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Review

Thermoregulatory disorders and illness related to heat and cold stress

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ABSTRACT

Thermoregulation is a vital function of the autonomic nervous system in response to cold and heat stress. Thermoregulatory physiology sustains health by keeping body core temperature within a degree or two of 37 °C, which enables normal cellular function. Heat production and dissipation are dependent on a coordinated set of autonomic responses. The clinical detection of thermoregulatory impairment provides important diagnostic and localizing information in the evaluation of disorders that impair thermoregulatory pathways, including autonomic neuropathies and ganglionopathies. Failure of neural thermoregulatory mechanisms or exposure to extreme or sustained temperatures that overwhelm the body's thermoregulatory capacity can also result in potentially life-threatening departures from normothermia. Hypothermia, defined as a core temperature of <35.0 °C, may present with shivering, respiratory depression, cardiac dysrhythmias, impaired mental function, mydriasis, hypotension, and muscle dysfunction, which can progress to cardiac arrest or coma. Management includes warming measures, hydration, and cardiovascular support. Deaths from hypothermia are twice as frequent as deaths from hyperthermia. Hyperthermia, defined as a core temperature of >40.5 °C, may present with sweating, flushing, tachycardia, fatigue, lightheadedness, headache, and paresthesia, progressing to weakness, muscle cramps, oliguria, nausea, agitation, hypotension, syncope, confusion, delirium, seizures, and coma. Mental status changes and core temperature distinguish potentially fatal heat stroke from heat exhaustion. Management requires the immediate reduction of core temperature. Ice water immersion has been shown to be superior to alternative cooling measures. Avoidance of thermal risk and early recognition of cold or heat stress are the cornerstones of preventive therapy.

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1. Introduction

Temperature is a critical variable in health and disease. Constraint of human body core temperature within a degree or two of 37 °C, which is the optimal temperature for normal cellular function, occurs in three ways. The first is stable climate, which maintains temperatures across most of the surface of planet Earth within a range compatible with human life. The second is the autonomic nervous system, which reacts robustly to thermal challenges by orchestrating a complex array of neural responses below the level of conscious awareness. The autonomic responses to cold stress include cutaneous vasoconstriction to retain bodily heat as well as metabolic and shivering thermogenesis. The autonomic responses to heat stress include cutaneous vasodilatation, which liberates heat by radiant and convective heat loss, and sweating, which liberates heat by evaporation. The third and perhaps least predictable is human behavior, which responds to thermal sensory input by seeking warmth or coolness, but which also is responsible for getting people into situations of cold or heat stress, some of which can threaten life or health. Another aspect to human behavior is the healthcare professional's response to thermoregulatory disorders, which draws from knowledge of autonomic physiology to treat patients who have been rescued from circumstances that challenge their capacity for thermoregulation.

This clinical review has a dual emphasis. The first is thermoregulatory disorders, which are disorders of the autonomic nervous system that impair the pathways involved in thermoregulation. Whereas these disorders sometimes present with symptoms related to heat or cold stress, more often the thermoregulatory deficit is incidental to symptoms and provides colocalizing information that is helpful to reaching an accurate diagnosis. The second is illness related to heat stress or cold stress, which encompasses common clinical presentations in which autonomic thermoregulatory function or dysfunction plays a role. Environmental conditions of extreme or prolonged heat or cold stress can overwhelm human thermoregulatory capacity, even in healthy persons, but especially for those whose capacity is impaired. Each year in the United States, for example, approximately 2000 people die from weather-related causes of death (Berko et al., 2014). The National Center for Health Statistics found that 63% of these were attributed to exposure to excessive or prolonged natural cold, hypothermia, or both; whereas 31% were attributed to exposure to excessive natural heat, heat stroke, or sun stroke. As these statistics were gathered from death certificates, the numbers may underestimate the true incidence of fatal thermoregulatory catastrophe (Berko et al., 2014).

2. Measurement of body temperature

The bodily temperatures most relevant in medicine are those of the internal organs, particularly the brain, heart and liver. The temperature of the vital internal organs is referred to as the core temperature. The clinical importance of the core temperature relates to the fact that the central nervous system, especially the cerebellum, and the liver are especially sensitive to heat stress (Atha, 2013; Kiyatkin, 2010). Heat-related injury also impacts the kidneys, gastrointestinal tract, and myocardium (Atha, 2013; Jardine, 2007; Wexler, 2002). A number of methods are available in clinical practice, and each has its advantages and disadvantages (Table 1).

2.1. Invasive techniques

Whereas direct measurement of brain temperature in clinical settings is impractical, the pulmonary artery temperature, as measured by a thermistor in a pulmonary artery catheter, is considered the gold standard for accurate determination of core temperature in clinical settings where invasive measurements are possible (Pearson et al., 2012; Lefrant et al., 2003). Other internal sites at which core temperature has been measured include the esophagus, intestines, rectum, and bladder (Lefrant et al., 2003; Robinson et al., 1998). Monitoring of esophageal temperature during left atrial radiofrequency procedures for atrial fibrillation, for example, has been shown to reduce the risk of thermal injury to the esophagus (Liu et al., 2012; Leite et al., 2011).

For the vast majority of patients who do not have indwelling catheters, rectal thermometry has evolved as the standard method for determining core temperature (Lefrant et al., 2003; Robinson et al., 1998). Rectal thermometry is not ideal, however, as rectal temperatures may lag changing temperatures in the blood and other deep organs (Robinson et al., 1998; Eichna et al., 1951). Rectal thermometry also involves physical and psychological discomfort, and there have been documented cases of nosocomial transmission of stool-borne pathogens (Livornese et al., 1992; McAllister et al., 1986) and, very rarely, traumatic injury to the rectum (Al-Qahanti et al., 2001).

2.2. Noninvasive techniques

In common clinical practice, noninvasive methods approximate core temperature indirectly. The traditional method of taking oral temperature with a sublingual mercury-in-glass thermometer has, in recent decades, yielded to new technologies that avoid the potential hazards of broken glass and liquid mercury (Zhen et al., 2014; Apa et al., 2013; Batra and Goyal, 2013; El-Radhi and Patel, 2006; Gasim et al., 2013; Jefferies et al., 2011; Penning et al., 2011). The most sensitive temperature sensors are thermistors, which are semiconductors, the electrical resistance of which varies in proportion to temperature (Bhavaraju et al., 2001). Other types of contact sensors include thermocouples, which are constructed with a pair of dissimilar metal wires joined at one end, resistance temperature detectors, which are wire windings or film serpentines, and liquid crystal strips. These have in common a temperature-dependent physical property that translates to a measurable change in an electric circuit to which the sensor is connected (Jones, 2009). Temperature can also be measured remotely by an infrared sensor pointed at the skin or tympanic membrane surface (Tse et al., 2015).

Numerous studies have compared the clinical use of rectal, oral, axillary, tympanic membrane, and temporal artery thermometry, with varying and at times conflicting results (Allegaert et al., 2014; Bodkin et al., 2014; Charafeddine et al., 2014; Odinaka et al., 2014; Zhen et al., 2014; Apa et al., 2013; Batra and Goyal, 2013; Gasim et al., 2013; Huggins et al., 2012; Edelu et al., 2011; Penning et al., 2011; Jefferies et al., 2011; El-Radhi and Patel, 2006; Craig et al., 2002; Greenes and Fleisher, 2001). Considering these studies as a whole, it may be concluded that the appropriate choice of method depends on the clinical context, as physiologic conditions vary considerably depending on whether the patient is hyperthermic or hypothermic, the external environment, the rate of thermal change, and the age and medical acuity of the patient.

Table 1
Comparison of methods for measuring body temperature.

Site of measurement	Advantages	Disadvantages
Forehead skin	Ease of use	Highly inaccurate
Axillary	Ease of use Inexpensive Approximates core temperature in newborns If normal, can rule out hypothermia	Inaccurate in children and adults due to air exposure and sweat
Oral	Ease of use Inexpensive	Hazards of broken glass and mercury Underestimates core temperature due to air or beverage exposure or variable probe placement
Tympanic membrane	Ease and speed of use More closely estimates core temperature than oral methods Reasonably accurate in children and adults	Accuracy is limited by air or cerumen in ear canal
Temporal artery	Ease of use in children Accuracy as compared to other noninvasive methods	Less accurate in children younger than 5 and febrile adults
Rectal	Accurate core temperature at steady state Most reliable for assessing exertional heat stroke	Uncomfortable Lags changes in core temperature May underestimate hepatic or brain hyperthermia Potential for transmission of stool-borne pathogens Rarely traumatic injury to rectum
Esophagus	Reduced risk of thermal injury to esophagus during left atrial ablation procedures	Requires an invasive esophageal probe
Bladder	Useful indicator of core temperature to prevent intraoperative and postoperative hypothermia	Requires insertion of a bladder catheter Lags changes in core temperature during cardiopulmonary bypass
Pulmonary artery	Most accurate core temperature	Requires an invasive pulmonary artery catheter

In the evaluation of hyperthermia, all but rectal temperature have been shown to be inadequate for monitoring individuals exercising outdoors in the heat (Bach et al., 2015; Casa et al., 2007a). Even rectal temperature, however, does not always accurately reflect the temperature in other deep organs, as in nonsteady state conditions rectal temperatures lag changes in core temperature (Giesbrecht, 2000). In particular, rectal temperature readings may underestimate hepatic temperature and the potential for hepatocellular heat-related damage, as metabolic activity in the liver contributes substantially to heat production (Jardine, 2007). Oral temperature, although easier to access, does not accurately reflect core temperature due to such factors as probe placement, ingestion of hot or cold fluids, and exposure to ambient air (Mazerolle et al., 2011).

In the evaluation of hypothermia, measurement of rectal temperature is the most commonly used method. Here also, rectal temperatures lag changes in core temperature, which is more accurately assessed by esophageal probes (Giesbrecht, 2000). Rectal thermometers used to assess hypothermia should be capable of giving accurate readings at temperatures below 34 °C (Cappaert et al., 2008). Although in cold environments oral, tympanic membrane, and axillary thermometers exposed to air temperatures cannot diagnose hypothermia, they can rule it out if the measured temperature is above 35 °C (Cappaert et al., 2008).

In the evaluation of children, less intrusive methods have been studied extensively. Axillary thermometry compares favorably to rectal measurement in newborns (Charafeddine et al., 2014) but is inaccurate in children and adults (El-Radhi and Patel, 2006). Infrared tympanic thermometry provides reasonably accurate estimates of core temperatures in children older than 5 years and adults and is useful in settings where ease and speed of use are important (Gasim et al., 2013; Apa et al., 2013; Edelu et al., 2011; Jefferies et al., 2011; Cabanac et al., 1987). Infrared tympanic thermometry has limited accuracy, however, as it measures the average temperature not only of the tympanic membrane but also the air within the external auditory canal and heat radiated from the inner canal wall. To reduce the influence of air on aural temperature measurement, a cotton ball may be inserted into the aural canal to insulate the probe from the environment (Giesbrecht, 2000). Additionally, cerumen may occlude the sensor's view of the tympanic membrane, and some device manufacturers add a correction factor that may not be valid for all conditions (Jefferies et al., 2011; Edelu et al., 2011; Craig et al., 2002). Insufficient agreement of infrared tympanic thermometry with rectal thermometry across a series of comparison studies has led some authors to recommend against its use in situations where precise measurement of body temperature is needed (Zhen et al., 2014; Huggins et al., 2012; Casa et al., 2007a; Craig et al., 2002; Nierman, 1991).

Temporal artery thermometry has been shown in comparison studies to provide accuracy superior to that of other noninvasive methods in a variety of clinical settings (Reynolds et al., 2014; Allegaert et al., 2014; Batra and Goyal, 2013; Greenes and Fleisher, 2001). Its diagnostic accuracy was lower in children younger than 5 years and in febrile adults (Bodkin et al., 2014; Odinaka et al., 2014; Penning et al., 2011).

Whereas core temperature is a useful objective measurement to define the boundaries of hazardous divergence from normothermia and to monitor clinical changes, it is important to remember that temperature is only a guide and not the endpoint of medical assessment. More important is the physiologic state of the patient. In both hyperthermic and hypothermic patients the cardinal signal of illness is a change in mental status (Santelli et al., 2014; Atha, 2013; Jardine, 2007; Giesbrecht, 2000).

3. Measurement of sweating

Anhidrosis, or the absence of sweating, is not easily assessed by the patient's history alone unless it is extensive enough to cause heat intolerance or so markedly asymmetric that it is noticeable to the patient (Cheshire and Kuntz, 2008). The patient who used to sweat profusely during exposure to hot weather or when exercising vigorously but whose skin now remains dry under those conditions may be suspected to have widespread anhidrosis (Cheshire and Kuntz, 2008; Cheshire and Freeman, 2003).

At the bedside, loss of sweating is usually inapparent unless the patient is in a hot environment. Changes in baseline resting sweat activity can be quite subtle. Asymmetric sweating loss, such as hemibody, regional or distal anhidrosis, is more easily discerned by palpating than visualizing the skin, as the texture of dry skin is less smooth (Cheshire and Kuntz, 2008).

A number of laboratory tests are available for more sensitive and precise clinical evaluation of sudomotor function (Illigens and Gibbons, 2009). These rely on measuring a change in electrical conductance, a color change in an indicator dye, a sweat imprint on a soft medium, or dynamic recording by a humidity sensor of sweat evoked by an axon reflex in response to iontophoresis of a cholinergic agonist (Table 2).

3.1. Sympathetic skin response

The sympathetic skin response consists of a momentary change of the electrical potential of the skin, which may be spontaneous or reflexively evoked by a variety of psychological stimuli (Vetrugno et al., 2003). This response is most easily recorded in the palms and soles, where sweating is controlled more by cortical than by hypothalamic processes and hence does not play a significant thermoregulatory role

Table 2
Comparison of methods of measuring sweating.

Method	Advantages	Disadvantages
Bedside examination	Requires no special equipment	Insensitive, particularly in a cool environment
Sympathetic skin response	Easily recorded with standard nerve conduction equipment	Responses are highly variable and attenuate with repeated stimulation Evaluates emotional more than thermoregulatory sweating
Thermoregulatory sweating test	Evaluates central and peripheral limbs of the thermoregulatory response Sensitive measure of the anatomical distribution of sweating and anhidrosis over the anterior body surface Evaluates the degree of anhidrosis as an indicator of susceptibility to heat stress Useful in evaluating both proximal and distal small fiber neuropathies Useful in diagnosing thoracic radiculopathy Useful in assessing anhidrosis following surgical sympathectomy	May not distinguish a central from a peripheral sudomotor deficit Messy, patient must shower to remove indicator dye Time-consuming to perform Requires bulky, specialized equipment and a dedicated room Anticholinergic medications can confound interpretation
Silastic imprint test	Evaluates the number, volume, and anatomic distribution of droplets from individual sweat glands Equipment is fairly simple Safe and well-tolerated	Time-consuming to analyze results
Quantitative sudomotor axon reflex test	Specifically evaluates the functional integrity of postganglionic sudomotor nerves Sensitive and reproducible in the evaluation of small fiber neuropathy	Mildly uncomfortable Anticholinergic medications can confound interpretation
Epidermal biopsy	Sensitive and reproducible in the evaluation of small fiber neuropathy Results are not confounded by medications	Invasive, requires punch biopsy of skin Mild local infection occurs rarely

(Quinton, 1983). Although simple to measure, this response has great variability as well as limited sensitivity and specificity in the diagnosis of autonomic neuropathies (Arunodaya and Taly, 1995; Gutrecht, 1994; Maselli et al., 1989; Niakan and Harati, 1988).

3.2. Thermoregulatory sweating test

Anatomic patterns of anhidrosis may be evaluated by the thermoregulatory sweating test (TST), which is a modification of Guttmann's quinizarin sweat test (Guttmann, 1947). The patient rests supine and unclothed on a movable cart within an enclosed cabinet, inside of which the temperature and humidity are carefully controlled, while the patient's skin and oral temperatures are continuously monitored. The heat is adjusted to induce a gradual rise in core temperature over 40 to 60 min to a target of 38.0 °C, which results in a maximal thermoregulatory sweating response (Fealey et al., 2008). Sweating over the anterior body surface is visualized by applying an indicator powder, such as corn starch mixed with alizarin red, which changes from yellow to purple when wet (Fealey et al., 2008).

The TST has been shown to be a sensitive measure of the distribution of thermoregulatory sweating over the anterior body surface (Fealey et al., 1989; Low et al., 2006). The result indicates the surface area that is recruited to sweat but not the volume of sweat produced (Fealey et al., 2008). The area that lacks sweating may be expressed quantitatively as the percent anhidrosis (Fealey et al., 2008). The anatomical pattern of anhidrosis can suggest specific categories of thermoregulatory disorders. For example, distal anhidrosis is typical of length-dependent small fiber neuropathies (Cheshire and Low, 2007; Low et al., 2006). Segmental or regional zones of anhidrosis may reflect localized areas of sympathetic denervation as can be seen in thoracic radiculopathy, cholinergic neuropathy, harlequin syndrome, Ross syndrome, autoimmune autonomic ganglionopathy, or multiple system atrophy (Cheshire and Low, 2007, 2008; Cheshire and Freeman, 2003; Fealey et al., 1989). Extensive anhidrosis correlates with heat intolerance (Mevorah et al., 1993).

As a normal TST requires both central and peripheral limbs of the sweating response to be intact, the TST alone cannot distinguish between a central or peripheral sudomotor deficit. When combined with a test of peripheral sudomotor function, localizing power is greater (Fealey et al., 2008; Cheshire and Low, 2007).

3.3. Silastic imprint test

The presence and volume of sweat droplets may be sampled in particular skin regions by the silastic imprint test. Silastic impression material is spread over a small area of the skin surface, which is then stimulated iontophoretically with acetylcholine or pilocarpine. Once the silastic has hardened, impressions left by sweat droplets from individual eccrine glands are photographed and optically quantified to construct sweat histograms (Stewart et al., 1994; Kennedy et al., 1984). A limitation of this method has been the presence of artifacts from hair, air bubbles, and variations in skin surface texture (Illigens and Gibbons, 2009). Newer silicone materials have lessened some of these artifacts (Vilches and Navarro, 2002).

A number of variations of this test have been developed. One is the dynamic sweat test, which utilizes digital video photography of pilocarpine-induced sweating through transparent tape powdered with corn starch to enhance visual contrast (Provitera et al., 2010). Another is the quantitative direct and indirect test (QDIRT), which analyzes high-resolution digital photographs of silicone impressions of sweat droplets (Gibbons et al., 2008).

3.4. Quantitative sudomotor reflex test

Anhidrosis caused by lesions at the level of the peripheral nerve may be evaluated by the quantitative sudomotor axon reflex test (QSART), which evaluates the postganglionic sudomotor axon (Low and Sletten, 2008). Acetylcholine electrophoresis is applied to the skin surface at four standard limb sites: typically the forearm, proximal leg, distal leg, and foot. The iontophoresed acetylcholine activates the sudomotor axon terminal, generating an action potential, which then travels antidromically along the sudomotor axon, and upon reaching a branch point travels orthodromically to release endogenous acetylcholine from a nerve terminal adjacent to the initially stimulated terminal. The released acetylcholine traverses the neuroglandular junction and binds to M_3 muscarinic receptors on eccrine sweat glands to evoke a sudomotor response. Sweat droplets are collected and evaporated in a capsule secured to the skin surface and piped to a hygrometer, which measures the sweat volume over time, which is typically 5 min of stimulation followed by 5 min of additional recording (Low and Sletten, 2008; Low et al., 1983).

Under controlled conditions, which include a sufficiently warm skin surface and the absence of anticholinergic medications, the QSART has been shown to be sensitive and reproducible in healthy subjects (Low et al., 1983) and in patients with axonal peripheral neuropathies (Low et al., 1983, 1986). Sudomotor volumes are approximately three times greater in men than in women and do not decrease with age (Low et al., 1983). QSART has proved to be useful in diagnosing and monitoring autonomic postganglionic involvement in peripheral neuropathies

(Low et al., 2006; Vinik et al., 2003; Stewart et al., 1992; Low et al., 1983).

3.5. Epidermal biopsy

Structural assessment of sweat gland innervation is possible by evaluation of epidermal nerve fiber density. Distal leg skin biopsy with quantification of the linear density of intraepidermal nerve fibers has been shown to be a reliable method for the diagnosis of small fiber neuropathy (Provitera et al., 2015; Joint Task Force of the EFNS and the PNS, 2010). Loss of sweat gland nerve fiber density correlates well with anhidrosis by TST (Loavenbruck et al., 2014) and with worsening peripheral neuropathy (Lauria et al., 2015; Gibbons et al., 2010; Gibbons and Freeman, 2009; Gibbons et al., 2009). With this technique mild localized skin infection has occurred at a frequency of 1.9: 1000 (Joint Task Force of the EFNS and the PNS, 2010).

4. Thermoregulatory disorders

Disorders that impair thermoregulatory autonomic pathways may increase the risk of heat-related or cold-related illness. However, they do not always present in this way, as patients may retain sufficient thermoregulatory capacity to tolerate and remain normothermic in their particular environments. The clinical value of tests that detect even asymptomatic degrees of thermoregulatory impairment lies in the diagnostic and localizing information they provide in the evaluation of a variety of autonomic neurologic disorders.

4.1. Small fiber neuropathies

A prime example of a clinically important thermoregulatory deficit in a normothermic patient is small fiber neuropathy. Many peripheral neuropathies selectively or disproportionately affect autonomic fibers, including those which innervate eccrine glands (Low and Sandroni, 2008). The aforementioned tests of sudomotor function are useful in the diagnosis and assessment of severity of distal small fiber neuropathies affecting sudomotor fibers and are particularly sensitive in comparison in detecting early or selectively small fiber neuropathies (Illigens and Gibbons, 2009; Cheshire and Low, 2007; Low et al., 1986). Nerve conduction studies, which preferentially evaluate large myelinated nerve fibers, may be normal in patients with neuropathies that selectively affect small caliber unmyelinated fibers (Low and Hilz, 2008; Low et al., 2006).

In one series of 40 patients suspected of having distal small fiber neuropathy on the basis of symptoms of distal burning, hyperalgesia, and allodynia, QSART was abnormal in 80% of patients, TST was abnormal in 72% of patients, and one or both tests were abnormal in 90% of patients (Stewart et al., 1992). In another study of 125 patients with symptoms of distal small fiber neuropathy related to a variety of causes, but mostly idiopathic, QSART demonstrated length-dependent abnormalities in 74% of patients, TST showed distal anhidrosis in 59%, and one or both tests showed distal abnormalities in 93% of patients (Low et al., 2006). In patients with various types of distal small fiber neuropathy, the presence of QSART deficits agreed well with skin biopsies showing loss of epidermal C-fibers (Singer et al., 2004; Novak et al., 2001).

Diabetic neuropathy is the most prevalent peripheral neuropathy in developed countries (Low and Hilz, 2008). In a large, longitudinal, population-based study in Rochester, Minnesota, clinical manifestations of peripheral neuropathy were present in approximately 50% of diabetic patients, of which approximately 10% had a clinical autonomic neuropathy (Dyck et al., 1993; Dyck et al., 1992). Distal anhidrosis was the most common pattern, with the proximal extent of anhidrosis progressing with the duration of neuropathy (Fealey et al., 1989).

The differential diagnosis of nondiabetic small fiber sensory and autonomic neuropathies is extensive and encompasses acute and chronic, self-limited and progressive phenotypes. Small fiber neuropathies range from idiopathic, autoimmune, paraneoplastic, hereditary, toxic and drug-related, to degenerative in etiology and have been reviewed in detail elsewhere (Gibbons, 2014; Themistocleous et al., 2014; Hoeijmakers et al., 2012; Low and Sandroni, 2008). Notably, Sjögren syndrome commonly impairs sudomotor function and can cause generalized anhidrosis (Fujita and Hatta, 2013; Pavlakis et al., 2012).

Autonomic ganglionic involvement should also be considered, particularly in acute or subacute presentations. Anhidrosis is among the clinical features of autoimmune autonomic ganglionopathy, which is characterized by antibodies against ganglionic α-3 acetylcholine receptors and typically presents with orthostatic hypotension, gastrointestinal dysmotility, bladder dysfunction, sicca symptoms, and impaired pupillary responses (Winston and Vernino, 2010; Gibbons and Freeman, 2009; Vernino et al., 2009).

4.2. Disorders of the response to cold

Many neurologic disorders can potentially impair the patient's response to cold (Table 3). Any disorder that restricts mobility, such as Parkinson's disease, stroke, spinal cord injury, or myopathy, may limit the ability to generate heat by muscle contraction or may delay efforts to reach shelter in cold weather (Meiman et al., 2015). Additionally, neurologic disorders that impair the sensation of cold or cause inappropriate cutaneous vasodilatation, such as some peripheral neuropathies and myelopathies, may decrease thermoregulatory peripheral vasoconstriction or the awareness of a cold environment (Petrone et al., 2014; Brown et al., 2012; Tesfaye et al., 1994).

Additionally, some central nervous system disorders, such as Wernicke's encephalopathy, may impair the generation of a thermoregulatory response in the hypothalamus (Reuter et al., 1985; Kearsley and Musso, 1980). Hypothermia has been described in the context of hypothalamic demyelination in multiple sclerosis (Geny et al., 1992). The epileptic patient who is postictal following a generalized seizure may be temporarily unable to withdraw from a cold environment. The risk of hypothermia is greater in those with dementia or who have consumed alcohol or sedative drugs that depress the sensorium (Daulatzai, 2010; Turk, 2010). Additionally, drugs such as the opioid meperidine and the α-adrenergic antagonist clonidine inhibit shivering (Cheshire, 2010).

Hypothermia does not typically occur in patients with hyperhidrosis, despite evaporative heat loss, unless the hyperhidrosis is unrelated to heat stress (Cheshire and Fealey, 2008). A notable exception is episodic spontaneous hypothermia with hyperhidrosis associated with agenesis of the corpus callosum (Shapiro et al., 1969). The latter feature appears not to be the causative basis for the hypothermia, as hypothermia occurs only in a small proportion of individuals with agenesis of the corpus callosum (Pazderska et al., 2013), and cases of Shapiro syndrome without corpus callosum agenesis have been described (Rodrigues Masruha et al., 2011; Dundar et al., 2008; Sheth et al., 1994). These patients do not shiver even during marked hypothermia (Sheth et al., 1994). Positron emission tomography in Shapiro syndrome has shown mild increases in metabolism in the tectal plate, posterior pons and medulla, and cerebellar vermis during hypothermic episodes (Pazderska et al., 2013). Decreased cerebrospinal fluid levels of homovanillic acid and 5-hydroxyindoleacetic acid suggest that these patients may have decreased activity in central dopaminergic and serotonergic pathways (Rodrigues Masruha et al., 2011).

Additional risk factors for hypothermia include endocrine disorders such as hypothyroidism, hypoglycemia, and adrenal insufficiency, which impair metabolic thermogenesis (Petrone et al., 2014; Ulrich and Rathlev, 2004).

4.3. Disorders of the response to heat

Numerous medical conditions can predispose to heat exhaustion or nonexertional heat stroke (Table 3). These include autonomic disorders

Table 3
Factors that may increase susceptibility to thermal illness.

Condition	Cold-related illness	Heat-related illness
Environmental	Exposure to extreme cold	Strenuous physical exercise in hot weather
	Prolonged exposure to mild cold	Summer heat waves
	Cold water immersion or submersion	Urban environments that retain heat
	Exposure to cold air, ice, or snow	Sequestration in hot parked automobiles
	Lack of shelter or insulating clothing	Personal protective equipment that renders sweating ineffective
	Malnutrition	
General medical	Hypoglycemia	Thyrotoxicosis
	Diabetic ketoacidosis	Pheochromocytoma
	Hypothyroidism	
	Adrenal failure	
	Hypopituitarism	
	Renal failure	
	Shock	
	Sepsis	
	Anorexia nervosa	
Neurological	Disorders that impair judgment	Disorders that cause widespread anhidrosis
	Dementia	Cholinergic neuropathy
	Head trauma	Autoimmune autonomic ganglionopathy
	Schizophrenia	Chronic idiopathic anhidrosis
	Hepatic encephalopathy	Botulism
	Disorders that impair mobility	Generalized small fiber neuropathy
	Recent trauma	Sjögren syndrome
	Stroke	Multiple system atrophy
	Spinal cord injury	Fabry's disease
	Parkinson's disease	Bilateral cervical sympathectomy
	Multiple system atrophy	Disorders that increase thermogenesis
	Myopathy	Status epilepticus
	Severe peripheral neuropathy	Neuroleptic malignant syndrome
	Disorders that impair thermal sensation	Malignant hyperthermia
	Peripheral neuropathy	
	Disorders that may impair thermoregulatory responses	
	Wernicke encephalopathy	
	Stroke	
	Spinal cord injury	
	Guillain–Barré syndrome	
	Amyotrophic lateral sclerosis	
	Multiple sclerosis	
	Myopathy	
Pharmacological	Alcohol	Carbonic anhydrase inhibitors
	Sedatives	Anticholinergics
	Phenothiazines	Antihistamines
	Opioids	Serotoninergics
	Clonidine	Psychomotor stimulants
	Neuromuscular blocking agents	Diuretics
	General anesthetics	

that cause widespread anhidrosis resulting in a compromised ability to liberate heat. Not all anhidrotic patients will experience heat-related illness, however, as anhidrosis may remain asymptomatic in the absence of heat stress (Cheshire, 2010).

Widespread anhidrosis as the predominant clinical presentation is often due to a cholinergic neuropathy, which may be accompanied by other signs or symptoms of cholinergic failure such as sicca syndrome, abnormal pupillary light responses, or intestinal pseudo-obstruction (Cheshire and Freeman, 2003). When the onset is acute or subacute, an autoimmune etiology should be considered. Antibodies to the ganglionic α-3 acetylcholine receptor are found in the sera of some patients (Gibbons and Freeman, 2009; Kimpinski et al., 2009; Klein et al., 2003).

Other cases are due to acquired idiopathic generalized anhidrosis, which is an immune-mediated disorder characterized by absence of sweating, urticaria, elevated IgE levels, atrophy and degeneration of the sweat glands, biopsies of which show infiltration by lymphocytes and mast cells (Murakami et al., 1988). Skin biopsies in some patients have shown occlusion of coiled ducts by an amorphous eosinophilic substance (Ogino et al., 2004). In other cases of anhidrosis the sweat glands are morphologically normal, and microneurography shows intact bursts of skin sympathetic activity consistent with deficient cholinergic transmission (Nakazato et al., 2004). Anhidrosis in some of these patients responds to steroids (Nakazato et al., 2004).

Another cholinergic neuropathy is Ross syndrome, which is characterized by the clinical triad of progressive segmental anhidrosis, Adie's tonic pupils, and areflexia (Macefield, 2012; Xavier et al., 2009; Ross, 1958). The anhidrosis, which may be extensive enough to cause heat intolerance, often occurs asymmetrically adjacent to areas of preserved or compensatory sweating (Xavier et al., 2009; Weller et al., 1992). Pharmacologic and histopathological studies have indicated a postganglionic cholinergic neuronal deficit (Perretti et al., 2003; Sommer et al., 2002; Wolfe et al., 1995).

Chronic idiopathic anhidrosis is a syndrome characterized by heat intolerance, in which patients become hot, flushed, dizzy, dyspneic, and weak in response to heat stress or exercise but do not sweat and is distinguished from generalized autonomic failure by the absence of orthostatic hypotension, somatic neuropathy, or other neurologic deficits (Low et al., 1985). Chronic idiopathic anhidrosis has been associated with hyperthermia and heat stroke (Freeman and Louis, 1994; Dann and Berkman, 1992).

Various other autonomic neuropathies may also increase the potential for developing hyperthermia. Severe diabetic autonomic neuropathy with widespread involvement of proximal sudomotor fibers occasionally causes heat intolerance (Low and Hilz, 2008; Cheshire and Low, 2007; Dyck et al., 1993). In a TST study of 51 patients with diabetic neuropathy, global anhidrosis was present in 16% (Fealey et al., 1989). Distal or generalized anhidrosis with heat intolerance may also occur along with xerostomia and xerophthalmia as part of an autonomic neuropathy in Sjögren syndrome (Goto et al., 2000; Wright et al., 1999; Katayama et al., 1995). Generalized anhidrosis with heat intolerance frequently occurs in Fabry's disease, which is an x-linked receive disorder of lipid metabolism in which deficiency of α-galactosidase A results in the accumulation of ceramide trihexoside in vascular endothelial cells (Germain, 2010; Kato et al., 1992; Kang et al., 1987). Patients who have undergone bilateral surgical cervical sympathectomy may become intolerant of heat, particularly if sudomotor innervation of the face is obliterated (Santelli et al., 2014; Cheshire, 2010).

Further, widespread anhidrosis is characteristic of both multiple system atrophy (Iodice et al., 2012; Kihara et al., 1991; Cohen et al., 1987) and pure autonomic failure (Bannister et al., 1967; Fealey et al., 1985). Spinal cord transection impairs thermoregulatory sweating below the level of the lesion (Downey et al., 1976; Huckaba et al., 1976; Seckendorf and Randall, 1961). Heat generation from the intense muscle contractions of an epileptic seizure may contribute to hyperthermia under existing conditions of external heat stress and may further complicate status epilepticus (Betjemann and Lowenstein, 2015). Muscle rigidity in Parkinson's disease, by contrast, does not cause hyperthermia (Gillman, 2010).

Also at potential risk are patients taking drugs that inhibit sweating. Carbonic anhydrase inhibitors, such as topiramate, zonisamide, and acetazolamide, inhibit sweat production at the level of the secretory coil clear cell or apex of ductal cells (de Carolis et al., 2003; Ben-Zeev et al., 2003). There have been reports of carbonic anhydrase inhibitors causing transient hypohidrosis with heat intolerance in children, who are approximately ten times more susceptible to the drugs' hypohidrotic effect than are adults (Incecik et al., 2012; Markowitz et al., 2010; Knudsen et al., 2003; Ben-Zeev et al., 2003; de Carolis et al., 2003; Arcas et al., 2001). Rarely, fatal heat stroke has been described in association with topiramate therapy (Borron et al., 2013).

Other common examples of drugs that inhibit sweating include M_3 anticholinergic agents, which include bladder antispasmodics, tricyclic antidepressants, and neuroleptics (Lee et al., 2015; Gillman, 2010; Cheshire and Fealey, 2008; Adubofour et al., 1996; Hermesh et al., 2000; Clark and Lipton, 1984). These drugs block the binding of

acetylcholine to the M_3 receptor at the neurocrine junction, which prevents the influx of extracellular calcium that triggers the efflux of potassium and chloride ions responsible for isotonic fluid egress from the luminal side of the clear cell (Low et al., 1992). Intoxication with drugs, such as salicylate and methylsalicylate, that uncouple oxidative phosphorylation also can cause hyperthermia (Clark and Lipton, 1984).

Hyperthermia is one of the cardinal signs of serotonin syndrome, the others being agitation, tremor, myoclonus, muscle rigidity, hyperreflexia, and hyperhidrosis. This dose-related, potentially fatal syndrome occurs in patients taking serotonin-selective reuptake inhibitors multiply or in combination with other drugs, such as meperidine, fentanyl, or tramadol, that enhance the availability of serotonin in the brain (Paden et al., 2013). The mechanism of hyperthermia and sweating is uncertain but may involve a direct effect on hypothalamic 5-HT receptors (Marcy and Britton, 2005).

Recreational abuse of psychomotor stimulants, such as cocaine, amphetamine, methamphetamine (METH), 3,4-methylenedioxy-methamphetamine (MDMA or "ecstasy"), or heroin, frequently cause hyperthermia. In the United States, stimulant drugs resulted in 93,562 emergency room visits in 2009 (NINDA, 2011). Elevated body temperature is a nearly universal presenting sign in such cases (Matsumoto et al., 2014). The mechanisms of hyperthermia have not been fully elucidated but likely involve a combination of central and peripheral effects. Exposure to these drugs causes the release of dopamine, serotonin, and norepinephrine in the central nervous system, with a direct effect on brain areas involved in thermoregulation, such as the hypothalamus, on which are located α_1 and β adrenoreceptors. In support of this hypothesis is the finding that propranolol prevents methamphetamine-induced hyperthermia in laboratory mice (Albers and Sonsalla, 1995). Evidence for a peripheral effect includes the observation that methamphetamine-induced hyperthermia in laboratory rats is prevented by sympathectomy or adrenalectomy, which suggests that stimulant release of norepinephrine from sympathetic nerve terminals increases thermogenesis in skeletal muscles under the influence of glucocorticoids (Makisumi et al., 1998). Contributing mechanisms to ensuing hyperthermia may include activation of astrocytes and microglia, peripheral catecholamine release, increased skeletal muscle metabolism, tachycardia, hypertension, peripheral vasoconstriction, and cytokine formation and release (Matsumoto et al., 2014; Kiyatkin, 2013; Kiyatkin, 2005).

Additionally, psychomotor stimulants acutely raise brain metabolism by increasing the release of monoamine neurotransmitters, which can cause pathological brain hyperthermia (brain temperature > 40 °C) that exceeds systemic hyperthermia (Matsumoto et al., 2014; Kiyatkin, 2013; Kiyatkin, 2005). When combined with potentially hyperthermic environmental conditions such as heat and exercise, amphetamine-like stimulants can induce heat stroke (Matsumoto et al., 2014; Kiyatkin, 2013; Kiyatkin, 2005). This tragic fact was highlighted by the death of 29-year-old British cyclist Tom Simpson while competing in the 1967 Tour de France. The outdoor temperature that day reached a sweltering 54 °C. Simpson collapsed during his approach of the summit of Ventoux, and resuscitation efforts were unsuccessful. On his body were found two empty tubes and a half-full one of amphetamine, the use of which at the time was legal in professional cycling (Fotheringham, 2012).

Another cause of hyperthermia is neuroleptic malignant syndrome, which is a potentially fatal, idiosyncratic condition that occurs in 0.2% of patients taking dopamine 2 receptor antagonists, particularly haloperidol, aripiprazole, or flupentixol (Su et al., 2014; Perry and Wilborn, 2012). Hyperthermia resulting from acute lithium intoxication has also been described (Gill et al., 2003). Clinical signs consist of hyperthermia, rigidity, hyperhidrosis, tachycardia, labile blood pressure, tremor, dysarthria, and delirium that progress over hours to days. Laboratory findings typically include elevations in creatine kinase, liver enzymes, and white blood count combined with low serum iron (Perry and Wilborn, 2012; Rusyniak and Sprague, 2006). Although its major feature of muscle rigidity seems to suggest that the hyperthermia results from a hypermetabolic state, the degree of muscle contraction is insufficient to induce hyperthermia (Gillman, 2010). Central dopaminergic impairment with defective heat dissipation has been proposed to explain the hyperthermia (Di Rossa et al., 1988).

Malignant hyperthermia is an autosomal dominantly inherited disorder of skeletal muscle calcium regulation that in up to 70% of cases is associated with mutations of the RYR1 gene encoding ryanodine receptor type 1 (Gomez, 2014; Larach et al., 2014; Rosenberg et al., 2007; Rusyniak and Sprague, 2006). Approximately 1% result from mutations of CACNA1S, which encodes a skeletal muscle calcium channel. Upon exposure to volatile anesthetic agents, either alone or in combination with a depolarizing muscle relaxant, genetically predisposed individuals develop uncontrolled skeletal muscle hypermetabolism causing hyperthermia, muscle rigidity, tachycardia, acidosis, and hyperkalemia. Rhabdomyolysis with subsequent elevation in creatine kinase may lead to renal failure (Larach et al., 2014; Rosenberg et al., 2007).

5. Hypothermia

Acute exposure to cold causes peripheral vasoconstriction, shivering, and increased metabolic heat production (Castellani et al., 2006), as well as attenuation of thirst (Kenefick et al., 2004). Acute cold stress also reduces plasma volume and increases urine flow rate (Castellani et al., 2006). The predominant mechanism of this so-called cold-induced diuresis is redistribution of plasma volume from the periphery to the central circulation in response to peripheral vasoconstriction (Freund and Sawka, 1996; Vogelaere et al., 1992; Lennquist et al., 1974). Cold-induced diuresis is attenuated in trained athletes (Yoshida et al., 1999) and does not appear to be explained adequately by inhibition of release of arginine vasopressin (Freund and Sawka, 1996; Hynynen et al., 1993).

Hypothermia is defined as a core body temperature of <35.0 °C (Petrone et al., 2014; Cheshire, 2010; Polderman, 2009; Cappaert et al., 2008; Jurkovich, 2007; Ulrich and Rathlev, 2004; Giesbrecht, 2000). As heat loss occurs more rapidly than heat production in the human body, any situation that promotes heat loss can hasten the onset of hypothermia (Ulrich and Rathlev, 2004). Approximately 60% of heat is lost through radiation, 10–15% through conduction and convection, and 25–30% through evaporation and respiratory expiration (Ulrich and Rathlev, 2004). In the United States, there are on average more than 1300 deaths per year from hypothermia, which is approximately twice the number of deaths annually as for exposure to heat (Meiman et al., 2015).

5.1. Causes of hypothermia

Hypothermia occurs following prolonged exposure to cold, wet, or windy conditions once the body's ability to maintain a normothermic core temperature is overwhelmed. Factors that can predispose to hypothermia include winter sports activities, cold water immersion, or lack of sufficiently warm clothing or shelter from environmental cold weather (Cappaert et al., 2008; Jurkovich, 2007). Neonates and the elderly are at increased risk as they are less able to generate heat by shivering or preserve heat by vasoconstriction. Children generate more metabolic heat than adults, which is usually sufficient to maintain body heat while exercising but not during prolonged rest (Falk, 1998). The risk of hypothermia is greater in those who are malnourished, alcoholic, mentally ill, septic, in shock, or whose mobility is limited by disability or recent injury, if they are less able to generate heat from muscle contraction or actively seek shelter (Brown et al., 2012; Brändström et al., 2012; Jurkovich, 2007; Ulrich and Rathlev, 2004; Biem et al., 2003). Hypothermia can occur even in warm environments under conditions that cause the body to lose more heat than it generates (Cappaert et al., 2008).

Hypothermia is also induced intentionally in medical settings for its neuroprotectant effect following cardiac arrest, stroke, traumatic brain or spinal cord injury. Therapeutic hypothermia has reached an acceptable level of safety through the development of sophisticated cooling systems using thermocouples and feedback sensors that allow for precise control of core temperature and is an area of active research in critical care medicine (Maznyczka and Gershlick, 2015; Sherman and Wang, 2014; Macleod et al., 2010).

5.2. Diagnosis of hypothermia

Hypothermia classically is defined as mild, moderate, or severe according to core temperature but is best understood as a decrease in body temperature that causes signs of physiologic dysfunction (Table 4) (Cappaert et al., 2008; Ulrich and Rathlev, 2004; Durrer et al., 2003). These categories derive from correlations of body temperature measurements with clinical presentations of accidental hypothermia (Brown et al., 2012; Giesbrecht, 2000) and induced hypothermia in the treatment of cardiac arrest, traumatic brain injury, and other medical conditions in the 1940s through the 1960s (Polderman, 2009). In general, the physiologic state of the patient is more important to monitor than the temperature (Giesbrecht, 2000).

Signs of mild hypothermia (core temperature 35°–32 °C) may include vigorous shivering, lethargy, apathy, impairment of fine motor skills, cold extremities, polyuria, pallor, tachypnea, and tachycardia. With development of moderate hypothermia (core temperature 32°–28 °C), physical signs may include depression of respirations and pulse, slurred speech, further impairment of mental function, paradoxical undressing, gross impairment of motor control, cessation of shivering, cyanosis, muscle rigidity, mydriasis, atrial or ventricular cardiac dysrhythmias, bradycardia, decreased blood pressure, hypoventilation, hyporeflexia, and loss of consciousness. If severe hypothermia (core temperature < 28 °C) develops, the patient may present with hypotension, pulmonary congestion and edema, muscle rigidity, areflexia, oliguria, spontaneous ventricular fibrillation, cardiac arrest, and coma (Durrer et al., 2003). The skin is cold to the touch, the pupils are dilated, and the pulse and respirations may be difficult to detect. Severe cases can mimic death. The clinical presentations of hypothermia, which are quite variable among patients, are reviewed in greater detail elsewhere (Brown et al., 2012; Brändström et al., 2012; Cheshire, 2010; Polderman, 2009; Cappaert et al., 2008; Jurkovich, 2007; Castellani et al., 2006; Ulrich and Rathlev, 2004; Giesbrecht, 2000; Fischbeck and Simon, 1981).

When the core temperature cannot readily be measured, the Swiss staging system distinguishes among five levels of hypothermia: HT I with clear consciousness and shivering, HT II with impaired consciousness without shivering, HT III with unconsciousness, HT IV with apparent death, and HT V with death due to irreversible hypothermia (Brown et al., 2012; Durrer et al., 2003).

Frostbite is a severe form of localized cold-induced tissue injury that occurs when skin or deeper tissue temperature falls below −2 °C, at which point ice crystals form at the cellular level, resulting in cellular dysfunction or destruction and, during rewarming, microvascular occlusion (Jurkovich, 2007). Severity ranges from hyperemia with edema to blistering, hemorrhagic vesicles, tissue necrosis, and gangrene (Cappaert et al., 2008; Jurkovich, 2007).

5.3. Management of hypothermia

Prevention of hypothermia during exposure to cold environments includes wearing sufficiently warm clothing as well as education about the risk factors and how to recognize the early signs of hypothermia. Clothing requirements in cold weather depend on metabolic rate, ambient temperature, water exposure, and wind velocity (Castellani et al., 2006). Heat loss can be minimized by wearing knit caps, balaclavas, headbands to cover the ears, and layering to adjust insulation as physical activity increases (Castellani et al., 2006). Heightened surveillance of exercisers is advised when wind-chill temperatures are below −27 °C (Castellani et al., 2006). Cold weather athletes should eat a well-balanced diet and replace fluid lost through sweating

Table 4
Clinical presentations of thermal illness.

	Hypothermia			Normothermia	Hyperthermia	
	Severe (<28 °C)	Moderate (28°–32 °C)	Mild (32°–35 °C)	37° ± 1 °C	Heat exhaustion	Heat stroke (>40.5 °C)
Mental status	Delirium, hallucinations, coma, may mimic death	Fatigue, agitation, confusion, hallucinations, lethargy, amnesia, paradoxical undressing	Impaired judgment, amnesia		Fatigue, thirst, irritability	Delirium, confusion, hallucinations, coma
Cutaneous	Frostbite	Cold, edematous	Vasoconstriction followed by hyperemia		Sweating, flushed	Flushed, loss of sweating in classical, but not exertional, heat stroke
Cardiovascular	Bradycardia, spontaneous atrial or ventricular fibrillation, hypotension, asystole at <20 °C	J waves, atrial fibrillation, hypotension	Tachycardia, PR and QT interval prolongation, hypertension		Tachycardia, postural syncope	Heart failure, hypotension, myocardial injury
Respiratory	Hypopnea, pulmonary edema, apnea at <24 °C	Hypopnea, impaired cough reflex	Tachypnea			
Muscular	Hypotonia, rhabdomyolysis	Loss of shivering, rigidity	Shivering		Weakness, cramps	
Neurologic	Dilated nonreactive pupils at <26 °C, stupor, areflexia	Sluggish pupillary responses, hyporeflexia, ataxia	Dysarthria, loss of fine motor skills		Headache, dizziness, paresthesia	Seizures
Hepatic	Decreased enzyme activity	Decreased enzyme activity				Hepatic injury
Renal	Oliguria	Diuresis, renal tubular acidosis	Diuresis from decreased hypothalamic release of antidiuretic hormone		Oliguria	Myoglobinuria, renal failure
Hematologic	Thrombocytopenia, disseminated intravascular coagulation, prolonged prothrombin time	Decreased platelet function	Hemoconcentration			Thrombocytopenia, disseminated intravascular coagulation, prolonged prothrombin time
Gastrointestinal	Pancreatitis, gastric erosions	Nausea, vomiting	Ileus, gastric erosions		Nausea, vomiting	Mucosal swelling, vomiting

(Cappaert et al., 2008). In the routine hospital environment, perioperative warming measures are necessary to prevent the heat loss that otherwise would occur during general anesthesia, which temporarily abolishes central thermoregulatory control, muscle contraction, and peripheral vasoconstriction (Horosz and Malec-Milewska, 2014).

Once hypothermia is recognized, prompt treatment is necessary to avert preventable death. Wet or damp clothing should be removed without delay, and the individual should be removed from wind or rain to a warm, dry, sheltered environment. Mild hypothermia is best managed with passive external warming using blankets or metaloplastic sheets that reflect heat. The head should be covered. All patients with hypothermia should be assumed to be dehydrated and receive supplemental fluids (Cappaert et al., 2008; Jurkovich, 2007; Ulrich and Rathlev, 2004; Delaney et al., 1989; Giesbrecht et al., 1987). Friction massage should be avoided as this can exacerbate tissue damage from frostbite (Cappaert et al., 2008).

Hypothermia is a condition of medical urgency. In addition to the measures for treating mild hypothermia, vital signs should be closely monitored. Any patient with suspected hypothermia who has signs of cardiac dysrhythmia should be moved gently to avoid precipitating paroxysmal ventricular fibrillation, as the myocardium is more sensitive to mechanical stimulation during deep hypothermia (Polderman, 2009; Cappaert et al., 2008; Ulrich and Rathlev, 2004). Peripheral pulses in hypothermic patients may be difficult to palpate. In situations where the EKG shows an organized cardiac electrical rhythm (other than fibrillation), cardiopulmonary resuscitation with chest compression is contraindicated, despite the absence of a palpable pulse, because chest compressions may convert an adequate perfusing rhythm to ventricular fibrillation (Jurkovich, 2007). The risk of ventricular fibrillation increases as core temperature in the severely hypothermic patient rises above 28 °C. Below that temperature, cardiac dysrhythmias tend to be refractory, for which reason resuscitative efforts should continue until the absence of electrographic cardiac activity is documented after the core temperature has risen to 28 °C–30 °C (Petrone et al., 2014).

Invasive active core warming methods may be indicated in patients with severe hypothermia. These methods include heated intravenous fluids, inhalation rewarming, or peritoneal lavage (Danzi and Pozos, 1994). Rewarming by hemodialysis has also been used and has the added benefit of treating accompanying hyperkalemia and renal failure. The most efficient (by an order of magnitude) method for rewarming is cardiopulmonary bypass or extracorporeal active core rewarming (CAVR), which is also the most invasive and is reserved for exceptionally severe cases in appropriately equipped medical settings (Petrone et al., 2014; Jurkovich, 2007; Giesbrecht, 2000). Antiarrhythmic drugs may be required (Cappaert et al., 2008; Jurkovich, 2007; Ulrich and Rathlev, 2004; Kornsberger et al., 1999; Walpoth et al., 1997; Daanen and Van de Linde, 1992; Giesbrecht et al., 1987). Severe hypothermia may exhibit afterdrop, which is a phenomenon in which heat-induced vasodilation in the arms and legs during external active rewarming with, for example, heating lamps sends a rush of relatively cold, acidic blood from the periphery to the core with the potential to trigger cardiac arrhythmias (Petrone et al., 2014; Ulrich and Rathlev, 2004). Active core rewarming methods avoid this problem (Jurkovich, 2007).

6. Hyperthermia

Hyperthermia classically is defined as a core body temperature of >40.5 °C (McGeehin and Mirabelli, 2001; Clark and Lipton, 1984). Some experts accept a definition of >40 °C (Atha, 2013; Jardine, 2007; Wexler, 2002). Core temperature alone, however, is inadequate, and the diagnosis of hyperthermia or heat stroke requires central nervous system dysfunction (Santelli et al., 2014; Atha, 2013; Jardine, 2007). The temperature threshold is somewhat arbitrary and has been based on cumulative experience with patients evaluated for heat-related illness. Correlations between body temperature and clinical consequences of hyperthermia have been limited by the practical difficulty of obtaining accurate core temperature measurements in the field, underrecognition of potentially unsafe elevations in core temperature, individual differences in heat tolerance and susceptibility, and the spectrum of variations in heat stress presentations (Sawka et al., 2001; Clark and Lipton, 1984). More important than measured temperature is the clinical condition of the patient (Anderson et al., 1983).

Fever, which this review does not address specifically, is a subtype of hyperthermia consisting of a regulated elevation in core temperature in response to a pathological process, such as an infection, in which the thermoregulatory system continues to function adequately. Unlike the hyperpyrexia of fever, other forms of hyperthermia do not subside when treated with cyclo-oxygenase inhibitors (Clark and Lipton, 1984).

In the United States more than 600 deaths occur annually from hyperthermia (Luber and Sanchez, 2006). During the years 1999–2003, a total of 3442 U.S. deaths resulting from exposure to extreme heat were reported, with an annual mean of 688 deaths. The cause of death was recorded as exposure to excessive heat in 2239 (65%), and for the remaining 1203 (35%) hyperthermia was recorded as a contributing factor (Luber and Sanchez, 2006). Some years have seen much higher rates of heat stroke. In the United States, a severe heat wave in 1980 resulted in 1700 deaths (Centers for Disease Control, 1981). In Europe, a severe heat wave in August 2003 resulted in 14,800 heat-related deaths in Lyon, France (Argaud et al., 2007).

These and other clusters of heat-related mortality during summer heat waves have raised medical and public awareness of heat stroke, which has improved recognition of vulnerable populations, such as the elderly, which have decreased capacity to dissipate heat or increased risk of dehydration (Santelli et al., 2014; Atha, 2013; Jardine, 2007). Prognostic factors contributing to heat-related deaths include being confined to bed (OR 6.44), not leaving home daily (OR 3.35), being unable to care for oneself (OR 2.97), preexisting psychiatric disease (OR 3.61), cardiovascular disease (OR 2.48), and pulmonary disease (OR 1.61), whereas factors associated with more favorable outcomes included functioning air conditioning (OR 0.23), visiting cool environments (OR 0.34), increasing social contact (OR 0.40), taking extra showers or baths (OR 0.32), and using fans (OR 0.60) (Bouchama et al., 2007).

Brain cells and hepatic cells are exquisitely sensitive to hyperthermia. Irreversible neuronal damage begins at temperatures at or above 40 °C, which is only 3 °C above normal baseline, and progresses exponentially with further increases in temperature (Kiyatkin, 2010). Cerebellar Purkinje cells are particularly vulnerable to heat injury (Kiyatkin, 2010). Hyperthermia also increases blood–brain-barrier permeability, allowing entry of potentially neurotoxic metabolites and substances that in conditions of health are retained in the periphery (Kiyatkin, 2010). Hepatic and renal insult may occur also as a consequence of secondary hypoperfusion as the sympathetic nervous system shunts blood flow to the skin to facilitate heat release (Atha, 2013). Cytokine-mediated systemic inflammatory responses and disseminated intravascular coagulation may lead to multiorgan failure and mortality (Atha, 2013; Jardine, 2007).

Computed tomography (CT) of the brain in acute heat stroke is usually normal (Albukrek et al., 1997). Magnetic resonance imaging (MRI) abnormalities are characteristically symmetric and include lesions hyperintense on FLAIR and DWI sequences in the cerebellum, external capsule and adjacent lateral putamen, medial thalamus, and hippocampus (Lee et al., 2009). Patchy cortical lesions may also be seen (Muccio et al., 2013). Punctate hemorrhagic lesions have been described in the cerebellar hemispheres, brain stem, corona radiata, and frontal lobes on susceptibility-weighted images (Li et al., 2015a; Zhang and Li, 2014; Murcia-Gubianas et al., 2012). Diffusion tensor imaging has shown fractional anisotropy of cerebellar white and gray matter (Li et al., 2015b).

Postmortem studies of heat stroke have demonstrated severe loss of cerebellar Purkinje cells and degeneration of Purkinje cell axons with myelin pallor of the white matter of the cerebellar folia and of the

hilum of the dentate nuclei. Brain areas such as Ammon's horn that are typically vulnerable to hypoxia were spared (Bazille et al., 2005).

6.1. Causes of hyperthermia

Heat-related illness may be divided into passively and actively induced mechanisms (Table 5). Classical heat stroke occurs in individuals who have impaired thermoregulatory physiology and are deficient in the mechanisms for heat dissipation or lack the awareness or the means to escape from a hot environment (Santelli et al., 2014; Clark and Lipton, 1984; Anderson et al., 1983; Hart et al., 1982; Centers for Disease Control, 1981). A paradoxical feature is that the skin may appear red, hot, and dry, as patients with classical heat stroke are often anhidrotic (Clark and Lipton, 1984). The absence of sweating in a heat-stressed individual should not be interpreted as evidence against hyperthermia.

Exertional heat stroke, by contrast, typically occurs in healthy young individuals who engage in strenuous physical exercise during hot weather or in environments that restrict heat dissipation (Clark and Lipton, 1984; Anderson et al., 1983). Sweating is an inadequate indicator of the degree of heat stress, but the cessation of sweating in exertional heat stroke may be an ominous sign (Clark and Lipton, 1984). The estimated 9000 high school athletes are treated for heat-related illness each year in the U.S. (Kerr et al., 2013). Exertional heat stroke is, in fact, one of the leading causes of preventable nontraumatic injury as well as a recognized cause of sudden death during sport (Casa et al., 2015; Casa et al., 2005). The risk is reduced but not eliminated by training (Sawka et al., 2001). At risk for exertional heat stroke are football players, cyclists, and runners when strenuous exercise is performed in very hot or humid conditions and evaporative cooling requirements exceed the environment's cooling capacity (Kerr et al., 2013; Sawka et al., 2001). Also at risk are firefighters, field laborers, toxicological clean-up workers, astronauts, and military forces training or on active duty when performing exertional activity while wearing protective clothing that retains body heat (National Institute for Occupational Safety and Health, NIOSH, 2013; Sawka et al., 2001).

During exercise the temperature of the brain is at least 0.2 °C higher than that of the body (Nybo et al., 2002). An analysis of 1866 sudden deaths in young American competitive athletes found that 46 (2%) were caused by heat stroke (Maron et al., 2009). A study of active U.S. military service members during 2010–2014 identified 344 incident cases of heat stroke and 1683 cases of other heat injuries, which represented crude incidence rates of 0.25 and 1.22 per 1000 person-years, respectively (AFHSC, 2015).

Every year, children left unattended in parked motor vehicles die from heat stroke. Temperatures inside parked vehicles rise rapidly, especially during the first 15 to 30 min. On hot days temperatures inside parked automobiles have been measured as high as 57 °C–78 °C, and even in modest weather temperatures can reach 47 °C (McLaren et al., 2005; Surpure, 1982). Highest temperatures occur in cars parked in direct sunlight (Surpure, 1982). Cracking windows does not prevent this rise (McLaren et al., 2005). In the U.S. from 1999 to 2007, the number of motor vehicle-related child hyperthermia fatalities was 231. Their average core body temperature was 41.8 °C (Booth et al., 2010).

Urban living is also a risk factor for heat-related illness. Higher rates of heat-related morbidity and mortality occur in city dwellers who reside on the top floors of apartment buildings or who do not have access to air conditioning. The “urban heat island effect” refers to patterns of city development, such as replacing trees with concrete surfaces, that cause urban areas to retain heat throughout the evening in comparison to suburban and rural areas (McGeehin and Mirabelli, 2001).

A simple tool for assessment of environmental heat safety is the wet bulb globe temperature (WBGT) index, which was developed by the U.S. military in the 1950s and is also used by civilian athletic groups to calculate and stratify heat injury risk. The index is a weighted average of measurements of heat (dry bulb temperature), humidity (wet bulb temperature), and reflected heat (black globe temperature). WBGT heat categorization has shown to be approximated by standard meteorological data (Patel et al., 2013).

Table 5
Clinical features of classical versus exertional heat stroke.

	Classical	Exertional
Circumstances	Often in epidemics during summer heat waves, occurs without preceding physical activity	Athletic activity or strenuous exertion during variably warm or hot weather or while wearing heat-retaining clothing
Age	Children and elderly	Adults young to middle age
Health	Illness or medication impairing thermoregulatory sweating	Healthy
Sweating	Often reduced or absent	May be present
Acid base disturbance	Respiratory alkalosis	Lactic acidosis
Acute renal failure	Rarely	Frequently
Rhabdomyolysis	Rarely	Frequently
Disseminated intravascular coagulation	Rarely	Frequently

6.2. Diagnosis of hyperthermia

Illness related to heat stress classically has been divided into heat cramps, heat exhaustion, and heat stroke (Anderson et al., 1983; Malamud et al., 1946). Heat cramps are involuntary muscle spasms that occur following exercise and respond to cooling, rest, and fluid and electrolyte replacement. Another minor form of heat stress is heat edema, which occurs in elderly individuals and consists of swelling of the feet and ankles in response to extreme heat. Miliaria, also known as heat rash or prickly heat, is common in hot and humid climates and presents with small, red, pruritic papules that result from plugging of sweat gland ducts from dead skin or bacteria (Anderson et al., 1983; Leithead, 1964).

Heat exhaustion is quite common and occurs along a continuum of core temperatures. In a study of healthy, heat acclimated male soldiers subjected to moderate to intense physical exercise in a hot climate, 50% of subjects incurred exhaustion from heat strain at core temperatures ranging from 38.7 °C to 39.5 °C (Sawka et al., 2001). Heat exhaustion is also related to high skin temperatures that are associated with peripheral displacement of blood, which reduces venous return, cardiac filling and stroke volume, resulting in cardiovascular strain (Sawka et al., 2001; González-Alonso et al., 1985).

The transition from heat exhaustion to heat stroke is important to recognize and may occur quickly. Heat stroke (core temperature > 40.5 °C) is the most serious degree of hyperthermia and if unrelieved is potentially deadly (Berko et al., 2014; Anderson et al., 1983). The presence or absence of sweating is an unreliable guide to diagnosing or excluding heat stroke. To distinguish nonfatal heat exhaustion from potentially fatal exertional heat stroke, and when monitoring the acute treatment of heat stroke, measurement of core temperature along with assessment of mental status are necessary (Atha, 2013; Cheshire, 2010; Sucholeiki, 2005; D'Angelo, 2004; Wexler, 2002; Bouchama and Knochel, 2002).

Hyperthermia may be classified in severity according to core temperature and signs and symptoms (Table 4). Signs of heat exhaustion (core temperature generally > 38 °C) include sweating, flushing, fatigue, and tachycardia. Prolonged heat stress can lead to dehydration or peripheral displacement of blood volume with postural syncope (Santelli et al., 2014; Atha, 2013). Heat exhaustion is characterized by profuse sweating, flushing, dizziness, headache, and paresthesia. Progressive depletion of sodium and water reduce intravascular volume, which may lead to weakness, muscle cramps, tachycardia, oliguria, nausea,

agitation, and mild confusion (Santelli et al., 2014; Jardine, 2007; Wexler, 2002). Heat exhaustion may be thought of as a protective mechanism that inhibits further work during conditions of excessive heat stress (Sawka et al., 2001).

As distinguished from heat exhaustion, heat stroke is often heralded by central nervous system dysfunction including confusion, delirium, hallucinations, seizures, or coma (Table 4). If epileptic seizures progress to status epilepticus, thermogenesis from convulsive muscle contraction can further exacerbate hyperthermia (personal experience). Cerebral hypoperfusion or coagulopathy occasionally produces focal neurological deficits (Anderson et al., 1983). Common additional manifestations of heat stroke include hypotension, lactic acidosis, renal failure, gastrointestinal tract mucosal swelling, thrombocytopenia, and disseminated intravascular coagulation. Irreversible injury to the brain, myocardium, kidney, and liver may occur (Atha, 2013; Jardine, 2007; Wexler, 2002; Bouchama and Knochel, 2002; Anderson et al., 1983).

The National Association of Medical Examiners Ad Hoc Committee on the Definition of Heat-Related Fatalities defines heat-related death as "a death in which exposure to high ambient temperature either caused the death or significantly contributed to it." Specifically, they recommend that the cause of death be certified as heat stroke or hyperthermia in cases where the measured antemortem temperature at the time of collapse was ≥40.6 °C, as well as in cases where the core temperature is lower, but cooling was attempted prior to arrival at the hospital or there is a clinical history of heat-related mental status changes and elevated liver and muscle enzymes (Donoghue et al., 1997).

6.3. Management of hyperthermia

Heat exhaustion can usually be managed conservatively by removing the individual from the circumstances that led to heat-related symptoms. The individual should rest in a cool, shaded environment and replace fluid and electrolytes orally. Cooling may be facilitated by the use of misting fans to moisten and blow a current of air across skin surfaces to promote evaporative heat loss. Refrigerated gel packs or ice packs may be applied to the forehead, neck, axillae, and groin. Excess insulating clothing should be removed. Treatment should begin as soon as symptoms occur in order to prevent progression to heat stroke (Bergeron, 2014; Atha, 2013; Wexler, 2002).

Patients who do not improve with conservative measures or who manifest mental status changes or cardiac dysrhythmias should receive prompt attention in an emergency room or other acute care facility. Treatment consists of administration of intravenous fluid when dehydration is suspected and correction of electrolyte imbalances involving sodium, potassium, phosphate, calcium, or magnesium metabolism as well as monitoring of core temperature (Santelli et al., 2014; Atha, 2013).

Hyperthermia is a medical emergency (Santelli et al., 2014). Prompt recognition is paramount. The top priority for treatment is rapid reduction of core temperature. Prehospital care should begin immediately, starting with dousing the patient with ice water, and then fanning to promote evaporative heat loss and monitoring the airway and circulation. Morbidity and mortality are greatly reduced if cooling measures are applied within 30 min of recognition (Atha, 2013). Cooling to a core temperature of approximately 38.5 °C within 30 min supports survival (Santelli et al., 2014; Clark and Lipton, 1984).

Ice water immersion remains the most effective intervention to lower core temperature quickly and reduce morbidity and the risk of fatality (Pryor et al., 2015; Newport and Grayson, 2012; Casa et al., 2007b; Costrini, 1990). The theoretical concern that ice cold water immersion might fail to cool down core temperature because of reflex peripheral vasoconstriction or shivering has been strongly refuted by empirical evidence of consistently superior cooling rates with cold water immersion as compared to other modalities (Casa et al., 2007b). Cooling blankets are ineffective (Atha, 2013).

In situations where ice water immersion is not available, continual dousing with ice water provides effective cooling (Casa et al., 2007b). Treatment should commence as soon as possible. Unlike normothermic individuals immersed in ice water, hyperthermic patients with exertional heat stroke generally do not shiver, unless they are cooled too long (Casa et al., 2007b). Shivering or muscle cramping, when they occur, can be managed with intravenous diazepam or chlorpromazine (Wexler, 2002; Eichner, 1998). Vigorous cooling efforts should be withdrawn once the rectal or esophageal temperature reaches 38 °C–39 °C (Stewart and Whitford, 2015; Atha, 2013). Use of a flexible rectal thermistor minimizes the potential for rectal trauma during cooling (Casa et al., 2007b).

If signs of dehydration are present, intravenous fluids should be administered to restore circulatory volume and maintain urine output. Not all patients who present with exertional heat stroke are dehydrated (Seraj et al., 1991), and as cardiac function may be impaired in heat stroke, during rehydration the patient should be monitored for signs of congestive heart failure (Santelli et al., 2014). Vasopressor therapy may be required temporarily (Jardine, 2007). The management of heat stroke requires close monitoring of cardiac and pulmonary function, mental status, hematologic and coagulation parameters, electrolytes, renal function, and hepatic enzymes to minimize organ damage (Santelli et al., 2014; Atha, 2013; Jardine, 2007; Wexler, 2002).

Drug-induced hyperthermia usually may be treated more conservatively unless heat exposure raises core temperature in excess of 40 °C. The precipitating medication should be stopped (Clark and Lipton, 1984).

7. What more might be done?

During the last several decades, the textile and clothing industries have developed protective clothing that insulates from cold weather and breathes during hot weather more effectively and comfortably than was possible for any previous generation in recorded history. Yet the incidence of illness related to hypothermia and hyperthermia has not significantly declined.

More effective prevention will require greater public awareness of the risk factors for heat-related and cold-related illness so that they may be avoided or minimized. City planners might design urban landscapes differently to create more thermally tolerable environments, which could confer additional esthetic benefits (Stone et al., 2014). Miniaturized electronics may eventually lead to the development of safe, comfortable, externally or internally placed smart devices to monitor temperature and signal early warnings of impending hypothermia or hyperthermia. Meanwhile, there is an ongoing need for preventive education of athletes, outdoor adventurers, and the healthcare professionals who are called to treat their illnesses related to cold and heat exposure.

8. Conclusion

Autonomic disorders frequently impair thermoregulatory systems, testing of which is an important component of clinical diagnosis. Additionally, thermoregulatory failure or exposure to environmental conditions that overwhelm the body's thermoregulatory capacity can present with hypothermia or hyperthermia, both of which carry substantial risk of morbidity and mortality. Prompt recognition and treatment are necessary to preserve life and health.

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