulating material (warm blanket)

Active
- (a) External
  - Immersion in hot water bath (40-45°C)
  - Electric blanket
  - Hyperthermia mattress
- (b) Core
  - Inhalation of heated inspired gasses
  - Dialysis
    - haemodialysis
    - peritoneal
  - Irrigation
    - mediastinal via thoracotomy
    - intragastric
  - Oesophageal thermal tube
  - Extracorporeal blood rewarming.

After Effects

Many elderly patients tend to have a residual hypothalamic dysfunction, rendering them susceptible to recurrent hypothermia.

Mortality

The mortality among hospitalized patients with hypothermia varies from 20-85%. Mortality has been related to several factors namely the severity of hypothermia, the duration prior to treatment, the degree of hypotension and associated underlying conditions, in

particular, the cardiovascular disease. Although rewarming technique is important, careful and meticulous supportive care may be responsible for the large differences in mortality report.

Heat Stroke

Heat stroke is a condition caused by excessive heat storage brought about by either "overloading" or failure of the thermoregulatory system during exposure to heat stress. It is the greatest threat to life among the heat disorders (ie, heat syncope, heat exhaustion and heat stroke). Overloading occurs when the rate of heat production or storage exceed the rate of heat loss. This is characteristically seen in young athletes or military recruits. Thermoregulatory failure refers to dysfunction in either central control or peripheral responses of heat loss mechanisms (sweating and vasodilation or skin blood flow). This is commonly found in the elderly, living without airconditioning in a hot and humid environment. Predisposing factors are dehydration, lack of acclimatization, obesity, infection, alcoholismmm, mental illness, and drugs impairing heat response (eg, phenothiazines, diuretics, and anticholinergics).

Pathophysiology and Clinical Presentation

The 3 cardinal signs of heat stroke are:

1. severe central nervous disturbance;

2. hyperpyrexia (core temperature 41-43°C); and

3. hot, dry skin, which is pink or ashen, depending on the circulatory state. Sweating may be profuse or absent.

Neurologic System - Confusion, aggressive behaviour, delirium, convulsions and pupillary abnormalities may progress rapidly to coma. There may be decorticate posturing, faecal incontinence, flaccidity or hemiplegia. Cerebellar symptoms including ataxia and dysarthria may be permanent in a small percentage of patients. The degree of damage is related to the duration and degree of hyperpyrexia as well as circulatory insufficiency.

Cardiovascular System - Hear rate increases at 10 beats/min for each 1°C rise in body temperature. The ECG may show ST segment depression and T wave changes, as well as supraventricular tachycardia. Cardiac output is initially elevated with low peripheral vascular resistance and high skin and skeletal muscle blood flow. Cardiac output eventually drops. Myocardial injury or an increased pulmonary vascular resistance, rather than peripheral pooling of blood, have been suggested to be the cause of circulatory failure.

Respiratory System - Initial respiratory alkalosis is usually followed by a mixed acid-base disorder in the presence of metabolic acidosis. Complications include aspiration, acute respiratory distress syndrome, and congestive heart failure with pulmonary oedema.

Renal, Fluid and Electrolyte Abnormalities - Dehydration and electrolyte (sodium, potassium, calcium, phosphorus and magnesium) deficiencies follow excessive sweating.

Acute tubular necrosis is common and is related to thermal parenchymal injury. Subsequent hypotension and/or rhabdomyolysis can precipitate renal failure.

Coagulation Abnormalities - Bleeding diathesis observed is possibly contributed by thrombocytopenia, disseminated intravascular coagulation and liver cell damage.

Management

Rapid and effective cooling and support of vital organ systems are the two principal therapeutic objectives. Clothing should be removed and the patient rapidly cooled externally by ice packs, air conditioning, ice water bath, or internally by peritoneal lavage or gastric lavage cooling. However, recently it has been shown that wetting the skin and using warm air to induce evaporation is superior to the conventional methods.

Hypovolaemia, dehydration and electrolyte imbalance must be corrected cautiously with crystalloids guided by urine output, central venous pressure, serum electrolyte values, and haematocrit. A Swan-Ganz catheter may be of value in fragile patients. Mannitol may be required to promote renal blood flow. Anuria, uraemia and hyperkalaemia are indications for early dialysis. Oxygen therapy and controlled ventilation may be indicated. Anticonvulsants (eg, diazepam) may be required. Phenothiazines should be used to suppress shivering. Prophylactic steroids or antibiotics are not recommended. Hypoglycaemia may be present and should be treated. Evidence for underlying illness should be sought and treated accordingly. Cooling should be stopped at 39°C, since core temperature will continue to decrease and hypothermia should be avoided. Dantrolene, appears promising, but needs further evaluation.

Malignant Hyperthermia (Hyperpyrexia)

Malignant hyperthermia (MH) is a pharmacogenetic disorder characterized by acute hypercatabolic reactions in skeletal muscles, triggered by certain drugs (mainly used in anaesthesia) and stresses. Triggering drugs include any of the potent inhalational agents, any depolarizing muscle relaxant (mainly suxamethonium), amide local anaesthetics, caffeine, and, rarely, halogenated X-ray contrast media such as Diodrast. The true incidence is difficult to determine. However, a figure around 1:40.000 of the unselected anaesthetized population has been suggested. Stress reactions may be triggered by strenuous exercise or massive skeletal injury, especially during hot and humid climate or under emotionally stressful conditions.

Aetiology and Pathophysiology

The aetiology of MH is still not entirely clear despite years of intensive research. However, the most acceptable explanation appears to be a sudden increase in myoplasmic calcium concentration. This probably is secondary to an increase in calcium released from the malfunctioned sarcoplasmic reticulum. The mechanisms proposed for the rise in myoplasmic calcium concentration include defective sarcoplasmic reticulum membrane itself, or some other part of the muscle, eg, mitochondria, excitation-contraction coupling, calmodulin (main intracellular calcium receptor), sarcolemma and adrenergic innervation pathway.

MH has a spectrum ranging from mild to severe manifestation. A modest increase of myoplasmic calcium in mild MH activates enough energy metabolic processes to stimulate

the production of heat, CO_2, lactic acid and oxygen consumption. In severe (classic) MH, the high level of myoplasmic calcium induces the following processes:

1. Myosin ATPase and sarcoplasmic reticulum ATPase is activated, thereby increasing heat production by accelerating the hydrolysis of ATP.

2. The configuration of troponin is changed, which allows contact of myosin to actin receptors, thus forming short and rigid actomyosin.

3. Calcium is taken up into the mitochondria, where it uncouples oxidative phosphorylation, leading to cessation of ATP production with further production of energy, CO_2, and lactic acid. This reduces the substrate for the active pumping of cellular and intracellular membrane, leading to increased permeability of ion and molecules in the direction of their natural concentration gradient. This causes further increases in cytoplasmic calcium. There is a leakage of potassium, phosphate, enzyme and myoglobin to the extracellular fluid, and entry of sodium and water intracellularly. Once ATP is depleted in the muscle, further treatment is probably futile.

MH appears to be a widespread membrane defect. The most adverse expression is in the skeletal muscles. Heart muscle, smooth muscle, brain cells, platelets and many other cell types may also be affected. The inheritance pattern is variable, and may be autosomal dominant, recessive and perhaps multigenic.

Clinical Presentation

Many MH susceptible patients lack obvious preoperative diagnostic clues, and an initial acute crisis may appear without warning, following a commonly used anaesthetic agent (such as suxamethonium and halothane). Early signs of MH are:

1. *Rigidity of jaw muscles* which may later become generalized.

2. *Tachycardia and cardiac arrhythmias* which include frequent ventricular extrasystoles, bigeminy and ventricular tachycardia. ECG may show tall peaked T waves characteristics of hyperkalaemia.

3. *Unstable blood pressure* - hypertension during the early stage, and hypotension is a late sign as the cardiac function becomes progressively impaired.

4. *Marked increase in CO_2 producting* leading to tachypnoea if patient is breathing spontaneously. A rising end-tidal CO_2 concentration despite an increase in ventilation is an early observable sign. Hence end-tidal CO_2 monitoring is a valuable adjunct to diagnosis. If a CO_2 absorber is in use, the temperature of the canister may rise, due to the accelerated chemical reaction within the soda-lime.

5. *Cyanotic mottling* of the skin, especially over the head, neck and upper chest.

Later signs are:

6. *Pyrexia* although the hallmark of MH is usually a later sign, and is influenced by the agents used. Suxamethonium in conjunction with halothane, induces an earlier and more rapid rise. The rate of rise in core temperature is variable (from 1°C/h to 1°C every 5 minutes).

7. *Acute pulmonary oedema* as a result of left ventricular failure commonly occurs in the late stage.

8. *Bleeding diathesis* may become apparent from disseminated intravascular coagulopathy.

9. *Other complications* include muscle swelling and pains, severe neurological damage, haemolysis, myoglobinaemia, myoglobinuria, renal failure from tubular necrosis.

Biochemical Changes

Laboratory investigations for the diagnosis and guidance of therapy include:

1. *Arterial Blood Gas Analyses* - A rise in CO_2 tension and a fall in oxygen tension in the mixed venous blood is an early finding during acute crisis, followed by a similar change in arterial blood, with a classical picture of mixed respiratory and metabolic acidosis (from increased lactate production).

2. *Serum Electrolytes* - There are major fluctuations in serum electrolyte levels. Serum potassium is usually elevated early, followed by a marked and prolonged fall. Variation in the serum calcium, phosphorus and magnesium levels may be observed.

3. *Serum Enzymes* - Creatinine kinase level increases markedly during the crisis, but in survivors, may reach their highest levels 24-48 hours later (as high as 1.000.000 units). Lactate dehydrogenase and aspartate aminotransferase are also very high during the first 72 hours in survivors.

4. *Haematological Studies* - Signs of haemolysis in blood and urine samples may be detected. Myoglobinaemia and myoglobinuria are common. Coagulation screen studies should be obtained, because lowered levels of Factor VIII and fibrinogen, together with thromocytopenia result in impaired coagulation.

5. *Blood Glucose, Lactate and Urea Nitrogen* - Accurate diagnosis requires skeletal muscle biopsy. Tests performed on the excised muscle include the caffeine halothane contracture (CHC) test, the caffeine skinned fibre tension test, the ATP depletion test, radioactive calcium uptake, and microscopy. Quin-2 test on lymphocytes is currently under investigation to evaluate its value as a non-invasive screening test.

Susceptibility to malignant hyperthermia is associated with clinical and subclinical myopathies. Early recognition is vital for the successful treatment of malignant hyperthermia. Routine monitoring of all patients undergoing anaesthesia must include heart rate, blood

pressure, ECG, end tidal CO_2, pulse oximetry, airway oxygen monitor, tidal volume, airway pressure, respiratory rate and body core temperature.

Management

1. *Termination of anaesthesia* and surgery if possible.

2. *Hyperventilation with oxygen* through a vapour free circuit.

3. *Dantrolene sodium* is partly responsible for the marked improvement in MH survival rate, and is currently accepted as the drug of choice. It must be given early while muscle perfusion is still adequate. An infusion of 1 mg/kg/min is given until reduction of heart rate, muscle tone and temperature occur, or a total dose of 10 mg/kg has been given. A dose exceeding 4 mg/kg is seldom required, although the optimal dose in humans is not yet known. After being controlled, MH may recur in the post-anaesthetic period. Dantrolene administration is immediately repeated at the first sign of such occurrence. A repeat prophylactic dose of 2.4 mg/kg after 10-12 h (which is the elimination half-life of Dantrolene) has been advocated.

Dantrolene is believed to relax skeletal muscle. It causes dissociation of muscle excitation-contraction coupling by interfering directly with sarcoplasmic reticulum calcium release or the preceding "trigger calcium", or both. However, its mode of action is not yet fully understood. It is metabolized in the liver, both by oxidation and reduction, followed by acetylation to form the reduced acetylated derivative of dantrolene (RAD)-metabolites, which themselves manifest some muscle relaxant properties. Dantrolene sodium is supplied in a vial containing 20 mg (together with 3.0 g of mannitol and enough sodium hydroxide to raise the pH to 9.5). The solution is irritant to veins and should be injected to a fast running drip or large vein.

While dantrolene itself has no myocardial effect, marked myocardial depression in animals has been reported after administration with verapamil. Simultaneous administration of these 2 drugs is contraindicated. Other side effects include drowsiness, nausea and vomiting, and synergism with neuromuscular blocking agents. Hepatic dysfunction, although documented in chronic oral administration, has not been shown following acute intravenous administration.

Prophylactic oral administration of dantrolene prior to anaesthesia in susceptible individuals is not been questioned, because an effective blood level cannot be guaranteed, and there are too many unpleasant side-effects. However, 2.4 mg/kg IV during induction of anaesthesia is recommended if there is a strong indication.

4. *Correction of acidosis* is achieved with sodium bicarbonate. Care should be taken against giving excessive alkali (noting the sodium hydroxide content in dantrolene). Over-correction of acidosis hjas been shown to lower the survival rate.

5. *Control of serum potassium,* if necessary, using glucose and insulin. Hypokalaemia may supervene.

6. *Mannitol and frusemide* is given to help reduce cerebral and muscle oedema, and prevent acute renal failure. The dose of mannitol is adjusted according to the mannitol given in conjunction with dantrolene.

7. *Control of arrhythmias* is undertaken with procaine or proacinamide. The dose should not exceed 7 mg/kg during crisis, as the myocardium is already compromised. Verapamil can be used, but never simultaneous with dantrolene. Repeated doses of 1.0 mg (0.015 mg/kg) propranolol IV (to a maximum of 0.15 mg/kg/6 h) may assist in lower the heart rate.

8. *Cooling* is started (although early diagnosis and dantrolene treatmetn may avoid aggressive cooling) with the following methods:

(a) ice packs and cooling blankets;

(b) ice water bath;

(c) cold intravenous solutions:

(d) internal cooling with cold solutions in the stomach and rectum;

(e) peritoneal dialysis using cold dialysate; and

(f) extracorporeal cooling if facility is available.

9. *Drugs* of marginal value are barbiturates, narcotics and antipyretics. Chlorpromazine increases heat loss by correcting peripheral vasoconstrictioon, and reduces heat production by inhibiting shivering, and may offer substantial benefit. Steroids have been recommended but their benefits are uncertain. Drugs which should *never* be given during a reaction include amide local anaesthetics, cardiac glycosides, calcium chloride, belladonna alkaloids and vasopressors.

10. *Movement* and handling of the patient should be minimized as they may precipitate ventricular arrhythmias.

11. *Monitoring* should include temperature, oximetry, end tidal CO_2, arterial and central venous pressures, urine output, ECG, arterial blood gases and pH, coagulation studies, and serum biochemistry such as electrolytes, glucose and enzymes levels.

The mortality rate from MH has declined from 86% in the 1960s to about 7% in the 1980s. This is attributed to the better understanding of the syndrome, advanced monitoring devices leading to early diagnosis, and vigorous treatment with early use of dantrolene.

Neuroleptic Malignant Syndrome

The neuroleptic malignant syndrome (NMS) is a relatively rare, but potentially fatal idiosyncratic response to neuroleptic drugs (eg, phenothiazines, butyrophenones, thioxanthenes

and miscellaneous antipsychotic agents such as loxapine). The syndrome is characterized by hyperthermia, muscular rigidity, akinesia, impaired consciousness and autonomic dysfunction. The estimated incidence is 0.5-1.0% of all patients exposed to neuroleptics. NMS affects all ages; 80% are under 40 years of age, and there is a male to female ratio of 2:1. The pathogenesis is believed to be related to dopamine - receptor blockade in basal ganglia and hypothalamus. Hyperthermia in NMS is probably due to impaired hypothalamic temperature regulation, and sustained muscle contraction.

Clinical Presentation

The syndrome may occur at any time during treatment with neuroleptic medication, frequently within 2 weeks of institution of therapy or when the dosage is increased. Serum levels are commonly within the normal range. The symptoms of NMS usually progress rapidly over 1-3 days, with hyperthermia (around 40°C), muscle rigidity, and resting tremor. Autonomic dysfunction (eg, tachycardia, labile blood pressure, and sweating) may be premonitory signs. Mental status varies from confusion to coma, and a variety of associated neurological signs, with disorders of speech and swallowing being most common, are present. Predisposing factors include functional psychoses and organic brain diseases.

Complications include acute renal failure from dehydration and/or myoglobinuria, pulmonary embolism with cardiac arrest, and acute myocardial infarction with pulmonary oedema. Persisting neurological sequelae has been reported in 10% of patients with parkinsonism, dyskinesia, dementia and ataxia. Laboratory findings are non specific. These include increased creatinine phosphokinase (CPK) level, non specific leucocytosis, abnormal liver function tests, acidosis, hypoxia, hypercarbia, and raised plasma and urinary catecholamine levels. Examination of cerebrospinal fluid are unremarkable. CT scans usually show no abnormalities. Those who survive recover in about 1-2 weeks (or longer with depot drug preparation).

A mortality rate of 20-30% has been reported. The association between malignant hyperthermia and NMS appears tenuous, and the 2 syndromes are probably distinct entities. NMS is differentiated from MH by its slow onset, moderate CPK rise, few associated metabolic changes, lack of family history, different triggering agents, and patient tolerance to anaesthetic agents.

Management

1. Immediate withdrawal of offending agent.

2. Supportive therapy:

(a) Cooling procedures as in MH.

(b) Treatment of cardiovascular instability.

(c) Mechanical ventilatory support if necessary.

(d) Treatment of dehydration with fluid therapy to maintain renal function.

3. Specific therapy:

(a) L-dopa with carbidopa (a dopa-decarboxylase inhibitor) mediate an increase in presynaptic synthesis and release of dopamine, and have been reported to be beneficial.

(b) Bromocryptine, a direct-acting dopamine agonist, has been successfully used with dantrolene.

(c) Dantrolene has been reported to alleviate manifestations of the syndrome at a dose as small as 100 mg/day either orally or IV. Until more is known about the pathophysiology of NMS, it is advisable to use a combination of dantrolene and dopaminergic drugs in its treatment.