

# Targeted Temperature Management in Brain Injured Patients



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## KEYWORDS

• Hypothermia • Fever • Hyperthermia • Normothermia

## KEY POINTS

- Evidence from animal models indicates that lowering temperature by a few degrees can produce substantial neuroprotection.
- In humans, hypothermia has been found to be neuroprotective with an impact on mortality and long-term functional outcome in cardiac arrest and neonatal hypoxic–ischemic encephalopathy.
- Clinical trials have explored the potential role of maintaining normothermia and treating fever in critically ill patients with brain injury.

## INTRODUCTION

A bulk of evidence from animal models indicates that lowering temperature by a few degrees can confer neuroprotection against ischemia.<sup>1</sup> In humans, targeted temperature management (TTM) has been found to be neuroprotective with a significant impact on mortality and long-term functional outcome in models of cardiac arrest and neonatal hypoxic–ischemic encephalopathy. In contrast, recent clinical trials in traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), ischemic stroke (AIS), meningitis, and status epilepticus (SE) have failed to demonstrate a significant outcome benefit. Heterogeneity and limitations in these studies preclude a definitive

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conclusion that therapeutic hypothermia is not helpful in these conditions. It remains unclear what degree of hypothermia (dose and duration) and the rate of rewarming to normothermia are optimal in different models of brain injury. Thus, the applicability of TTM on clinical grounds remains a subject of ongoing research. The problem with TTM and induction of therapeutic hypothermia is multifactorial. First, diseases are different at the pathophysiologic level, so the extrapolation of the experience from certain models is not biologically plausible across other diseases; second, subjects are different and the dose, duration, and the rewarming phase may need to be adjusted for each patient. Arguing for a different approach such as a patient specific dose based on weight or body surface area and third, the thermoregulatory defenses may overcome the neuroprotective effect conferred by TTM.

This review discusses basic concepts necessary to understand the physiologic interactions of thermoregulation, the effects of thermal modulation in critically ill patients, the proposed mechanisms of action of temperature modulation, and finally, the practical aspects of TTM in the most important forms of brain injury in light of recent clinical studies, and potential approaches to induce TTM in critically-ill neurological patients.

## **METABOLISM AND HEAT PRODUCTION**

Thermoregulation is one of the most sophisticated functions in the human physiology. Fluctuations in temperature modulate important behavioral and physiologic functions. Healthy humans are able to control temperature tightly. The brain is the most metabolically demanding organ in humans. Although it represents about 2% of the total body weight, it accounts for 20% to 25% of total body glucose and oxygen metabolism and consumption. This high metabolic rate of oxygen consumption ( $CMRO_2$ ) and rate of glucose consumption is explained by the multiple cerebral processes that depend on energy expenditure. The metabolism and heat production of the human brain at rest is about 3.0 to 3.5 mL  $O_2$ /100 g/min and 0.6 J/g/min.<sup>2,3</sup> The trade-off of this high metabolic activity in proportion to the weight is the production of heat, which needs to be dissipated by complex thermoregulatory mechanisms.

## **THERMOREGULATORY CONTROL**

In humans, core body temperature ( $T_c$ ) is more tightly regulated than other important physiologic variables such as heart rate and blood pressure, even during illness. Body temperature is sensed by the transient receptor potential (TRP) ion channels.<sup>4,5</sup> Sensory neurons express thermal TRPs and are activated within different ranges of temperature thresholds.<sup>6,7</sup> The hypothalamus, the dominant thermoregulatory body in humans, receives thermal inputs from the skin, peripheral tissues, core organs, and the central nervous system. Behavioral and autonomic defenses then prepare the body to counteract the effects of changes in temperature. Behavioral responses include activities, mostly learned, such as choosing what to dress, seeking cover, opening or closing a window, and seeking shelter or exposure. Autonomic defenses such as arteriovenous shunt vasomotion (dilatation and constriction) and shivering are less powerful than behavioral defenses overall, but far more crucial for critically ill patients.

Arteriovenous shunts are specialized thermoregulatory structures located primarily in the fingers and toes. Although arteriovenous shunts are small structures and numerically limited, they convey significant blood flow regulation as compared with regular capillaries, and constitute a potent thermoregulatory mechanism in humans.<sup>8</sup> Arteriovenous shunt vasomotion is the most frequently activated and metabolically efficient (as compared with shivering and sweating) thermoregulatory defense mechanism. The threshold for arteriovenous shunt contraction is 37°C. Once activated, the rapid

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