Hypothermia and targeted temperature management in cats and dogs

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Abstract

Objective – To review current knowledge surrounding the effects, treatment, and prognosis of hypothermia in people, dogs, and cats, as well as the application of therapeutic hypothermia in clinical medicine.

Etiology – Hypothermia may be a primary or secondary condition, and may be due to environmental exposure, illness, medications, anesthesia, or trauma. Hypothermia has been applied therapeutically in human medicine for a variety of conditions, including postcardiac arrest. In veterinary medicine, the technique has been applied in cardiac surgeries requiring bypass and in a patient with intractable seizures.

Diagnosis – Hypothermia can be diagnosed based on presenting temperature or clinical signs, and appropriate diagnosis may require nontraditional thermometers.

Therapy – Rewarming is the primary treatment for accidental hypothermia, with intensity ranging from passive surface rewarming to extracorporeal rewarming. The goal is to return the core temperature to a level that restores normal physiologic function of all body processes. Other supportive therapies such as intravenous fluids are typically indicated, and if cardiopulmonary arrest is present, prolonged resuscitation may be required. In cases of secondary hypothermia, reversal of the underlying cause is important.

Prognosis – There are few prognostic indicators in human and veterinary patients with hypothermia. Even the most severely affected individuals, including those presenting in cardiopulmonary arrest, have potential for complete recovery with appropriate therapy. Therapeutic hypothermia has been shown to improve outcome in people following cardiac arrest. Further studies are needed to examine this application in veterinary medicine, as well as appropriate therapy and prognosis for cases of spontaneous hypothermia.

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Abbreviations

aPTT	activated partial thromboplastin time
PT	prothrombin
TBI	traumatic brain injury
TTM	targeted temperature management

Introduction

Hypothermia is defined as a subnormal body temperature in a homeothermic organism.[1] Hypothermia can occur due to environmental exposure (accidental), or can be secondary to illness, medications, anesthesia, or trauma. Hypothermia is an uncommon cause of death in people, with approximately 1,500 deaths in the United States and 300 in the United Kingdom annually.[2,3] The incidence of hypothermia in veterinary patients is unknown. Despite advances in medicine, there are still many uncertainties regarding the best treatment of hypothermia in both human and veterinary patients, and prognosis remains difficult to predict even in the most severely affected individuals.

Therapeutic hypothermia has been introduced as a technique for select disease processes in human medicine, and is beginning to be applied in veterinary medicine. Familiarity with the pathogenesis and physiologic effects of hypothermia is necessary to properly guide treatment of the hypothermic patient and to safely apply therapeutic hypothermia in appropriate cases.

Normal Thermoregulation

Heat is produced as a result of normal metabolism. At rest, the primary contributors are the highly metabolically active brain and major trunk organs, with 20–30% generated in skeletal muscle.[4] This can be altered by changes in basal metabolic rate, muscle activity, hormones such as thyroxine and growth hormone, and sympathetic stimulation.[4] The human body is described as having 2 compartments: the peripheral tissue compartment and the core compartment. The core compartment comprises the head and trunk, and is defined as containing well-perfused tissues where temperature is held fairly constant.[5] This comprises 50–60% of body mass in adults.[6] The peripheral compartment is comprised of the arms and legs, containing nonhomogenous temperature.[5] Typically this compartment is 2–4°C below the temperature of the core compartment, and temperature tends to decrease distally in the limbs and toward the skin surface.[5,7]

All heat produced by the body is eventually lost to the environment to maintain homeostasis.[5] Heat loss can occur through convection, conduction, radiation, or evaporation. Convection is heat transfer from the body to the surrounding air, while conduction is the direct transfer of heat between the body and surfaces in contact with the body. Radiation is heat loss to objects in the environment that are not in direct contact with the body and does not depend on the temperature of the surrounding air. All objects that have temperatures greater than absolute zero emit electromagnetic radiation, and this transfers heat in the form of infrared thermal radiation.[8] Evaporative heat loss occurs when moisture on the skin or from the respiratory tract changes state from liquid to gas. When evaporation occurs, heat is dissipated.[8]

Heat loss in normal animals is primarily through convection or conduction, unlike the radiant heat loss of human beings.[9] Evaporative heat loss through panting is also an important mechanism in dogs. The heat content of the peripheral compartment can change dramatically with alterations in the surrounding environment. Flow of heat from the core to the periphery is dependent on conduction of heat through large vessels into the limbs and subsequently into tissues.[5] Convection can be altered through changes in peripheral blood flow (such as with vasoconstriction), arterio-venous countercurrent exchange, and the inherent core-to-peripheral heat gradient (as heat will tend to flow down its concentration gradient). Conduction primarily depends on the diffusion coefficient of the tissue itself.[5] Fat is an effective insulator, conducting only one-third of the heat of other tissues.[4] Fur acts as an insulator by trapping air against the skin, which has a low thermal conductivity.[10] However, rain-soaked or wet fur does not effectively insulate, as water has a high thermal conductivity, and a wet patient is predisposed to hypothermia.[4] Other predisposing factors for developing hypothermia include minimal body fat, high surface area:body mass ratio, age, immobility, underlying disease, and lack of acclimatization.[1,3,11] Geriatric patients in particular are susceptible to developing hypothermia as they typically have many predisposing factors, as well as impaired physiologic responses to the cold.[3] Neonates are similarly predisposed, due to their high surface area:mass ratio and decreased heat production.[12–14]

Temperature is regulated by the thermoregulatory center of the anterior hypothalamus. Thermoreceptors are present in the hypothalamus itself as well as the skin, spinal cord, abdominal viscera, and great veins. Both heat and cold receptors exist, with cold receptors predominating. Stimulation of the cold receptors results in rapid responses such as widespread vasoconstriction and piloerection to minimize heat loss, mediated by the sympathetic nervous system. Later physiologic responses aim to increase heat production through increased skeletal muscle activity (ie, shivering) and thyroxine secretion.[3,4]

Classifications of Hypothermia

Hypothermia is classified as primary (accidental) or secondary. Primary hypothermia occurs when an animal with normal heat production is exposed to a cold environment for a prolonged period. Secondary hypothermia results from an illness, injury, or drug therapy that alters the heat production and thermoregulatory ability of an animal.[1] Secondary hypothermia can occur even in relatively warm environments.[2] Commonly encountered causes of secondary hypothermia include surgery and anesthesia,[13] trauma, critical illness,[1] and following overzealous treatment of heatstroke.[15] Wong proposed a classification scheme for human hypothermia patients in 1983 that was intended to be for communication only, based on arbitrary intervals, and was without specific clinical implications.[16] Clinical hypothermia was described as mild, moderate, deep, and profound, corresponding with decreasing body temperature only. This scheme was widely adopted in both human and veterinary medicine to describe hypothermic patients, although it may be more accurate for patients with primary hypothermia.[1] Oncken et al noted in a retrospective review of veterinary hypothermia that adverse effects occur at higher temperatures in secondary hypothermia as compared to primary, and proposed a separate classification scheme for secondary hypothermia patients (Table 1).[1]

In human literature, the Swiss system of staging hypothermia (Table 2) is preferred when core temperature

Table 1: Classifications of hypothermia based on core temperature

	Primary hypothermia	Secondary hypothermia[§]
Mild	32–37°C (90–99°F)[*][§]	36.7–37.7°C (98–99°F)
Moderate	28–32°C (82–90°F)[*][§]	35.5–36.7°C (96–98°F)
Severe	20–28°C (68–82°F)[*][§]	33–35.5°C (92–96°F)
Profound/Critical	Profound < 20°C (< 68°F)[§]	Critical < 33°C (< 92°F)

[*]Data modified from Dhupa.[12]
[§]Data modified from Oncken et al.[1]

Table 2: Swiss Hypothermia Staging System

HT I	Clear consciousness with shivering	32–35°C (89.6–95.0°F)
HT II	Impaired consciousness without shivering	28–32°C (82.4–89.6°F)
HT III	Unconsciousness	24–28°C (75.2–82.4°F)
HT IV	Apparent death	13.7–24°C (56.6–75.2°F)
HT V	Death due to irreversible hypothermia	< 9–13.7°C (48.2–56.6°F)

Modified from Durrer et al.[17] HT, hypothermia.

Table 3: Markers used to determine hypothermic death in people

	HT IV (apparent death)	HT V (death)
Physical examination	No vital signs, compressible chest, kneadable abdominal muscles	No vital signs, chest not compressible, abdominal muscles not kneadable
ECG	Ventricular fibrillation or asystole	Asystole
Core temperature	Above 13.7°C (56.6°F)	Below 13.7°C (56.6°F)
Serum potassium concentration[*]	< 12 mmol/L	> 12 mmol/L

[*]Human literature suggests that serum potassium concentration should only be used to classify HT IV versus HT V when the patient has been asphyxiated and is hypothermic, such as in avalanche burials or drowning. Modified from Durrer et al.[17] HT, hypothermia.

can't be readily measured, such as in mountain rescue scenarios.[2] The advantage to this system is that it is based on physical examination findings that are correlated with certain degrees of hypothermia, and core temperature does not necessarily need to be measured to apply the scale. Various versions of this classification system have been adopted by human medical groups such as the International Commission for Mountain Emergency Medicine. However, it can be difficult to separate Hypothermia Level IV from Hypothermia Level V based on physical examination alone, and other markers have been recommended by International Commission for Mountain Emergency Medicine to classify these patients (Table 3).[17]

Physiologic Effects of Mild, Moderate, and Severe Hypothermia

Behavioral/neuromuscular

A healthy animal responds to cold temperature exposure and mild hypothermia by behavioral changes, such as seeking shelter or curling up. As shivering and nonshivering thermogenesis begin, heat production increases, but at the cost of significantly increased basal metabolic rate, energy requirements, and oxygen consumption.[5] Ataxia may be seen in veterinary patients with mild hypothermia;[18] people display confusion or amnesia.[3,19] If thermogenesis fails, the animal progresses to moderate and severe levels of hypothermia.

The core temperature below which shivering ceases varies widely in human reports, and has been reported to fall between 24 and 35°C (75–95°F).[3,19] Initially muscle stiffness predominates, but as moderate hypothermia approaches severe, hyporeflexia is apparent, which progresses to areflexia at core temperatures < 28° (< 82°F).[19] For every 1°C drop in core temperature there is a 6–7% decline in cerebral blood flow, resulting in a concurrent deterioration in mentation.[9] Altered mental status may result in maladaptive behavior, such as no longer seeking shelter. At body temperatures < 33°C (< 92°F) there are significant changes in cerebral electrical activity, and temperature-dependent enzymes in the brain cease to function.[20] Below 29°C (85°F), the hypothalamus loses all ability to regulate body temperature, worsening the hypothermia.[4] The electroencephalogram shows no activity at 20°C (68°F).[3,21] Cerebral edema is possible in moderate to severe hypothermia, secondary to decreased cerebral blood flow and ischemic injury.[9] Despite this, the marked

reduction in metabolic demands inherent in the suppression of brain and muscle activity significantly increases tolerance to ischemia.[3] In a normothermic state, the brain can withstand 5–6 minutes of ischemia. With every 5°C (9°F) decrease in core temperature, this time doubles.[22]

Cardiovascular

With mild hypothermia, there is an initial peripheral vasoconstriction secondary to sympathetic stimulation. This minimally decreases heat loss by reducing flow of heat from the core compartment to the periphery.[5] The sympathetic stimulation also results in tachycardia. In moderate hypothermia, bradycardia predominates due to decreased spontaneous depolarization of the cardiac pacemaker cells.[3,9] Because of this, bradycardia caused by hypothermia is typically unresponsive to atropine.[3,9] Moderate to severe hypothermia is also marked by vasodilation and hypotension, primarily caused by reduced α_1-receptor affinity for norepinephrine with decreasing temperature.[1,23] Hypovolemia secondary to the diuretic effects of cold (see section on renal effects of hypothermia) may also contribute to hypotension. The net effect of these changes is a progressive reduction in cardiac output as hypothermia progresses.

Arrhythmias and conduction abnormalities are abundant in hypothermic patients. Cold slows myocardial conduction, resulting in abnormal depolarization and repolarization. Specifically, prolonged action potential duration, lengthened PR and QT intervals, and widened QRS complexes may be seen. [3,24] The J wave or Osborn wave is a positive deflection at the QRS-ST segment frequently seen in people with hypothermia.[3,24] Dr. Osborn first identified this ECG "current of injury" at the J-point in dogs with experimentally induced hypothermia in 1953.[25] While there are no published reports of this finding in clinical veterinary medicine, it may be seen rarely in a clinical setting.[12] Initially thought to be pathognomonic of hypothermia, the J-wave has also been identified in people with other conditions such as hypercalcemia, or can be an inherited variation.[26,27] When associated with hypothermia, the amplitude, and duration have been observed to increase with decreasing body temperature, and a visible J-wave can persist for 12–24 hours after normothermia is achieved.[28] The J-wave typically resolves with rewarming and does not require specific treatment.

Sinus bradycardia, junctional bradycardia, premature atrial, and ventricular beats, atrial fibrillation, idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation are arrhythmias documented in people with hypothermia.[24] Both slow and rapid atrial fibrillation as well as ventricular tachycardia have been documented in hypothermic dogs, and isorhythmic AV dissociation in

1 cat.[29–32] Atrial fibrillation is the most common arrhythmia in severely hypothermic people, and appears to be common in veterinary patients as well.[24,33] Ventricular fibrillation becomes increasingly common with decreasing temperature, and at lower temperatures will be refractory to defibrillation until the body temperature is increased above 26–27°C (80–82°F).[9] As noted previously, hypothermia-induced bradyarrhythmias typically are refractory to atropine; in addition, they are often refractory to pacing due to higher electrical thresholds being required.[24] Most arrhythmias and conduction abnormalities resolve spontaneously and do not require specific treatment aside from rewarming. If rewarming does not occur, bradycardia eventually progresses to asystole.

Respiratory

Mild hypothermia is marked by tachypnea, increased respiratory secretions and bronchospasm.[3,14] Moderate hypothermia results in respiratory depression (slower respiratory rate and smaller tidal volumes) because carbon dioxide production decreases secondary to decreased metabolism. Respiratory depression can progress to apnea in severely hypothermic patients. A left shift of the oxygen-hemoglobin dissociation curve occurs at 30°C (86°F), impairing oxygen offloading to tissues.[3] This, along with capillary blood sludging, predisposes to peripheral tissue hypoxia.[13] However, oxygen consumption and carbon dioxide production decrease to 50% at 30°C (86°F).[3] Due to these reduced metabolic requirements, the cellular damage is minimized despite the hypoxic environment.[14]

Hepatic/gastrointestinal

Hypothermia results in reduced hepatic blood flow,[3] hepatic enzyme activity, hepatic metabolism,[1] and bile flow.[34] Hepatic impairment reduces clearance of endogenous substances such as lactate as well as medications.[3] Therefore, any drugs that require hepatic metabolism should be administered cautiously during hypothermia. The metabolism of many medications has been documented to be affected by hypothermia, including propranolol, fentanyl, morphine, midazolam, phenobarbital, pentobarbital, propofol, volatile anesthetics, and neuromuscular blocking agents such as vecuronium, rocuronium, and atracurium.[18,34]

Decreased gastrointestinal motility occurs at core temperatures of 34°C (93.2°F), and generalized ileus is observed by 28°C (82°F).[3] There is increased risk of gastrointestinal ulceration in hypothermic patients, likely due to reduced local perfusion, increased gastric acid production, and reduced duodenal bicarbonate secretion.[3,35] Pancreatitis was commonly noted on

autopsy in people who succumbed to hypothermia[36] and is thought to be secondary to poor perfusion and microcirculatory thrombosis.[3] Insulin production is decreased during hypothermia, which can result in hyperglycemia.[9]

Renal

The phenomenon of "cold diuresis" is one of the earliest effects of mild hypothermia, and occurs before any reduction in core temperature.[3] Cold diuresis refers to the increase in urine production with exposure to cold temperatures, and is initially caused by increased renal blood flow secondary to peripheral vasoconstriction.[3] With progression of hypothermia, this diuresis is augmented by reduced antidiuretic hormone concentration.[9] Fluid loss at this stage can be dramatic and result in hypovolemia. In moderate to severe hypothermia, renal blood flow is reduced due to low cardiac output and the hypovolemia from the earlier diuresis.[18] Acute kidney injury is common in people with accidental hypothermia and is characterized by ischemic injury on histopathologic examination.[3]

Clinical pathology abnormalities

The effects of hypothermia on the coagulation system are complex, but culminate in a clinically hypocoagulable state. Cold directly inhibits the enzymatic clotting cascade despite normal concentrations of clotting factors.[37] This process is not reflected in standard prothrombin/activated partial thromboplastin time (PT/aPTT) analysis since the blood is warmed for testing.[37] Therefore the hypothermic patient will likely have normal PT/aPTT values despite the clinical coagulopathy. A significantly prolonged PT/aPTT should trigger a search for concurrent disease or toxicosis. The inhibition of coagulation factors is reversible with rewarming alone; administration of plasma products in these patients is not appropriate.[3,37] Contributing to the coagulopathy is the effect of hypothermia on platelet function and transient thrombocytopenia. Platelets are temporarily sequestered in the spleen and liver in hypothermic patients; this abnormality is typically reversed with rewarming.[9] Poor platelet aggregation due to impaired platelet function also occurs and is multifactorial. Production of thromboxane B2 (a marker of thromboxane A2 concentration) is temperature dependent;[38] hypothermic patients also have decreased platelet granule secretion and decreased von Willebrand factor receptor expression.[39]

A recent study investigating the effect of in vitro hypothermia on thromboelastography tracings found temperatures $\leq 30°C$ (86°F) resulted in a significant increase in K values and decrease in α values.[40] K and α values are both numeric values derived from the TEG tracing curve, and are indications of the rate of clot formation.[41] The ultimate strength of the clot was not affected.[40] It is important to note this was an in vitro study and samples were obtained from healthy, normothermic animals. Thromboelastography has been evaluated in healthy dogs with induced hypothermia; prolonged R and K times were identified.[42] R time corresponds to the time from the start of the test, to the initial formation of a fibrin clot.[41] This study also identified reduced platelet counts and reduced platelet aggregation in these dogs.[42]

Leukopenia often occurs in response to hypothermia and may be noted on CBC.[43] This is typically attributed to a decreased circulating pool of leukocytes, impaired release from bone marrow, and compromised neutrophil and monocyte migration into tissues, although the exact mechanism of these changes is poorly understood.[44,45] These changes are associated with increased infection rate and impaired wound healing in people with perioperative hypothermia,[46] but this has not been found in dogs.[47]

Electrolyte imbalances are often seen in hypothermia and are unpredictable.[1] In general, patients tend to exhibit serum hyponatremia and hyperkalemia due to reduced function of membrane sodium/potassium pumps.[9] In people, serum potassium concentration > 12 mmol/L is considered a negative prognostic indicator and is cited as a deciding factor for termination of cardiopulmonary resuscitation of the hypothermic patient.[17]

Blood glucose concentration is frequently affected by hypothermia and depends greatly on the temperature and duration of exposure. Hyperglycemia is seen early in hypothermia and can be attributed to the effects of increased sympathetic tone and decreased insulin production. Hypoglycemia may develop in prolonged or severe hypothermia, and is due to consumption of physiologic energy stores, decreased gluconeogenesis, and diuresis.[20]

Diagnosis

Any patient presenting with a history of exposure to cold temperatures should have a temperature measured. Core temperature measurements are ideal; in human medicine a probe in the distal one-third of the esophagus is preferred for core temperature measurement in hypothermic, intubated patients.[2] Rectal temperature measurement at 15 cm is recommended in people when esophageal measurement is not possible, but tends to lag behind core temperature changes.[2] Infrared measurements of skin temperature, aural, and oral thermometers are often inaccurate in hypothermic people, presumably secondary to vasoconstriction and

wider-than-normal core to peripheral temperature gradient.[2] In addition, rectal thermometers commonly used in veterinary medicine do not register temperatures in the ranges of moderate to severe hypothermia. This could lead to underestimation of the severity of the patient's condition. The use of nonstandard thermometers, such as electronic thermistor-type probes is recommended.[2,9]

Ruling out death in severely hypothermic patients can be challenging. The combination of unconsciousness, bradycardia, poorly palpable pulses, and hypoventilation may lead to a misdiagnosis of death. In people, determining if a patient is truly deceased or has a chance of recovery with aggressive care is important, as this may direct a rescue team toward discontinuing resuscitation efforts. The delineation between Hypothermia Level IV (apparent death) and Hypothermia Level V (death due to irreversible hypothermia) is made based on electrocardiographic and physical examination findings, serum potassium concentration, and may be correlated to core temperature (Table 3).[17] An electrocardiograph should be performed to confirm a lack of electrical activity, and emergency room ultrasound can be utilized to visualize cardiac contractions.[20] Even patients presenting with true asystole may be able to recover; resuscitation even after hours of cardiac arrest in people has been documented.[17]

Therapy

Rewarming should be considered the main treatment for primary hypothermia. It is important to attempt to identify underlying causes of secondary hypothermia and to treat these concurrently.

Rewarming

Three methods of rewarming are recognized: passive surface, active surface, and active core rewarming. Passive surface rewarming allows the animal's intrinsic heat production to increase core temperature via shivering while preventing further heat loss. These methods include drying wet fur and covering with blankets or bubble wrap, and are best suited to an otherwise healthy patient with mild hypothermia.[1,14] Passive surface rewarming will likely be ineffective as a sole treatment if there is an absence of shivering.[24]

Active surface rewarming applies heat to the surface of the animal to increase core temperature. These methods include water blankets, forced warm air, heat lamps, and water bottles; these are ideal for patients with moderate to profound hypothermia. Care must be taken to avoid burns since patients may not be able to move away from a heat source and vasoconstricted skin cannot diffuse direct heat appropriately. It has been suggested that active surface rewarming be applied only to the trunk; heat applied to the limbs may result in peripheral vasodilation, hypotension, and decreased neuronal feedback to the thermoregulatory center.[1]

Active core rewarming involves directly supplying heat to the core compartment, and can involve a range of interventions. These include warmed intravenous fluids, warmed/humidified inhaled air, warm water enemas, warm urinary bladder/peritoneal/pleural lavage with sterile isotonic crystalloid fluid, and extracorporeal rewarming. It has been recommended to warm IV fluids to 40–42°C (104–107.6°F), and peritoneal/pleural lavage to 40–43°C (104–109.4°F).[13] Fluids can be warmed using numerous methods, including but not limited to immersion of IV tubing in warm water, microwaving of the fluid bag, in-line fluid warmers, and prewarming of fluids in a convection oven.[48,49] Microwave heating of fluid bags has been shown to be an effective way to increase the temperature, but there can be major differences in amount of time required to warm to the appropriate temperature. One group suggested a mathematical algorithm to calculate the time necessary, based on the wattage of the microwave, and overall recommended microwaving for < 80 seconds to avoid overheating.[50] In addition, there are concerns regarding uneven heating and potential instability of the non-polyvinyl chloride components of the bags during microwaving.[51,52] Warming of the fluid bag alone may be insufficient to provide warm fluids to the patient, as significant heat is lost in the fluid line.[53] An in-line warming device can significantly increase the outflow temperature of fluids.[48]

Warmed, humidified air is most easily administered in intubated patients using commercial humidifiers, but there are also devices that deliver warmed, humidified oxygen to the spontaneously breathing patients.[a] The benefit of warmed air is not the overall increase in core temperature, as this is typically only 0.5°C (~1°F) per hour. It is instead delivery of warm air directly to the major vessels in the neck and chest, and thereby warming of the brainstem and cardiac tissue.[54]

When core rewarming is instituted, active surface rewarming should always be performed concurrently to avoid creating temperature gradients.[1] Core rewarming methods are typically reserved for severe to profound hypothermia, although there is no contraindication to using some of the less invasive core warming methods (warmed inhaled air, warmed intravenous fluids) in moderate hypothermia. It is recommended to maintain active rewarming until 37°C (98.6°F) to restore coagulation and cardiovascular function to normal.[1] Once a patient has been rewarmed to this temperature, withdrawal of active forms of rewarming with continued passive rewarming is prudent to avoid creating hyperthermia. Body temperature should be monitored closely

even after active rewarming stops so that subsequent temperature decreases can be identified and active rewarming reinstated as indicated.

Prehospital rewarming is instituted during the rescue of hypothermic people; the intensity varies depending on the degree of hypothermia. Mildly affected patients who are still shivering are typically treated by preventing further heat loss (exchanging wet clothes for dry, insulating the patients) and providing hot drinks, and such people are not always hospitalized.[17] Similar steps such as drying the haircoat and wrapping in blankets seem reasonable for owners to take during transport of mildly affected (conscious and shivering) hypothermic veterinary patients. Any patient that is more severely affected (not shivering or unconscious) must be treated more gently; people with more advanced hypothermia are handled carefully to avoid triggering life-threatening arrhythmias.[17] "Rescue collapse" is cardiac arrest that occurs in deeply hypothermic people related to rescue and transport, and is due to cardiac arrhythmias triggered by interventions such as catheterization and inadvertent further cooling.[2] While this complication has not been documented in veterinary patients, owners should be instructed that any unconscious or non-shivering veterinary patient suspected to be hypothermic should be transported rapidly and carefully to a veterinarian, with rewarming instituted at the hospital. If there is likely to be a significant delay until an owner can reach a veterinarian, beginning passive and active surface rewarming is reasonable until appropriate veterinary care can be instituted.

Other therapies
Fluid support during rewarming is essential, as patients typically will be hypovolemic due to earlier cold diuresis. Fluid overload can occur if normal shock volumes are administered due to the return of vascular tone with rewarming and endothelial leakage, particularly in cats.[1] Moderate intravascular support through a combination of crystalloids and colloids should be goal directed and involve frequent reassessment. Fluids should be supplemented with glucose and electrolytes as clinicopathologic data dictate. In addition, administration of room-temperature fluids may result in further drop in core temperature, and thus fluids should be warmed to avoid this.[1,55] Vasopressors should be reserved for those with hypotension unresponsive to fluid therapy, but are likely to be ineffective unless adequate rewarming is also provided.[24]

As neutrophil function is decreased in hypothermia, and leukocyte sequestration occurs, prophylactic antibiotics may be administered at the discretion of the clinician. Antibiotics are recommended in people with primary hypothermia who are pediatric, geriatric, or immunocompromised.[14,20] Hypothermic patients may have reduced hepatic metabolism and therefore it is reasonable to avoid administration of antibiotics until normothermia is achieved.

Despite the presence of coagulopathy in hypothermic patients, plasma transfusion is not recommended. As noted previously, there is no inherent coagulation factor deficiency, simply an inhibition of the enzymatic reactions. Therefore supplementing plasma will not correct the coagulopathy; only rewarming can reverse the coagulopathic defect.[3,9] In addition, transfused plasma is typically administered at room temperature, which may lead to further core temperature drop.

There has been no benefit seen to corticosteroid or thyroxine administration in people; therefore, their routine use in hypothermic veterinary patients cannot be recommended.[56] Mentation should be monitored with rewarming, and if not improving despite increasing core temperature, cerebral edema may be present and should be treated with standard hyperosmotic agents such as mannitol.

Antiarrhythmic therapy may be warranted and should be tailored to the specific arrhythmia present. Ventricular fibrillation may be unresponsive to defibrillation until significant rewarming has taken place. Pacing for bradyarrhythmias is generally not required and may be ineffective due to higher threshold requirements.[24] In fact, excessive increase of the heart rate in a hypothermic patient may decrease myocardial contractility.[34,57] Any treatment in these cases should not be considered ineffective until it has been administered to a normothermic patient without the desired response, as the majority of arrhythmias and ECG abnormalities resolve spontaneously with rewarming.[24]

Should cardiopulmonary arrest be present in a severely hypothermic patient, prolonged resuscitation may be required and can be successful.[58] In human literature, there are numerous reports of patients surviving seemingly insurmountable periods of non perfusing ventricular fibrillation or even asystole. The lowest recorded core temperature in a surviving person was 13.7°C; this patient survived with neurologic deficits.[59] Two hundred seventy-three minutes of manual CPR in a hypothermic patient is the longest recorded with intact neurologic outcome, although manual CPR was followed by cardiopulmonary bypass in this case.[60] One man was resuscitated through cardiopulmonary bypass and extracorporeal rewarming and had complete recovery after 6 hours and 52 minutes of hypothermic cardiac arrest.[60] There is 1 report of a man with hypothermic cardiac arrest resuscitated after 6.5 hours of manual CPR with peritoneal lavage, warm intravenous fluids, and blankets.[61] It was 70 minutes from the onset of cardiac

arrest until start of CPR. While family members did not find him to be mentally altered, his physicians found he had "slow cerebration" on examination.[61] Peritoneal lavage and warm intravenous fluids were successfully used as the sole methods of rewarming in an elderly patient in ventricular fibrillation with a core temperature of 24°C (75.2°F).[62] Such reports are important because as veterinarians, we often receive patients after prolonged cardiopulmonary arrest, and these cases show that survival may be possible in cases of hypothermia. While extracorporeal rewarming is limited to centers offering dialysis or cardiac bypass, other rewarming techniques used in the reports can be used in any facility. Extracorporeal rewarming has long been considered the gold standard of care in people with hypothermic cardiac arrest.[63] A recent review of accidental hypothermia recommended avoiding extracorporeal rewarming unless the patient does not respond to standard medical therapy, due to the risks of hemorrhage and thrombosis.[2]

In regards to specific medications and therapies during CPR in the hypothermic patient, guidelines vary in human medicine. The American Heart Association recommends administering vasopressors and defibrillation according to standard advanced life support guidelines concurrent with rewarming.[64] The European Resuscitation Council recommendations differ slightly. This group recommends up to 3 defibrillations in severe hypothermia, but if these are unsuccessful, withholding additional attempts until the core temperature exceeds 30°C (86°F). They also recommend withholding epinephrine until the temperature is > 30°C (86°F), and doubling the interval between doses until > 35°C (95°F).[65] There have not been guidelines regarding hypothermic cardiopulmonary resuscitation published in veterinary medicine.

Complications

Complications associated directly with rewarming can include afterdrop, rewarming shock, increases in the metabolic rate and subsequent increases in oxygen consumption, burn injury from surface rewarming, and overzealous treatment resulting in hyperthermia.[1,13] The "afterdrop" phenomenon, in which body temperature drops during rewarming, is theorized to be due to movement of cold peripheral blood to the core, and warm core blood to the periphery.[1] It is important to anticipate the possibility for afterdrop as rewarming begins and take care to actively warm the animal's trunk rather than extremities, and to use core rewarming techniques when possible. Proper application of active external and minimally invasive core rewarming has eliminated reports of afterdrop in human medicine.[2]

Rewarming shock refers to surface rewarming resulting in rapid peripheral vasodilation and blood pooling,

particularly evident when extremities are warmed in the absence of core rewarming. An already compromised cardiovascular system is unable to compensate for this, and hypotension and distributive shock result.[1,13] Fluid therapy with warmed IV fluids concurrent with external rewarming is recommended to avoid rewarming shock and afterdrop.[1] However, cats in particular appear to be prone to volume overload as temperature returns to normal.[1] Fluid therapy should be goal directed in all patients, and may need to be more conservative in hypothermic cats. "Rescue collapse," or cardiac arrest secondary to rescue efforts, is the most dramatic immediate complication seen in severely hypothermic people.[2]

Following the rewarming period, there is a high rate of multiorgan dysfunction in people, presumably secondary to ischemia-reperfusion injury. This can require hemodialysis, mechanical ventilation, and extended hospital stays. In veterinary patients, these complications can be not only life threatening, but may result in euthanasia due to associated financial burden or poor prognosis. The frequency of multiorgan dysfunction following hypothermia in veterinary patients is unknown.

Prognosis

There is no validated prognostic indicator of survival from hypothermia in human or veterinary patients. Blood potassium concentration, lactate concentration, and pH have all been evaluated.[17] A recent review of accidental hypothermia victims from Norway supported that severe hyperkalemia may be prognostic. No patients with serum potassium concentration > 12 mmol/L survived, and survivors had significantly lower potassium concentration on admission than nonsurvivors.[58] These investigators also found better survival in more recent time periods (1999–2013 compared to 1985–1998), likely due to more proficient care techniques and changes in attitude regarding outcomes in these patients.[58] However, it should be noted this study had a very small sample size of 34 people.

While cardiac arrest at presentation has not been directly evaluated, human case reports imply that even the most severely affected can recover without long-term complications. There are few indications in people with hypothermia to terminate or not attempt CPR; these include obvious signs of irreversible death (decapitation, hemisection, rigor mortis, decomposition),[64] avalanche burial for > 35 minutes, airway packed with snow, serum potassium > 12 mmol/L, and if the patient is rewarmed to > 32°C with persistent asystole.[17] Cardiac arrest known to occur prior to cooling is associated with worse outcome in people,[2] and cold water drowning may have improved survival over warm water.[66]

Therapeutic Hypothermia/Targeted Temperature Management

Therapeutic hypothermia or "targeted temperature management" (TTM) is the intentional and tightly controlled reduction of a patient's core temperature. The rationale for using TTM varies depending on the disease being treated but centers around the reduction in metabolic demand. Following cardiac arrest, traumatic brain injury (TBI), or global ischemic events, mild hypothermia is proposed to reduce blood–brain barrier permeability, modulate the inflammatory response, reduce cerebral and other organ metabolic demand, reduce mitochondrial injury and mitochondrial dysfunction, attenuate the excitatory neurotransmitter response and calcium-dependent signaling, reduce reactive oxygen species production, and reduce cell death from necrosis and apoptosis.[67,68] Most importantly, following out-of-hospital cardiac arrest of adults, TTM is the sole treatment shown to improve neurologically intact survival.[69,70] The facts that this treatment does not need to be in place prior to arrest, and can be instituted after the return of spontaneous circulation have been key to its success in human medicine.

Application of TTM in human medicine

The first trials that examined TTM were published in 2002, and similarly reported increased survival and improved neurologic status as compared to standard normothermic treatment.[71,72] Older recommendations for TTM were cooling to 32–34°C (89.6–93.2°F) for 12–24 hours in adults who are resuscitated following out-of-hospital arrest with an initial rhythm of ventricular fibrillation or ventricular tachycardia that remain comatose.[69,70,73] It is thought that patients resuscitated after pulseless electrical activity and asystole may also benefit.[73] The application in patients having experienced in-hospital arrest is less clear, with most studies showing no difference from standard therapy and no improvement in neurologic function. Poor compliance and poor application of therapy may confound these results.[74,75] Currently, the American Heart Association guidelines state that TTM should be applied in all comatose adult patients with return of spontaneous circulation after cardiac arrest, at a selected and steadily maintained temperature between 32-36°C, for at least 24 hours.[69] Unlike earlier recommendations, this included patients with any rhythm, cause of arrest, or location of arrest, due to the general evidence of benefit and little harm in all groups. The temperature range was altered to give clinicians a choice of avoidance of some side effects in patients who might be at increased risk, such as bleeding at lower temperatures. These guidelines also recommended against

pre-hospital cooling, and emphasize the avoidance of fever.[69] A 2013 Cochrane review investigated the use of TTM in children, but was unable to comment on efficacy due to a lack of strong studies.[76]

Targeted temperature management has also been applied clinically following TBI. Targeted temperature management may be effective in patients with TBI with intracranial hypertension if maintained for 48 hours–5 days and followed by slow rewarming (1°C [~1.8°F]/4 hours).[67] A Cochrane review concluded that TTM may be effective at reducing death or unfavorable outcome in people with TBI, but significant benefit was only found in low-quality trials.[77]

Process of TTM

The full process of TTM is beyond the scope of this discussion and the reader is referred elsewhere.[34] Briefly, TTM involves 3 stages: induction, maintenance, and rewarming. During induction, the goal is to reduce the core temperature to the chosen level of hypothermia (typically 32–34°C [89.6–93.2°F]) as quickly as possible. Cooling techniques involve the use of circulating cool water pads, cold saline infusion, bladder irrigation, ice packs, and endovascular catheters to increase convective or conductive heat loss.[34] It has been recommended by some to avoid the use of ice packs as these have been associated with overshoot and delayed time to target temperature. Endovascular catheters are typically multilumen heat exchangers that allow rapid and precise cooling. Recently, there has been concern for high risk of catheter thrombosis using this technique; however the rate of thrombus formation was similar to other indwelling femoral catheters and the risk was reduced with concurrent use of heparin.[78]

During the maintenance phase of TTM, the temperature is tightly controlled and only minor fluctuations are acceptable (0.2–0.5°C [~0.36–0.9°F]).[34] Current recommendations are to maintain hypothermia for 12–24 hours.[69] During this time, intensive nursing care is required and mechanical ventilation is typically necessary.[79] In the rewarming phase, the core temperature is slowly increased to normothermia, with special attention to avoiding hyperthermia. This is typically done at a rate of 0.2–0.5°C (~0.36–0.9°F)/hour.[34] Temperature must be monitored carefully and the gold standard is considered to be blood temperature measured with a pulmonary arterial catheter.[34] Most other devices do not detect changes in core temperature rapidly enough to work with the fast-acting cooling devices now in use, and the lag time can result in overshoot and excessively low core temperatures.[34] Esophageal and rectal temperatures can be used, but have lag times of approximately 5 and 15 minutes compared to the gold standard.[34]

Each stage has its own challenges and associated complications. Induction is associated with hypovolemia, electrolyte disturbances, and hyperglycemia, although this can be minimized by rapid induction. Shivering is also a challenge in this stage; shivering will not only increase the core temperature but also increases the metabolic rate and oxygen consumption. This can be avoided with proper sedation and analgesia; small doses of opiates are effective at attenuating shivering in people. Benzodiazepines, propofol, and clonidine are also frequently used. Paralytic agents are reserved for short-term use and are not recommended for use during the maintenance phase. Surface or skin counterwarming is the process of providing warmth to the hands, face, or feet, and is effective at reducing shivering in people.[34] In the maintenance phase, complications are similar to those seen with any prolonged sedation, such as bed sores, pneumonia, and other infections.[34] With rewarming comes the return of electrolyte and hemodynamic imbalances, which are best avoided with slow rewarming.[34]

A recent trial by Nielsen et al examined the application of TTM at 33°C versus 36°C (91.4 versus 96.8°F) and found no difference in mortality and neurologic outcome between these groups.[80] There was an increase in serious adverse effects in the 33°C group, such as hypokalemia and longer duration of ventilation than in the 36°C group.[80] This study included patients with arrest rhythms other than ventricular fibrillation or pulseless ventricular tachycardia; therefore, further study is required to determine if there should be a change in standard temperature goals.

Adverse effects
Adverse effects related to TTM reflect the expected effects of mild hypothermia on all body systems. While some of these effects are "normal" or "physiologic" for a hypothermic patient, they may be undesirable and require treatment nonetheless.[34] A recent review of out-of-hospital cardiac arrest patients treated with TTM found arrhythmias, pneumonia, metabolic, and electrolyte disorders, and seizures to be common.[81] The occurrence of seizures was within the range previously reported for patients following cardiac arrest. Sustained hyperglycemia and seizures treated with anti-convulsants were associated with increased mortality; however, this association has been demonstrated previously in other critically ill populations and thus may be unrelated to the TTM specifically. This study also found an increase in bleeding events and sepsis following invasive procedures but these were not associated with increased mortality.[81] In fact, despite the known multifactorial coagulopathy in hypothermia, significant bleeding problems in the general TTM population have not been reported.[34] Shiv-

ering, cardiovascular changes, insulin resistance, decreased drug clearance, leukopenia, and thrombocytopenia have also been reported as common complications of TTM.[34] Medications cleared through hepatic metabolism are typically reduced in dose or frequency, and therapeutic drug level monitoring is recommended.[82] Despite these effects, the benefits of TTM are generally considered to outweigh the risks in the studied patient populations, and the 2012 Cochrane review found there was no significant difference in adverse events between TTM and control populations.[34,70,81,83]

Application of TTM in veterinary medicine
The veterinary literature has limited reports of TTM; most reports describe its use in select referral centers to facilitate cardiac bypass and surgery. The cannulae needed in small breed dogs are often too small to allow high flow rates typically needed in bypass, with the result being low venous return to the patient. Induction of hypothermia decreases oxygen consumption and allows metabolic demands to be met using the same small cannulae and a low flow rate used during cardiac bypass. This also minimizes organ dysfunction in the event of low circulation or circulatory arrest.[84,85]

Moon et al published a case series in 1993 of 19 dogs where hypothermia was applied intraoperatively in cardiac or extensive thoracic/abdominal surgery. Thirty-two percent of the dogs experienced cardiac arrest, although all were successfully resuscitated and overall 90% survived. The temperatures used in this study were much lower than what is now used in TTM and were applied for a shorter duration.[86] Since that time there have been numerous case reports and case series describing the use of TTM in surgical correction of congenital and acquired heart defects in a number of dogs and 1 cat, with perioperative survival rates of 93–100%.[84,85,87] Hayes et al published a case report of a dog with TBI and intractable seizure activity in which TTM was applied as a component of the seizure management.[88] The patient made a full neurologic recovery following discharge.[88] This is the first report of therapeutic hypothermia in veterinary medicine used outside a surgical setting. However, it should be noted that TTM is not currently recommended as standard care in people with TBI.[77]

The use of TTM following cardiac arrest has not been reported in clinical veterinary medicine. Applications are somewhat difficult to extrapolate from human literature, as the recommendations for TTM are generally for those with out-of-hospital cardiac arrest with ventricular fibrillation, which is an uncommon rhythm for our veterinary patients. The recently published RECOVER guidelines recommend mild therapeutic hypothermia at 33°C (91.4°F) ± 1°C (~1.8°F) for 24–48 hours in dogs and

cats that remain comatose after successful resuscitation from cardiopulmonary arrest if mechanical ventilation, 24 hour monitoring, intensive nursing care, and advanced critical care are available.[89,90] If this level of care is not available, TTM should not be undertaken and transfer to a tertiary care facility should be considered. However, if mild accidental hypothermia is present following cardiac arrest, the RECOVER guidelines recommend not to rapidly rewarm.[89,90] The emphasis on avoidance of fever in the human literature in post arrest care should also be considered when managing these veterinary patients. Future prospective trials on use of TTM in postarrest care and TBI are needed.

Summary and Recommendations

The effects of accidental hypothermia are complex, affect nearly everybody system, and are potentially life-threatening. Prominent among these are arrhythmias, cardiovascular depression, coagulopathy, and a reduction in the metabolic rate. Aggressive care is required in most patients, and centers around increasing the core temperature through a variety of rewarming techniques. The majority of adverse effects of hypothermia are reversible when the core temperature has been returned to normal. Patients presenting in cardiopulmonary arrest with primary hypothermia may require prolonged CPR. As evidenced by the human literature, complete recovery is possible, even without the use of advanced life support methods.

Targeted temperature management is used frequently in people who remain comatose after cardiac arrest and has improved survival and neurologic outcome. Application of TTM to veterinary patients at this time is primarily limited to facilitating the use of bypass in cardiac surgery in small breed dogs. The use of TTM following cardiopulmonary resuscitation in veterinary medicine requires further investigation.

Footnotes

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References

1. Oncken A, Kirby R, Rudloff E. Hypothermia in critically ill dogs and cats. Compend Contin Educ Pract Vet 2001; 23(6):506–520.
2. Brown DJ, Brugger H, Boyd J, et al. Accidental hypothermia. N Engl J Med 2012; 367(20):1930–1938.
3. Mallet M. Pathophysiology of accidental hypothermia. QJM 2002; 95(12):775–785.
4. Guyton A. Body temperature, temperature regulation, and fever. In: Guyton AC, Hall JE. eds. Textbook of Medical Physiology. 11th ed. Philadelphia: Saunders Elsevier; 2006, pp. 889–904.
5. Sessler DI. Perioperative heat balance. Anesthesiology 2000; 92(2):578–596.
6. Matsukawa T, Sessler DI, Sessler A, et al. Heat flow and distribution during induction of general anesthesia. Anesthesiology 1995; 82(3):662–673.
7. Burton A. Human calorimetry: the average temperature of tissues of the body. J Nut 1935; 9(3):261–280.
8. Crawshaw L, Rausch R, Wallace H. Thermoregulation. In: Auerbach PS. ed. Wilderness Medicine. 6th ed. St. Louis: Mosby; 2011, pp. 104–115.
9. Wingfield WE. Accidental Hypothermia. In: Wingfield W, Raffe M. eds. Veterinary ICU Book. Jackson Hole: Teton New Media; 2002, pp. 1116–1129.
10. Randall D, Burggren W, French K. Energetic costs of meeting environmental challenges. In: Randall D, Burggren W, French K. eds. Animal Physiology. 5th ed. New York: WH Freeman and Co; 2002, pp. 699–736.
11. Sugano Y. Seasonal changes in heat balance of dogs acclimatized to outdoor climate. Jpn J Physiol 1981; 31(4):465–475.
12. Dhupa N. Hypothermia in dogs and cats. Compend Contin Educ Pract Vet 1995; 17(1):61–68.
13. Armstrong SR, Roberts BK, Aronsohn M. Perioperative hypothermia. J Vet Emerg Crit Care 2005; 15(1):32–37.
14. Danzl DF, Pozos RS. Accidental hypothermia. N Engl J Med 1994; 331(26):1756–1760.
15. Hemmelgarn C, Gannon K. Heatstroke: clinical signs, diagnosis, treatment, and prognosis. Compend Contin Educ Pract Vet 2012; 35(7):E1–E7.
16. Wong K. Physiology and pharmacology of hypothermia. West J Med 1983; 138(2):227–232.
17. Durrer B, Brugger H, Syme D. The medical on-site treatment of hypothermia: ICAR-MEDCOM recommendation. High Alt Med Biol 2003; 4(1):99–103.
18. Todd J. Hypothermia. In: Silverstein D, Hopper K. eds. Small Animal Critical Care Medicine. 2nd ed. St. Louis: Elsevier Saunders; 2015; pp. 789–795.
19. Fischbeck KH, Simon RP. Neurological manifestations of accidental hypothermia. Ann Neurol 1981; 10(4):384–387.
20. Haldane S, McCullough S, Raffe M. Hypothermia. Stand Care 2003; 5(5):6–10.
21. FitzGibbon T, Hayward JS, Walker D. EEG and visual evoked potentials of conscious man during moderate hypothermia. Electroencephalogr Clin Neurophysiol 1984; 58(1):48–54.
22. Roe B. Deep hypothermia and circulatory arrest in the adult. In: Utley J. ed. Pathophysiology and Techniques of Cardiopulmonary Bypass, Vol. 2. Baltimore: Williams and Wilkins; 1982; pp. 36–39.
23. Roberts M, Chilgren J, Zygmunt A. Effect of temperature on alpha-adrenoceptor affinity and contractility of rabbit ear blood vessels. J Vasc Res 1989; 26(4):185–196.
24. Aslam AF, Aslam AK, Vasavada BC, et al. Hypothermia: evaluation, electrocardiographic manifestations, and management. Am J Med 2006; 119(4):297–301.
25. Osborn JJ. Experimental hypothermia: respiratory and blood pH changes in relation to cardiac function. Am J Physiol 1953; 175(3):389–398.
26. Olgers T, Ubels F. The ECG in hypothermia: Osborn waves. Neth J Med 2006; 64(9):350–351.
27. Antzelevitch C, Yan G-X. J wave syndromes. Heart Rhythm 2010; 7(4):549–558.
28. Van Mieghem C, Sabbe M, Knockaert D. The clinical value of the ECG in noncardiac conditions. Chest 2004; 125(4):1561–1576.
29. Campbell S, Day T. Spontaneous resolution of hypothermia-induced atrial fibrillation in a dog. J Vet Emerg Crit Care 2004; 14(4):293–298.
30. Zenoble R, Hill B. Hypothermia and associated cardiac arrhythmias in 2 dogs. J Am Vet Med Assoc 1979; 175(8):840–842.
31. Pereira NJ, Glaus T, Matos JN. ECG of the month. J Am Vet Med Assoc 2014; 244(12):1384–1386.
32. Singletary GE, Kent M, Calvert CA. ECG of the month. J Am Vet Med Assoc 2007; 231(1):44–46.
33. Okada M. The cardiac rhythm in accidental hypothermia. J Electrocardiol 1984; 17(2):123–128.

34. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med 2009; 37(3):1101–1120.

35. Takeuchi K, Suzuki K, Araki H, et al. Roles of endogenous prostaglandins and nitric oxide in gastroduodenal ulcerogenic responses induced in rats by hypothermic stress. J Physiol 1999; 93(5):423–431.

36. Foulis AK. Morphological study of the relation between accidental hypothermia and acute pancreatitis. J Clin Path 1982; 35(11):1244–1248.

37. Rohrer M, Natale A. Effects of hypothermia on the coagulation cascade. Crit Care Med 1992; 20(10):1402–1405.

38. Valeri CR, Feingold H, Cassidy G, et al. Hypothermia-induced reversible platelet dysfunction. Ann Surg 1987; 205(2):175–181.

39. Lynn M, Jeroukhimov I, Klein Y, et al. Updates in the management of severe coagulopathy in trauma patients. J Intensive Care Med 2002; 28(2):s241–s247.

40. Taggart R, Austin B, Hans E, et al. In vitro evaluation of the effect of hypothermia on coagulation in dogs via thromboelastography. J Vet Emerg Crit Care 2012; 22(2):219–224.

41. Donahue SM, Otto CM. Thromboelastography: a tool for measuring hypercoagulability, hypocoagulability, and fibrinolysis. J Vet Emerg Crit Care 2005; 15(1):9–16.

42. Ao H, Moon JK, Tashiro M, et al. Delayed platelet dysfunction in prolonged induced canine hypothermia. Resuscitation 2001; 51(1):83–90.

43. Shenaq S, Yawn D, Saleem A, et al. Effect of profound hypothermia on leukocytes and platelets. Ann Clin Lab Sci 1986; 16(2):130–133.

44. Biggar WD, Bohn D, Kent G. Neutrophil circulation and release from bone marrow during hypothermia. Infect Immun 1983; 40(2):708–712.

45. Biggar W, Bohn D, Kent G, et al. Neutrophil migration in vitro and in vivo during hypothermia. Infect Immun 1984; 46(3):857–859.

46. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. N Engl J Med 1996; 334(19):1209–1216.

47. Beal MW, Brown DC, Shofer FS. The effects of perioperative hypothermia and the duration of anesthesia on postoperative wound infection rate in clean wounds: a retrospective study. Vet Surg 2000; 29(2):123–127.

48. Chiang V, Hopper K, Mellema MS. In vitro evaluation of the efficacy of a veterinary dry heat fluid warmer. J Vet Emerg Crit Care 2011; 21(6):639–647.

49. Smith C, Wagner K. Principles of fluid and blood warming in trauma. Internat Trauma Care 2008; 18(1):71–79.

50. Lau B, Tsui BC. A simple calculation for warming saline using a microwave. Can J Anaesth 2004; 51(s1):A5.

51. Anshus JS, Endahl GL, Mottley JL. Microwave heating of intravenous fluids. Am J Emerg Med 1985; 3(4):316–319.

52. Leaman PL, Martyak GG. Microwave warming of resuscitation fluids. Ann Emerg Med 1985; 14(9):876–879.

53. Faries G, Johnston C, Pruitt KM, et al. Temperature relationship to distance and flow rate of warmed IV fluids. Ann Emerg Med 1991; 20(11):1198–1200.

54. Forgey W. Basic Essentials: Hypothermia. 2nd ed. Merrilville: Falcon Press Publishing; 1999, pp. 59–60.

55. Silbergleit R, Satz W, Lee DC, et al. Hypothermia from realistic fluid resuscitation in a model of hemorrhagic shock. Ann Emerg Med 1998; 31(3):339–343.

56. Connolly E, Wothley L. Induced and accidental hypothermia. Resuscitation 2000; 2(1):22–29.

57. Lewis ME, Al-Khalidi AH, Townend JN, et al. The effects of hypothermia on human left ventricular contractile function during cardiac surgery. J Am Coll Cardiol 2002; 39(1):102–108.

58. Hilmo J, Naesheim T, Gilbert M. "Nobody is dead until warm and dead": prolonged resuscitation is warranted in arrested hypothermic victims also in remote areas—a retrospective study from northern Norway. Resuscitation 2014; 85(9):1204–1211.

59. Gilbert M, Busund R, Skagseth A, et al. Resuscitation from accidental hypothermia of 13.7 C with circulatory arrest. Lancet 2000; 355(9201):375–376.

60. Mark E, Jacobsen O, Kjerstad A, et al. Hypothermic cardiac arrest far away from the center providing rewarming with extracorporeal circulation. Int J Emerg Med 2012; 5(1):1–3.

61. Lexow K. Severe accidental hypothermia: survival after 6 hours 30 minutes of cardiopulmonary resuscitation. Arctic Med Res 1990; 50:112–114.

62. Freude T, Gillen S, Ehnert S, et al. Therapeutic peritoneal lavage with warm saline solution as an option for a critical hypothermic trauma patient. Wien Klin Wochenschr 2014; 126(1–2):56–61.

63. Brodmann Maeder M, Martin D, Balthasar E, et al. The Bernese Hypothermia Algorithm: a consensus paper on in-hospital decision-making and treatment of patients in hypothermic cardiac arrest at an alpine level 1 trauma centre. Injury 2011; 42(5):539–543.

64. Hoek TLV, Morrison LJ, Shuster M, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2010; 122(18 suppl 3):S829–S861.

65. Nolan JP, Soar J, Perkins GD, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. Resuscitation 2010; 81(10):1400–1433.

66. Tipton MJ, Golden FSC. A proposed decision-making guide for the search, rescue and resuscitation of submersion (head under) victims based on expert opinion. Resuscitation 2011; 82(7):819–824.

67. Sinclair HL, Andrews P. Bench-to-bedside review: hypothermia in traumatic brain injury. Crit Care 2010; 14(1):204. Doi: 10.1186/cc8220.

68. Polderman KH. Mechanisms of action, physiological effects, and complications of hypothermia. Crit Care Med 2009; 37(7):S186–S202.

69. Callaway CW, Donnino MW, Pink EL, et al. Part 8: Post–cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Circulation 2015; 132(18 suppl 2):S465–S482.

70. Arrich J, Holzer M, Havel C, et al. Hypothermia for neuroprotection in adults after cardiopulmonary resuscitation. Cochrane Database Syst Rev 2012; 9:1–33.

71. Holzer M, Cerchiari E, Martens P, et al. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002; 346(22):1756–1756.

72. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. N Engl J Med 2002; 346(8):557–563.

73. Nolan JP, Morley PT, Hoek TV, et al. Therapeutic hypothermia after cardiac arrest. An advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. Circulation 2003; 108(1):118–121.

74. Nichol G, Huszti E, Kim F, et al. Does induction of hypothermia improve outcomes after in-hospital cardiac arrest? Resuscitation 2013; 84(5):620–625.

75. Kory P, Fukunaga M, Mathew JP, et al. Outcomes of mild therapeutic hypothermia after in-hospital cardiac arrest. Neurocrit Care 2012; 16(3):406–412.

76. Scholefield B, Duncan H, Davies P, et al. Hypothermia for neuroprotection in children after cardiopulmonary arrest. Evid Based Child Health 2013; 8(5):1584–1613.

77. Sydenham E, Roberts I, Alderson P. Hypothermia for traumatic head injury. Cochrane Database Syst Rev 2009; 2:1–55.

78. Maze R, Le May MR, Froeschl M, et al. Endovascular cooling catheter related thrombosis in patients undergoing therapeutic hypothermia for out of hospital cardiac arrest. Resuscitation 2014; 85(10):1354–1358.

79. Polderman KH. Application of therapeutic hypothermia in the intensive care unit. J Intensive Care Med 2004; 30(5):757–769.

80. Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 C versus 36 C after cardiac arrest. N Engl J Med 2013; 369(23):2197–2206.

81. Nielsen N, Sunde K, Hovdenes J, et al. Adverse events and their relation to mortality in out-of-hospital cardiac arrest patients treated with therapeutic hypothermia. Crit Care Med 2011; 39(1):57–64.

82. Zanelli S, Buck M, Fairchild K. Physiologic and pharmacologic considerations for hypothermia therapy in neonates. J Perinatology 2010; 31(6):377–386.

83. Green RS, Howes DW. Stock your emergency department with ice packs: a practical guide to therapeutic hypothermia for survivors of cardiac arrest. CMAJ 2007; 176(6):759–762.

84. Uechi M, Mizukoshi T, Mizuno T, et al. Mitral valve repair under cardiopulmonary bypass in small-breed dogs: 48 cases (2006–2009). J Am Vet Med Assoc 2012; 240(10):1194–1201.

85. Kanemoto I, Taguchi D, Yokoyama S, et al. Open heart surgery with deep hypothermia and cardiopulmonary bypass in small and toy dogs. Vet Surg 2010; 39(6):674–679.

86. Moon P, Ilkiw J. Surface-induced hypothermia in dogs: 19 cases (1987–1989). J Am Vet Med Assoc 1993; 202(3):437–444.

87. Uechi M, Harada K, Mizukoshi T, et al. Surgical closure of an atrial septal defect using cardiopulmonary bypass in a cat. Vet Surg 2011; 40(4):413–417.

88. Hayes GM. Severe seizures associated with traumatic brain injury managed by controlled hypothermia, pharmacologic coma, and mechanical ventilation in a dog. J Vet Emerg Crit Care 2009; 19(6):629–634.

89. Smarick SD, Haskins SC, Boller M, Fletcher DJ. RECOVER evidence and knowledge gap analysis on veterinary CPR. Part 6: post-cardiac arrest care. J Vet Emerg Crit Care 2012; 22(s1):S85–S101.

90. Fletcher DJ, Boller M, Brainard BM, et al. RECOVER evidence and knowledge gap analysis on veterinary CPR. Part 7: clinical guidelines. J Vet Emerg Crit Care 2012; 22(s1):S102–S131.