Hypothermia, Hyperthermia, and Rhabdomyolysis

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Objectives:

- To understand the physiologic responses associated with hypothermia
- To outline supportive measures and rewarming techniques for management of hypothermia
- To describe predisposing factors for heat stroke, the clinical manifestations, and cooling methods
- To discuss the clinical presentations and management of malignant hyperthermia and neuroleptic malignant syndrome
- To describe etiologies, clinical presentation, and treatment of rhabdomyolysis

Key words: heat stroke; hyperthermia; hypothermia; malignant hyperthermia; neuroleptic malignant syndrome; rhabdomyolysis

Temperature Regulation

The balance between heat production and heat loss normally maintains the core body temperature at 36.6 ± 0.38°C (97.9 ± 0.7°F). Heat is produced from the dissolution of high-energy bonds during metabolism. At rest, the trunk viscera supply 56% of heat; during exercise, muscle activity may account for 90% of generated heat. Heat production may increase two- to fourfold with shivering and more than sixfold with exercise. Most heat loss (50 to 70%) normally occurs through radiation. Conduction of heat through direct contact with cooler objects or loss of heat due to convection accounts for a smaller percentage of heat loss. Evaporation of sweat from the skin is the major mechanism of heat loss in a warm environment.

The anterior hypothalamus is responsible for the perception of temperature and initiation of physiologic responses. Information is received from temperature-sensitive receptors in the skin, viscera, and great vessels, as well as receptors located in the hypothalamus. When a temperature increase is sensed, hypothalamic modulation results in increased sweating (a cholinergically mediated response), cutaneous vasodilation, and decreased muscle tone. Conversely, a decrease in temperature results in decreased sweating, cutaneous vasoconstriction, and increased muscle tone and shivering. These homeostatic mechanisms deteriorate with age.

Hypothermia

Definition and Etiologies

Hypothermia is defined as the unintentional lowering of core body temperature (tympanic, esophageal, or rectal) to < 35°C (< 95°F). Multiple factors may lead to increased heat loss, decreased heat production, or impaired thermoregulation (Table 1). Hypothermia may be characterized as primary (accidental), due to exposure to cold temperatures, or secondary, resulting from a disease process such as myxedema or sepsis. Exposure is often found in hypothermic patients, along with underlying chronic disease processes or impairment from ethanol, drugs, or mental illness. Immersion hypothermia is often distinguished from nonimmersion hypothermia because it occurs more rapidly and is more often accompanied by asphyxia. Hypothermia is frequently noted in trauma patients and is associated with increased mortality rates.

To facilitate management and anticipate physiologic changes, hypothermia can be classified by the degree of temperature reduction. Mild hypothermia refers to core temperatures of 32 to 35°C (90 to 95°F); moderate hypothermia, 28 to 32°C (82 to 90°F); and severe hypothermia, < 28°C (< 82°F).

Pathophysiology

General Metabolic Changes: Hypothermia produces multisystemic involvement that varies with core temperature (Table 2). The initial response to cold is cutaneous vasoconstriction, which results in shunting of blood from colder extremities to the body core. Vasodilation secondary to ethanol can prevent this normal compensatory response. Vasoconstriction fails at temperatures < 24°C (< 75°F), and the rate of heat loss increases due to relative vasodilation. Heat production is increased two- to fivefold by the onset of shivering with core temperatures of 30 to 35°C (86 to 95°F). Shivering continues until glycogen

stores are depleted, which usually occurs when the body temperature reaches 30°C (86°F).

Cardiovascular System: An initial tachycardia is followed by progressive bradycardia. The pulse rate decreases by 50% when core temperature reaches 28°C (82°F). Bradycardia is secondary to alterations in conductivity and automaticity that are generally refractory to standard treatment (*eg*, atropine). Cardiac function and blood pressure also decline proportionately as the core temperature decreases. Systemic vascular resistance predictably increases.

Table 1. *Factors Predisposing to Hypothermia*

- Increased heat loss
  - Environmental exposure
  - Skin disorders
    - Burns
    - Dermatitis
    - Psoriasis
  - Vasodilation
    - Alcohol
    - Drugs (phenothiazines)
  - Iatrogenic
    - Heat stroke treatment
    - Environmental cold (operating suite)
- Decreased heat production
  - Endocrine disorders
    - Hypopituitarism
    - Hypothyroidism
    - Hypoadrenalism
  - Insufficient fuel
    - Hypoglycemia
    - Anorexia nervosa
    - Malnutrition
    - Extreme exertion
  - Neuromuscular inefficiency
    - Extremes of age
    - Inactivity
    - Impaired shivering
- Impaired thermoregulation
  - Peripheral dysfunction
    - Neuropathies
    - Spinal cord transection
    - Diabetes
  - Central dysfunction
    - CNS hemorrhage/trauma
    - Cerebrovascular accident
    - Drugs
      - Sedatives
      - Alcohols
      - Cyclic antidepressants
      - Narcotics
    - Neoplasm
    - Parkinson's disease
    - Anorexia nervosa
- Miscellaneous states
  - Sepsis
  - Pancreatitis
  - Carcinomatosis
  - Uremia
  - Giant cell arteritis
  - Sarcoidosis

Hypothermia produces a variety of myocardial conduction abnormalities. Atrial fibrillation is common and usually converts to sinus rhythm spontaneously during rewarming. At temperatures of < 29°C (< 84°F), ventricular fibrillation (VF) can occur spontaneously or be induced by movement or invasive procedures (*eg*, central line, nasogastric tube). Asystole occurs at temperatures < 20°C (<68°F). VF and other arrhythmias are extremely refractory to defibrillation and drug treatment until the core temperature increases to ~30°C (~86°F).

Although many ECG abnormalities have been described, the most characteristic of hypothermia is the J wave (also called the Osborne wave) at the junction of the QRS complex and ST segment (Fig 1). The J wave can occur in patients with core temperatures of < 32°C (< 90°F) and it is almost always present at temperatures of < 25°C (< 77°F). It has been observed that the size of the J wave may be inversely correlated with temperature. The presence of this wave is not pathognomonic for hypothermia, nor does it have prognostic value. It is important to distinguish J waves from ST segment elevation indicating myocardial infarction. Prolongation of the P–R, QRS, and Q–T intervals may be noted.

Other Organ Systems: As temperature decreases, tidal volume and respiratory rate will decrease. The cough reflex may be blunted, and cold-induced bronchorrhea may contribute to atelectasis. Hypoxemia may develop early depending on the circumstances (*eg*, water immersion, aspiration). Although renal blood flow and glomerular filtration rate decrease in hypothermia, there is an initial cold-induced diuresis due to the relative central hypervolemia resulting from peripheral vasoconstriction. Additional contributory factors include the inhibition of antidiuretic hormone release and renal tubular concentrating defects. Ethanol exacerbates the diuresis. With warming, volume depletion may become evident.

With mild hypothermia, victims may exhibit confusion, lethargy, or combativeness. Below a core temperature of 32°C (90°F), the patient is usually unconscious with diminished brainstem function. Pupils dilate below a core temperature of 30°C (86°F). Intestinal motility decreases at < 34°C (< 93°F), resulting in the com-

Table 2. *Manifestations of Hypothermia**

Core Temp (°C)	Musculoskeletal	Neurologic	Other
		Mild Hypothermia	
36	Shivering begins	Slurred speech	
34	Maximal shivering	Increased confusion	
33	Decreased shivering	Stupor	Decreasing BP; respiratory alkalosis, cold diuresis
		Moderate Hypothermia	
32	Shivering nearly absent; onset of muscle rigidity	Pupils dilated	Arrhythmias; J waves on ECG
30		DTRs absent	Severe hypoventilation
28	Extreme muscle rigidity	No voluntary movement	Shock; inaudible heart sounds
		Severe Hypothermia	
26			
24	Patient appears dead		Severe risk of VF; minimal cardiac activity
22			
20		Isoelectric EEG	Asystole
18		Isoelectric EEG	Asystole

*DTR = deep tendon reflex. To convert Celsius to Fahrenheit temperature, multiply by 9/5, then add 32.

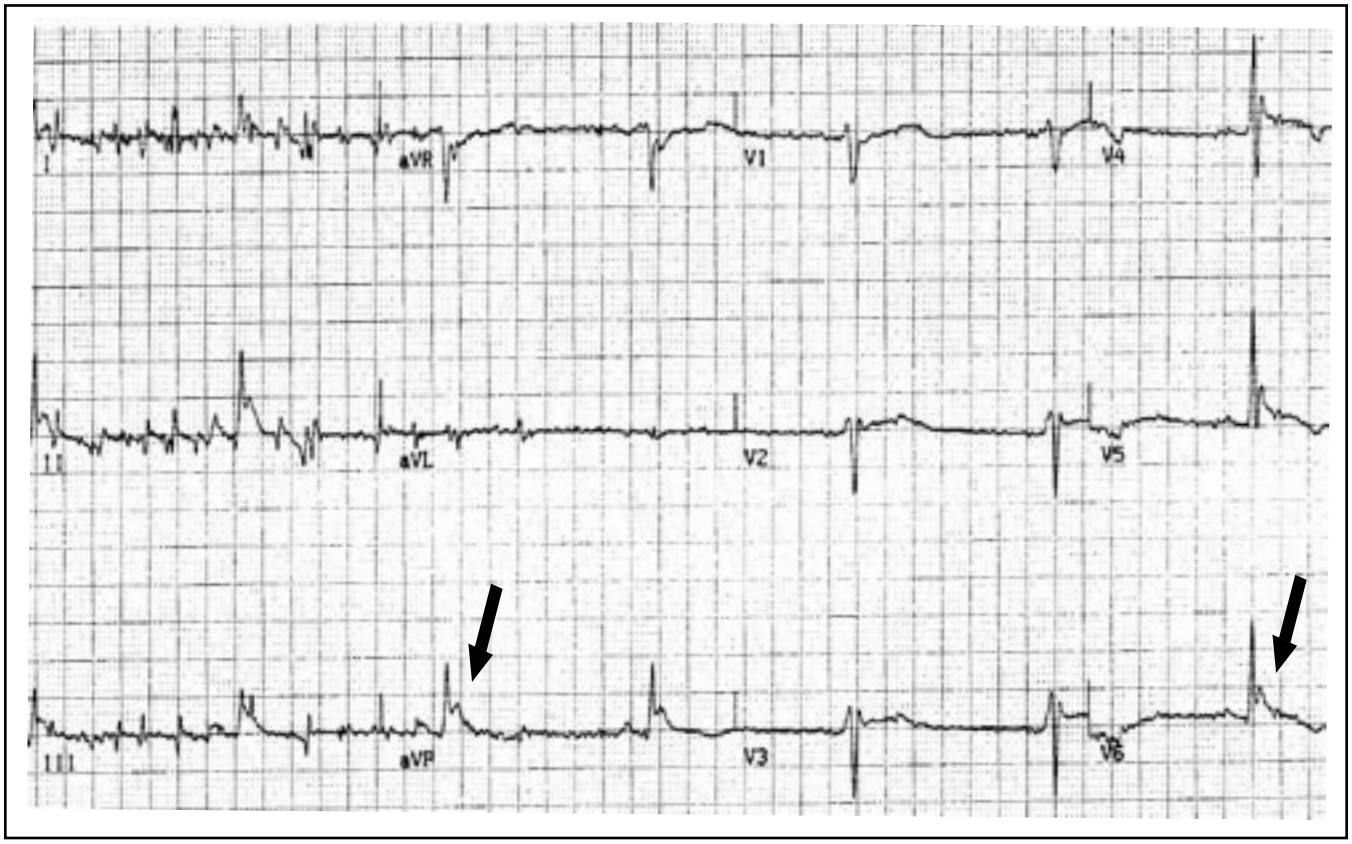

Figure 1. ECG of hypothermic patient showing J wave (arrow).

mon finding of ileus. Hepatic dysfunction affects the generation of glucose as well as drug metabolism.

Laboratory Findings: The physiologic changes described are reflected by clinical laboratory tests. An increased hematocrit is usually found, with normal or low platelet and white blood cell counts. The increase in hematocrit is due to hemoconcentration and splenic contraction. However, restoration of intravascular volume and warming often result in a mild anemia. Platelet and white blood cell counts may drop as temperatures decrease due to sequestration. Platelet dysfunction occurs with hypothermia and may compromise hemostasis. Although disseminated intravascular coagulation (DIC) may develop, initial coagulation studies (prothrombin time, partial thromboplastin time) are often normal as these laboratory measurements are performed on warmed blood. Electrolytes are variable and no consistent changes are predictable. Increased values of BUN and creatinine result from hypovolemia. Hyperglycemia is common as a result of catecholamine-induced glycogenolysis, decreased insulin release, and inhibition of insulin transport. Hypoglycemia may be evident in malnourished and alcoholic patients. The acid-base status is difficult to predict in hypothermia, but factors such as respiratory acidosis, lactate generation from shivering, decreased acid excretion, and decreased tissue perfusion contribute to acidemia. There is general agreement that arterial blood gas values do not need to be corrected for temperature. However, the Pa_{O_2} should be corrected to evaluate oxygen delivery and the alveolar-arterial gradient.

Diagnosis

The clinical manifestations of hypothermia vary with the etiology, acuteness of onset, severity, and duration. It is imperative to recognize early signs of mild hypothermia, especially in the elderly. These patients may present with confusion, lethargy, impaired judgment, and the unusual manifestation of "paradoxical undressing." More severe hypothermia results in manifestations that are easily recognizable: muscle rigidity, decreased reflexes, decreased respiratory rate, bradycardia, hypotension, and even the appearance of death. The clinical suspicion of hypothermia should be confirmed with an accurate core temperature measurement. Any low temperature (35°C or 95°F) should be checked with a thermometer capable of registering lower temperatures. A rectal probe is most practical even though it may lag behind core changes. The probe should be inserted to an adequate depth (approximately 15 cm), avoiding cold fecal material. An esophageal probe is an alternative, but readings may be falsely elevated in the intubated patient who receives heated oxygen. Thermistors in bladder catheters provide readings similar to intravascular devices. Reliability of tympanic temperature devices has not been established in hypothermia.

Management

Hospital Management: The severity of hypothermia, clinical findings, and comorbid conditions of the patient determine the aggressiveness of resuscitation techniques. The following measures should be instituted as indicated.

1. *Airway management*. Intubation is often necessary for airway protection and/or delivery of supplemental oxygen. The orotracheal route is preferred because of the risk of traumatic bleeding with the nasal route. However, muscle rigidity may preclude orotracheal intubation. Endotracheal tube cuff pressures should be monitored after rewarming because volume and pressure will increase.
2. *Supplemental oxygen*. Pulse oximetry cannot be relied on to guide therapy in conditions of hypothermia and hypoperfusion.
3. *Cardiopulmonary resuscitation.* Cardiopulmonary resuscitation should be initiated if the patient is pulseless (assess for 30 to 45 s) or has a nonperfusing rhythm such as asystole or ventricular fibrillation. Chest wall compression is often difficult.
4. *ECG monitoring*.
   - *In bradycardia:* Avoid pharmacologic manipulation and pacing.
   - *In VF:* Initial defibrillation should be attempted even if the temperature is < 30 to 32°C (< 86 to 90°F). If unsuccessful, institute rewarming. Avoid IV drugs until the temperature increases to ~30°C (~86°F) and then use the lowest effective dose. Dosing intervals should be increased in hypothermic patients. Epinephrine and vasopressin have improved coronary artery perfusion pressure in hypothermic animals. The efficacy of amiodarone has not been established in

hypothermia, but it is a reasonable initial antiarrhythmic drug. Magnesium sulfate has also been used successfully. Lidocaine has limited efficacy and procainamide may increase the incidence of VF.

- *In asystole:* Follow advanced cardiac life support guidelines and administer pharmacologic agents when the temperature approaches 30°C (86°F).

5. *Core temperature monitoring.*
6. *Rewarming* (see below).
7. *IV fluids.* All patients require fluids for hypovolemia. Warm normal saline solution containing glucose is a reasonable choice. Increased fluid requirements are often necessary during rewarming to prevent or treat hypotension. Lactated Ringer's solution should be avoided because of impaired hepatic metabolism of lactate.
8. *Vasopressor drugs.* Hemodynamic instability should first be addressed with volume replacement. Vasopressor drugs have a minimal effect on constricted vessels and increase the risk of dysrhythmias.
9. *Nasogastric or orogastric tube.* Insert to relieve gastric distention.
10. *Urinary catheter.*
11. *Venous access.* Peripheral venous catheters are preferred. Central venous lines (subclavian, internal jugular) are not routinely recommended because they may precipitate dysrhythmias.
12. *Laboratory studies.* Studies should include complete blood count, prothrombin time, partial thromboplastin time, electrolytes, creatine kinase level, and arterial blood gases. Thyroid function evaluation, toxicology screen, and blood cultures are obtained as warranted.
13. *Search for associated conditions* requiring urgent intervention, such as hypoglycemia, sepsis, adrenal insufficiency, and hypothyroidism.

Rewarming Methods: Choices and controversies—Although warming is the primary treatment for hypothermia, controversy exists as to the optimal method, duration, and rate of rewarming. Rapid rewarming does not necessarily lead to improved survival. No controlled studies comparing rewarming methods exist and rigid treatment protocols cannot be recommended. Three types of rewarming procedures exist: passive external rewarming (PER), active external rewarming (AER), and active core rewarming (ACR).

PER is the least invasive and the slowest method. It involves placing the patient in a warm environment, providing warm clothing or blankets, and allowing the body to regain heat. This technique should be applied as the sole method only in patients with mild hypothermia. The patient must be able to generate heat for PER to be effective. Rewarming rates with PER in mild hypothermia range from 0.5 to 2.0°C/h (1 to 3.6°F/h).

AER involves the external application of heat, such as warming blankets, heating pads, radiant heat lamps, or immersion in warm water. Currently, forced-air warming devices are the most effective and practical means of applying AER, particularly in the perioperative period. A potential disadvantage of this method is the theoretical concern of "after-drop." When a heat source is applied, peripheral vasodilation occurs and colder peripheral blood is transported to the relatively warmer core, thereby reducing the core temperature. After-drop has been hypothesized to increase the incidence of VF. In response to this concern, it has been suggested that heat be applied only to the thorax, leaving the extremities vasoconstricted. The advantages of AER are its ease of institution, ready availability, low cost, and noninvasiveness. Earlier studies showing high mortality when AER was utilized have not been supported by more recent experience. AER is often combined with ACR techniques in patients with moderate or severe hypothermia.

ACR is the most rapid and most invasive method, and involves the application of heat to the body core. ACR is indicated in patients with a core temperature of < 28°C (< 82°F) or with an arrested cardiac rhythm. Techniques for ACR include heated humidified oxygen, heated IV fluids, thoracic lavage, peritoneal lavage, gastric/rectal lavage, hemodialysis, continuous arteriovenous/venovenous rewarming, and cardiopulmonary bypass.

One of the simplest methods to institute is warm, humidified, inhaled oxygen (42 to 45°C, or 107.6 to 113°F), which prevents further respiratory heat loss and may result in a modest heat gain. A rewarming rate of 1 to 2.5°C/h (2 to 4.5°F/h) can be expected. This technique should be used routinely on most victims of moderate to severe hypothermia. Heated IV fluids (40 to 42°C. or 104 to 107.6°F) are also easy to institute. Although gastric, bladder, or rectal lavage with warm fluids is a simple procedure, there is little information regarding the efficacy of this method. It

should generally be used only as an adjunct until more invasive rewarming methods can be initiated.

For patients with severe hypothermia, more invasive ACR is preferred: peritoneal lavage, thoracic lavage, hemodialysis, continuous arteriovenous/venovenous rewarming, and cardiopulmonary bypass. These procedures require specialized equipment and intensive care. However, they are very efficient at rewarming and, in the case of cardiopulmonary bypass, may provide for hemodynamic stabilization of the patient. Peritoneal lavage can be instituted through a peritoneal dialysis catheter, using dialysate heated to 40 to 45°C (104 to 113°F). Closed thoracic lavage involves placement of anterior and posterior chest tubes, infusion of heated saline (40 to 42°C, or 104 to 107.6°F) through the anterior tube, and gravity drainage from the posterior tube. Hemodialysis, utilizing a two-way-flow catheter, may be best suited for the patient who does not have hemodynamic instability. Continuous arteriovenous/venovenous rewarming utilizes a modified fluid warmer with 40°C (104°F) water infused through the inner chamber. Cardiopulmonary bypass (femoral-femoral or atrial-aortic) is the most invasive and labor-intensive technique for rewarming. It has the advantage of providing complete hemodynamic support and rapid rewarming rates (1 to 2°C every 3 to 5 min).

The choice of rewarming methods may combine techniques, such as truncal AER with ACR, using heated oxygen and IV fluids. Availability of resources may be a decisive factor in choosing the method of rewarming. In all cases, complications of rewarming such as DIC, pulmonary edema, compartment syndromes, rhabdomyolysis, and acute tubular necrosis must be anticipated.

Outcome From Hypothermia

There are currently no strong predictors of death or permanent neurologic dysfunction in severe hypothermia. Therefore, there are no definitive indicators to suggest which patients can or cannot be resuscitated successfully. Core temperature before rewarming and time to rewarming do not predict outcome. Severe hyperkalemia (>10 mEq/L) may be a marker of death. In general, resuscitative efforts should continue until the core temperature is 32°C (90°F). However, the decision to terminate resuscitation must be individualized based on the circumstances.

Hyperthermia

Heat Stroke

Definition: Heat stroke is a life-threatening medical emergency that occurs when homeostatic thermoregulatory mechanisms fail. This failure usually results in elevation of body temperature to > 41°C (> 105.8°F), producing multisystem tissue damage and organ dysfunction. Two syndromes of heat stroke occur: classic heat stroke (nonexertional) and exertional heat stroke. Classic heat stroke typically affects infants and elderly individuals with underlying chronic illness. The occurrence of classic heat stroke is often predictable when heat waves occur. The syndrome develops over several days and results in significant dehydration and anhidrosis. Exertional heat stroke typically occurs in young individuals such as athletes and military recruits exercising in hot weather. These individuals usually have no chronic illness, and this syndrome occurs sporadically and often unpredictably. Dehydration is mild and ~50% of individuals will have profuse sweating.

Predisposing Factors: Heat stroke results from increased heat production and/or decreased heat loss (Table 3). Environmental factors of high heat and humidity contribute to heat production as well as limit heat loss. Sympathomimetic drugs, such as cocaine and amphetamines, increase muscle activity and may also disrupt hypothalamic regulatory mechanisms. Numerous drugs interfere with the ability to dissipate heat. Drugs with anticholinergic effects, such as cyclic antidepressants, antihistamines, and antipsychotics, inhibit sweating

Table 3. *Predisposing Factors for Heat Stroke*

Increased Heat Production
Exercise
Fever
Thyrotoxicosis
Hypothalmic dysfunction
Drugs (sympathomimetics)
Environmental heat stress
Decreased Heat Loss
Environmental heat stress
Cardiac disease
Peripheral vascular disease
Dehydration
Obesity
Skin disease
Anticholinergic drugs
Ethanol
β-blockers

and disrupt hypothalamic function. Ethanol may contribute to heat stroke by several mechanisms: vasodilation resulting in heat gain, impaired perception of the environment, and diuresis. β-Adrenergic blockers may impair cardiovascular compensation and decrease cutaneous blood flow. Factors that increase the risk of death, as identified in the July 1995 heat wave in Chicago, include being confined to bed because of medical problems and living alone.

Diagnosis: The diagnosis of heat stroke requires a history of exposure to a heat load (either internal or external), severe CNS dysfunction, and elevated temperature (usually > 40°C , or > 104°F). The absolute temperature may not be critical because cooling measures often have been instituted before the patient is admitted to a health-care facility. Sweating may or may not be present.

Clinical Manifestations: Profound CNS dysfunction is a defining characteristic of heat stroke. Dysfunction may range from bizarre behavior, delirium, and confusion to decerebrate rigidity, cerebellar dysfunction, seizures, and coma. These changes are potentially reversible, although permanent deficits can occur. Lumbar puncture results may show increased protein, xanthochromia, and lymphocytic pleocytosis.

Tachycardia, an almost universal cardiovascular finding in heat stroke, occurs in response to peripheral vasodilation and the need for increased cardiac output. The peripheral vascular resistance is usually low unless severe hypovolemia is present. Compensatory vasoconstriction occurs in the splanchnic and renal vascular beds. If the patient is unable to increase cardiac output, hypotension develops. A variety of ECG changes have been described in heat stroke, including conduction defects, increased Q-T interval, and nonspecific ST-T changes.

Tachypnea may result in a significant respiratory alkalosis. However, victims of exertional heat stroke usually have lactic acidosis. Hypoglycemia may be present in exertional heat stroke victims owing to increased glucose utilization and impaired hepatic gluconeogenesis. Hypoglycemia may be present in exertional heat stroke victims as a result of increased glucose utilization and impaired hepatic gluconeogenesis. Rhabdomyolysis and renal failure occur more commonly with exertional heat stroke and may be caused by myoglobinuria, thermal parenchymal damage, or decreased renal blood flow due to hypotension. Hematologic effects include hypocoagulability, which may progress to DIC. Hepatic injury results in cholestasis and elevation of transaminase levels.

An inflammatory response may cause or contribute to the clinical manifestations of heat stroke. Increased concentrations of endotoxin, tumor necrosis factor, soluble tumor necrosis factor receptor, and interleukin-1 have been demonstrated in heat stroke victims. Interleukin-6 and nitric oxide metabolite concentrations correlate with the severity of illness. Endothelial cell activation / injury is suggested by findings of increased concentrations of circulating intercellular adhesion molecule-1, endothelin, and von Willebrand-factor antigen.

Electrolyte concentrations are variable in heat stroke. Hyperkalemia can result from rhabdomyolysis, but hypokalemia occurs more commonly. Hypocalcemia can occur, particularly with rhabdomyolysis, but usually does not require therapy.

Differential Diagnosis: The history and physical findings usually indicate the diagnosis of heat stroke. In the absence of adequate history, other processes to be considered include CNS infection, hypothalamic lesions, thyroid storm, and other hyperthermic syndromes such as neuroleptic malignant syndrome.

Treatment: Along with resuscitative measures, immediate cooling should be instituted for any patient with a temperature of > 41°C (> 105.8°F). Two methods of cooling have been used: conductive cooling and evaporative cooling. Because definitive human studies are lacking, the optimal cooling method remains controversial.

Direct cooling by enhancing conduction of heat from the body is accomplished by immersing the patient in cold water. Skin massage to prevent cutaneous vasoconstriction in the limbs has been recommended. Shivering can result in an undesirable increase in heat production. This method requires considerable staff time and makes it difficult to treat seizures and perform other resuscitative measures. Variants of this method include ice-water soaks and application of ice packs to the axillae, groin, and neck.

Evaporative cooling is a widely used practical cooling method. The patient is placed nude on a stretcher and sprayed with warm (not cold) water. Air flow is created with use of fans to enhance evaporative cooling. This method allows personnel to institute other resuscitative measures while cooling occurs. Other cooling methods, such as peritoneal lavage, iced gastric lavage, or cardiopulmonary by-

pass, have not been effectively tested in humans. Antipyretics are not indicated and dantrolene is ineffective.

In addition to cooling, most patients will require intubation for airway protection. Supplemental oxygen should be instituted for all patients. The type and quantity of IV fluids should be individualized based on assessment of electrolytes and volume status. Overaggressive hydration may result in cardiac decompensation during cooling, especially in the elderly. Hypotension usually responds to cooling as peripheral vasodilation decreases. Vasopressor agents that result in vasoconstriction can decrease heat exchange and are not recommended for initial management of hypotension. A thermistor probe should be used for monitoring of core temperature during cooling efforts. Cooling should be stopped at 38.0 to 38.8°C (100.4 to 102°F) to prevent hypothermic overshoot.

Outcome: With appropriate management, the survival rate from heat stroke approaches 90%. However, morbidity is related to the duration of hyperthermia and to underlying conditions. Advanced age, hypotension, coagulopathy, hyperkalemia, acute renal failure, and prolonged coma are associated with a poor prognosis. Elevated lactate levels are associated with a poor prognosis in classic heat stroke but not exertional heat stroke. In retrospective studies, rapid cooling (< 1 h) was associated with a decreased mortality.

Malignant Hyperthermia

Definition: Malignant hyperthermia (MH) is a drug- or stress-induced hypermetabolic syndrome characterized by hyperthermia, muscle contractures, and cardiovascular instability. It results from a genetic defect of calcium transport in skeletal muscle. The primary defects are postulated to be impaired reuptake of calcium into the sarcoplasmic reticulum, increased release of calcium from the sarcoplasmic reticulum, and a defect in the calcium-mediated coupling contraction mechanism. Sustained muscle contraction results in increased oxygen consumption and heat production. It is genetically transmitted as an autosomal-dominant trait and occurs in 1 in 50 to 1 in 150,000 adults who receive anesthesia.

Triggers: Halothane and succinylcholine have been involved in the majority of reported cases of MH. Additional potentiating drugs include muscle relaxants, inhalational anesthetic agents, and drugs such as ethanol, caffeine, sympathomimetics, parasympathomimetics, cardiac glycosides, and quinidine analogs. Less commonly, MH can be precipitated by infection, physical or emotional stress, anoxia, or high ambient temperature.

Clinical Manifestations: Manifestations of MH usually occur within 30 min of anesthesia in 90% of cases. However, onset of the syndrome may occur postoperatively. Muscle rigidity begins in the muscles of the extremities or the chest. In patients receiving succinylcholine, the stiffness most commonly begins in the jaw. The development of masseter spasm after administration of a paralyzing agent must be considered an early sign of possible MH. Tachycardia is another early, although nonspecific, sign. Monitoring of arterial blood gases or end-tidal CO_2 may detect an early increase in CO_2. Hypertension and mottling of the skin also occur. The increase in temperature usually occurs later, but it is followed rapidly by acidosis, ventricular arrhythmias, and hypotension. Laboratory abnormalities include increased sodium, calcium, magnesium, potassium, phosphate, creatine kinase, and lactate dehydrogenase levels. Lactate levels are increased and arterial blood gases indicate hypoxemia and an increase in $Paco_2$.

Treatment: Once the diagnosis of MH is entertained, the inciting drug should be discontinued immediately. The most effective and safest therapy is dantrolene, which prevents release of calcium into the cell by the sarcoplasmic reticulum. Uncoupling of the excitation contraction mechanism in skeletal muscle decreases thermogenesis. Dantrolene should be administered by rapid IV push, beginning at a dose of 1 to 2.5 mg/kg and continuing until the symptoms subside or the maximum dose of 10 mg/kg has been reached. Decreasing muscle rigidity should be evident within minutes. Subsequent doses of 4 to 8 mg/kg every 6 h should be continued for 24 to 48 h. If dantrolene is ineffective or slowly effective, evaporative cooling methods can also be utilized. Calcium channel blockers are of no benefit in MH.

Neuroleptic Malignant Syndrome

Definition: Neuroleptic malignant syndrome (NMS) is an idiosyncratic reaction, usually to neuroleptic drugs, characterized by hyperthermia, muscle rigidity, alterations in mental status, autonomic dysfunction, and rhabdomyolysis. It may occur in

up to 1% of all patients taking neuroleptic agents; it affects the young more than the old, and affected individuals are more likely to be male than female. The pathogenesis is unknown, but it is thought to be related to CNS dopamine antagonism and altered hypothalamic temperature set point.

Triggers: Although the majority of cases have been associated with haloperidol, the following agents have been associated with NMS: butyrophenones (*eg*, haloperidol); phenothiazines (*eg*, chlorpromazine, fluphenazine); thioxanthenes (*eg*, thiothixene); dopamine-depleting agents (*eg*, tetrabenazine); dibenzoxazepines (*eg*, loxapine); and withdrawal of levodopa/carbidopa or amantadine. Rechallenge with an inciting drug may not result in recurrence of NMS kinase. Various diagnostic criteria have been proposed (Table 4), but NMS remains a clinical diagnosis based on exposure to neuroleptic agents or other dopamine antagonists in association with characteristic manifestations.

Clinical Manifestations: NMS usually occurs 1 to 3 days after initiating a neuroleptic agent or changing the dose, and the syndrome may last for a period of 1 to 3 weeks. Hyperthermia is universally present and the average maximal temperature is 39.9°C (103.8°F). Autonomic dysfunction includes tachycardia, diaphoresis, blood pressure instability, and arrhythmias. Autonomic dysfunction may precede changes in muscle tone. A general increase in muscle tone or tremors occurs in > 90% of patients. Early manifestations of changes in muscle tone include dysphagia, dysarthria, or dystonia. Altered mental status occurs in 75% and can range from agitation to coma. Rhabdomyolysis occurs frequently with elevations of creatine kinase. Various diagnostic criteria have been proposed (Table 4), but NMS remains a clinical diagnosis based on exposure to neuroleptic agents or other dopamine antagonists in association with characteristic manifestations.

Treatment: Dantrolene is the most effective agent for reducing muscle rigidity and decreasing temperature. It is given in the same doses as described for MH. In addition, dopamine agonists have been reported to have beneficial effects in NMS. These drugs include bromocriptine (2.5 to 10 mg three times daily), amantadine (100 mg twice daily), and levodopa/carbidopa. Supportive therapies must also be instituted as indicated. Complications may include respiratory failure, cardiovascular collapse, renal failure, arrhythmias, or thromboembolism.

Table 4. *Diagnostic Criteria for NMS**

Major Criteria
Fever
Muscle rigidity
↑ Creatinine kinase
Minor Criteria
Tachycardia
Abnormal blood pressure
Tachypnea
Altered consciousness
Diaphoresis
Leukocytes

* Diagnosis of NMS is suggested by the presence of all three major criteria or by the presence of two major and four minor criteria.

Rhabdomyolysis

Definition

Rhabdomyolysis is a clinical and laboratory syndrome resulting from skeletal muscle injury with release of cell contents into the plasma. Rhabdomyolysis occurs when demands for oxygen and metabolic substrate exceed availability. This syndrome may result from primary muscle injury or secondary injury due to infection, vascular occlusion, electrolyte disorders, or toxins. Table 5 provides an overview of causes of rhabdomyolysis.

Manifestations

Table 5. *Causes of Rhabdomyolysis*

Traumatic	Infections	Toxins/Drugs	Metabolic Disorders
Crush syndrome	Coxsackievirus	Alcohol	Enzyme deficiencies
Muscle compression	Gas gangrene	Amphetamines	Hyperosmolar states
Hyperthermic syndromes	Hepatitis	Carbon monoxide	Hypokalemia
Burns	Influenza B virus	Cocaine	Hypomagnesemia
Electrical injury	Legionella	Phencyclidine	Hypophosphatemia
Exertion	Salmonella	Snake/spider venom	Inflammatory muscle disease
Seizures	Shigella	Statins	Thyroid disease
Vascular occlusion	Tetanus	Steroids	Vasculitis

Clinical manifestations of rhabdomyolysis consist of myalgias, muscle swelling and tenderness, discoloration of the urine, and features of the underlying disease. However, overt symptoms or physical findings may not be present. Laboratory evaluation reflects muscle cell lysis with elevation of muscle enzyme levels (creatine kinase, lactate dehydrogenase, aldolase, and aspartate aminotransferase), hyperkalemia, hyperphosphatemia, and hypocalcemia. Coagulation abnormalities consistent with DIC may occur. Renal failure may result secondary to release of myoglobin and other toxic muscle components. A urine dipstick positive for blood and an absence of red blood cells on microscopic examination suggest the presence of myoglobinuria.

Treatment

The treatment of rhabdomyolysis is aimed at treating the underlying disease and preventing complications. Maintenance of intravascular volume and renal perfusion is the most important aspect of preventing renal failure. Volume resuscitation should target a urine output of 2 to 3 mL/kg/h. Although increased urine output is beneficial, other interventions to prevent renal failure are more controversial. Alkalinization of the urine may be helpful, but clinical relevance has not been established. The greatest benefit of administering sodium bicarbonate may be restoration of intravascular volume rather than a change in pH. Treatment with bicarbonate should be individualized, based on the patient's ability to tolerate the sodium and fluid load. Loop diuretics and osmotic diuretics have been advocated to be protective of the kidneys, but convincing clinical data are lacking. Loop diuretics theoretically can worsen renal tubular acidosis, which is thought to potentiate myoglobin-induced nephropathy. Diuresis should not be attempted without adequate volume replacement.

Electrolyte abnormalities should be anticipated and treated expeditiously. The most life-threatening abnormality is hyperkalemia. Hypocalcemia does not usually require treatment and empiric administration of calcium may exacerbate muscle injury.

The patient must be closely observed for the development of a compartment syndrome. Monitoring of intracompartmental pressures may be required. Fasciotomy is often recommended for intracompartmental pressures of > 30 to 35 mm Hg.

Suggested Readings

Hypothermia

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Notes