Pathophysiology

Nervous System

Numbing cold depresses the central nervous system, producing impaired memory and judgment, slurred speech, and decreased consciousness. During cold-weather expeditions, leaders are prone to risk-taking behavior and its attendant trauma. Temperature-dependent enzyme systems in the brain do not function properly at cold temperatures that are well tolerated by the kidneys. As a result, most patients are comatose below 30°C (86°F), although some remain amazingly alert.

Neurons are initially stimulated by a 1°C (1.8°F) drop in temperature, but the brain does not always cool uniformly during accidental hypothermia. After the initial increase, there is a linear decrease in cerebral metabolism by 6% to 10% per degree Celsius from 35°C (95°F) to 25°C (77°F). Hypothermia can afford cerebral protection because of the diminished cerebral metabolic requirements for oxygen.

The electroencephalogram is abnormal below 33.5°C (92.3°F) and becomes silent at 19°C to 20°C (66.2°F to 68°F). The triphasic waves commonly noted in hypothermia are also observed in various metabolic, toxic, and diffuse encephalopathies. Visual evoked potentials, another objective measure of cerebral function, become smaller as the mercury drops. After cerebral cortical function becomes impaired, lower brainstem functions are also deranged.

Cerebrovascular autoregulation is protectively intact until the temperature drops below 25°C (77°F). Although vascular resistance is increased, blood flow is disproportionately redistributed to the brain. In canine studies, blood flow in the brain, muscle, kidneys, and myocardium recovers quickly to control levels after rewarming. Flow deficits persist in the pulmonary, digestive, and endocrine systems for up to 2 hours after rewarming.

Chilling the peripheral nervous system increases muscle tension and preshivering tone, eventually leading to shivering. Shivering, which is also centrally controlled, is a much more efficient heat producer than are voluntary muscle contractions of the extremities.

Cardiovascular System

Many cardiovascular responses caused by or associated with hypothermia are well described. Cold stress increases consumption of myocardial oxygen. Autonomic nervous system stimulation causes tachycardia and peripheral vasoconstriction, both of which increase systemic blood pressure and cardiac afterload.

As core temperature drops, there is a fairly linear decrease in pulse rate. After premonitory tachycardia, decremental bradycardia produces a 50% decrease in heart rate at 28°C (82.4°F). Because this bradycardia is caused by decreased spontaneous depolarization of pacemaker cells, it is refractory to atropinization. If there is a “relative” tachycardia not consistent with the degree of hypothermia, the clinician should be concerned. Associated conditions include occult trauma with hypovolemia, drug ingestion, and hypoglycemia.

During hypothermic bradycardia, unlike normothermia, systole is prolonged longer than diastole. In addition, the conduction system is much more sensitive to cold than is the myocardium, so the cardiac cycle is lengthened. Cold-induced changes in pH, oxygen, electrolytes, and nutrients also alter electrical conduction.

Hypothermia progressively decreases mean arterial pressure and cardiac index. Cardiac output drops to about 45% of normal at 25°C (77°F). Systemic arterial resistance, determined by invasive hemodynamic monitoring, is increased. Even after rewarming, cardiovascular function may remain temporarily depressed, with impaired myocardial contractility, metabolism, and peripheral vascular function.

Mild, steady hypothermia in patients with poikilothermic thermoregulatory disorders causes electrocardiographic (ECG) alterations and conduction abnormalities. First the PR, then the QRS, and most characteristically the QTc intervals are prolonged. Clinically invisible increased preshivering muscle tone can obscure the P waves; ST-segment and T-wave abnormalities are inconsistent. Of note, ordinary surface ECG electrodes, when attached to dry skin, will accurately reflect cardiac electrical activity. Needle electrodes are not necessary to detect weak ECG signals.
The J wave (Osborn wave or hypothermic hump; (Figure 5-2), first described by Tomaszewski in 1938, occurs at the junction of the QRS complex and the ST segment. It is not prognostic but is potentially diagnostic. [112,197] J waves occur at any temperature below 32.2° C (90° F) and are most frequently seen in leads II and V6. When core temperature falls below 25° C (77° F), J waves are found in the precordial leads (especially V3 or V4). The size of the J waves also increases with temperature depression, but is unrelated to arterial pH. [373] J waves are usually upright in aVL, aVF, and the left precordial leads. [3,175,262]

![Figure 5-2](image)

**FIGURE 5-2** The J or Osborn wave of hypothermia. Note that the obvious J waves were not properly interpreted by the computer.

J waves may represent hypothermia-induced ion fluxes, resulting in delayed depolarization or early repolarization of the left ventricle, or there may be an unidentified hypothalamic or neurogenic factor. J waves are *not* pathognomonic of hypothermia but occur also with central nervous system lesions, focal cardiac ischemia, and sepsis. They may also be present in young, healthy persons. When pronounced, J waveform abnormalities can simulate myocardial infarction. Computer software is not widely available that can successfully recognize and suggest the diagnosis of hypothermia. [202,235,255]

The prehospital capability to differentiate between J waves and injury current is important in rural and wilderness settings. [57] Thrombolysis is unstudied in hypothermia but would be expected to exacerbate coagulopathies. [110]

Below 32.2° C (90° F), all types of atrial and ventricular arrhythmias are encountered. [75] The His-Purkinje system is more sensitive to cold than is the myocardium. As a result, conduction velocity decreases and electrical signals can disperse. Because conduction time is prolonged more than the absolute refractory period, reentry currents can produce circus rhythms that initiate ventricular fibrillation (VF).

In addition to causing bradycardia, widening the QRS complex, and prolonging the QT interval, hypothermia increases the duration of action potentials (Figure 5-3, online). [21,22] During rewarming, nonuniform myocardial temperatures can disperse conduction and further increase the action potential duration, another mechanism to develop the unidirectional blocks that facilitate reentrant arrhythmias. At temperatures between 25° and 20° C (77° and 68° F), myocardial conduction time is prolonged further than the absolute refractory period. Another arrhythmogenic mechanism is development of independent electrical foci that precipitate arrhythmias.
Various electrolyte abnormalities can further complicate the situation during hypothermic conditions, because they exacerbate the effects of prolonged action potentials. Most conspicuously, hypothermia-induced cellular calcium loading mimics digitalis toxicity and may predispose to a forme fruste of torsades de pointes.

Hypothermia-induced VF and asystole often occur spontaneously below 25° C (77° F). The VF threshold and transmembrane resting potential are decreased. Because the heart is cold, the conduction delay is facilitated by the large dispersion of repolarization, and the action potential is prolonged. The increased temporal dispersion of the recovery of excitability is linked to VF. Nature's model of resistance to VF is the heart of hibernating animals during rewarming. Animals with this capacity seem to be protected by a shortened QT duration and a calcium channel handling system that prevents intracellular calcium overload.

Asystole and VF may both result from hypovolemia, tissue hypoxia, therapeutic manipulations, acid–base fluxes, autonomic dysfunction, and coronary vasoconstriction coupled with increased blood viscosity. Other causes may include rough handling or jostling, sudden vertical positioning, and acute metabolic stress from exertion or very rapid rewarming.

Core Temperature Afterdrop

Core temperature afterdrop refers to the continued decline in a hypothermic patient's temperature after removal from the cold (see also Chapter 6). Contributing to afterdrop is the simple temperature equilibration between the warmer core and cooler periphery. Circulatory changes account for another set of observations. The countercurrent cooling of blood that perfuses cold extremities results in core temperature decline until the existing temperature gradient is eliminated. In cold-water immersion, post-rescue collapse may also result from abrupt hypotension after loss of hydrostatic squeeze contributed by the water.

The incidence and magnitude of core temperature afterdrop vary widely in clinical experiments and in surgically induced hypothermia. Hayward measured his own esophageal, rectal, tympanic, and cardiac temperatures (via flotation tip catheter) during rewarming after being cooled in 10° C (50° F) water. On three different days, rewarming was achieved via shivering thermogenesis, heated humidified inhalation, and warm bath immersion. Coincident with a 0.3° C (0.5° F) afterdrop during warm bath immersion, his mean arterial pressure fell 30% and his peripheral vascular resistance fell 50%. Therefore the circulatory mechanism is another major contributor to afterdrop.

A human study of peripheral blood flow during rewarming from mild hypothermia suggests that minimal skin blood flow changes can also lead to afterdrop (Figure 5-4). The largest core temperature afterdrops occur when subjects are rewarmed with plumbed garments and heating pads.
In summary, core temperature afterdrop appears to become most clinically relevant when a large temperature gradient exists between the periphery and the core, particularly in dehydrated, chronically cold patients. Both conductive and convective mechanisms are responsible for afterdrop.\[104\] Stimulating peripheral blood flow can increase afterdrop. Major afterdrops are also observed when frostbitten extremities are thawed before crystalloid volume resuscitation and thermal stabilization of the core temperature.

### Respiratory System

Any exposure to a big chill initially stimulates respiratory drive, which is followed by progressive depression of respiratory minute volume as cellular metabolism is depressed. The respiratory rate often falls to 5 to 10 breaths/min below 30°C (86°F), and ultimately brainstem neurocontrol of ventilation fails. An important physiologic observation is that carbon dioxide production drops 50% for each 8°C (14°F) fall in temperature. In severe hypothermia, carbon dioxide retention and respiratory acidosis reflect the aberrant responses to normothermic respiratory stimuli.\[99\]

Other pathophysiologic factors contributing to ventilation–perfusion mismatch include decreased ciliary motility, increased quantity and viscosity of secretions, hypothermic acute respiratory distress syndrome, and noncardiogenic pulmonary edema.\[332\] The thorax loses elasticity, and pulmonary compliance drops. The respiratory “bells” stiffen and fail because contractile efficiency of the intercostal muscles and diaphragm declines.

Pertinent potentially protective or detrimental factors that affect tissue oxygenation in endothermic humans are listed in Box 5-1.

### BOX 5-1

#### Oxygenation Considerations During Hypothermia

**Detrimental Factors**

- Oxygen consumption increases with rise in temperature; use caution if rewarming is rapid; shivering also increases demand
- Decreased temperature shifts oxyhemoglobin dissociation curve to the left
- Ventilation–perfusion mismatch; atelectasis; decreased respiratory minute volume; bronchorrhea; decreased protective airway reflexes
- Decreased tissue perfusion from vasoconstriction; increased viscosity
- “Functional hemoglobin” concept: capability of hemoglobin to unload oxygen is lowered
- Decreased thoracic elasticity and pulmonary compliance
Protective Factors

- Reduction of oxygen consumption by 50% at 28°C (82.4°F), 75% at 22°C (71.6°F), and 92% at 10°C (50°F)
- Increased oxygen solubility in plasma
- Decreased pH and increased PaCO₂ shift oxyhemoglobin dissociation curve to right

Renal System

The kidneys respond briskly to hypothermia-induced changes in the vascular tree's capacitance. Peripheral vasoconstriction can result initially in a relative central hypervolemia, producing diuresis, even with mild dehydration. In addition, renal blood flow is depressed by 50% at 27°C to 30°C (80.6°C to 86°F), which decreases glomerular filtration rate. Nevertheless, there is an initial large diuresis of this dilute glomerular filtrate, which does not efficiently clear nitrogenous wastes.

The etiology of the cold diuresis is multifactorial. Some of the suggested mechanisms include inhibition of antidiuretic hormone (ADH) release and decreased renal tubular function. Neither hydration nor ADH infusions seem to influence the diuretic response, which appears to be an attempt to compensate for initial relative central hypervolemia caused by vasoconstrictive overload of capacitance vessels.

The diuresis may also be pressure related, caused by impaired autoregulation in the kidneys. Cold diuresis has circadian rhythmicity and correlates with periods of shivering. Cold water immersion increases urinary output 3.5 times, and the presence of ethanol impressively doubles that diuresis.

Coagulation

Coagulopathies often develop in hypothermic patients because the enzymatic nature of the activated clotting factors is depressed by cold. In vivo, prolonged clotting is proportional to the number of steps in the cascade. For example, at 29°C (84.2°F), a 50% to 60% increase in the partial thromboplastin time (PTT) would be expected. Kinetic tests of coagulation, however, are performed in the laboratory at 37°C (98.6°F). As the blood warms in the machine, the enzymes between the factors in the cascade are activated. The sample of warmed in vitro blood then clots normally.

The reversible hemostatic defect created by hypothermia may not be reflected by the “normal” prothrombin time (PT), PTT, or international normalized ratio (INR). This coagulopathy is basically independent of clotting factor levels and cannot be confirmed by laboratory studies performed at 37°C (98.6°F). Treatment is rewarming and not simply administration of clotting factors. When rapid rewarming is difficult, concentrations of 0.01 to 1 nM of desmopressin may partially reverse hypothermia-induced coagulopathy in vitro.

Thrombocytopenia as a cause of bleeding becomes progressively significant in severe hypothermia. Proposed mechanisms include direct bone marrow suppression and splenic or hepatic sequestration. Thromboxane B₂ production by platelets is also temperature dependent, so cooling skin temperature produces reversible platelet dysfunction. Thrombocytopenia is a common but poorly recognized corollary of hypothermia in older adults and neonates.

Coagulopathy in trauma patients is attributed to enzyme inhibition, platelet alteration, and fibrinolysis. The critical temperature at which enzyme activity slows significantly is 34°C (93.2°F). In addition, clot strength weakens as a result of platelet malfunction. Fibrinolysis is not significantly affected at any temperature in the range measured (33°C to 37°C [91.4°F to 98.6°F]) (see Trauma, later).

Physiologic hypercoagulability also develops during hypothermia, with a sequence similar to that seen in disseminated intravascular coagulation (DIC). This produces a higher incidence of thromboembolism during hypothermia. Causes include thromboplastin release from cold tissue, simple circulatory collapse, and release of catecholamines and steroids. Because fibrin split-product levels can be normal, bleeding is not always considered a hematologic manifestation of DIC.

Whole blood viscosity increases with the hemoconcentration seen after diuresis and the shift of fluid out of vascular compartments. Red blood cells (RBCs) simply stiffen and have diminished cellular deformity when chilled. The elevated viscosity of hypothermia is also exacerbated by cryoglobulinemia. Cryofibrinogen is a cold-precipitated fibrinogen occasionally seen with carcinoma, sepsis, and collagen vascular diseases. Blood viscosity is also increased by the transient increases in platelet and RBC counts seen with mild surface cooling. This could explain the increased mortality from coronary
and cerebral thromboses that occur in winter. [225]